Antiepileptic Drugs In Neurosurgery

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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.

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Antiepileptic drugs

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

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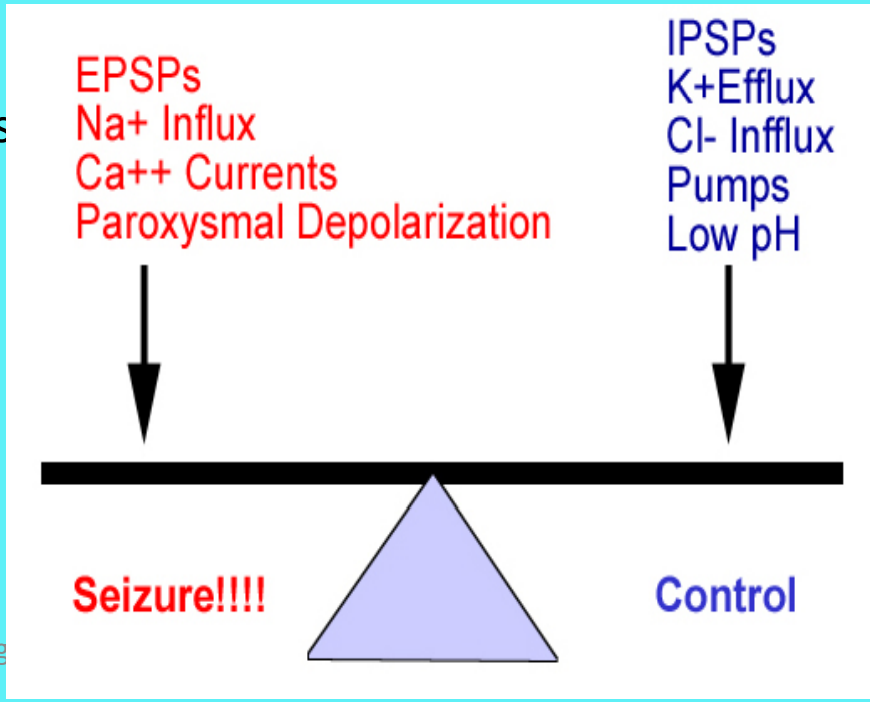
History

- Modern Treatment Of Seizures Started In 1850 With Bromides
- 1910: Phenobarbital
- 1940: Phenytoin (PHT)
- 1968: Carbamazepine (CBZ) For Trigeminal Neuralgia, in 1974, Approved For Partial Seizures.
- 1978: Valproate
- 1999: Levetiracetam

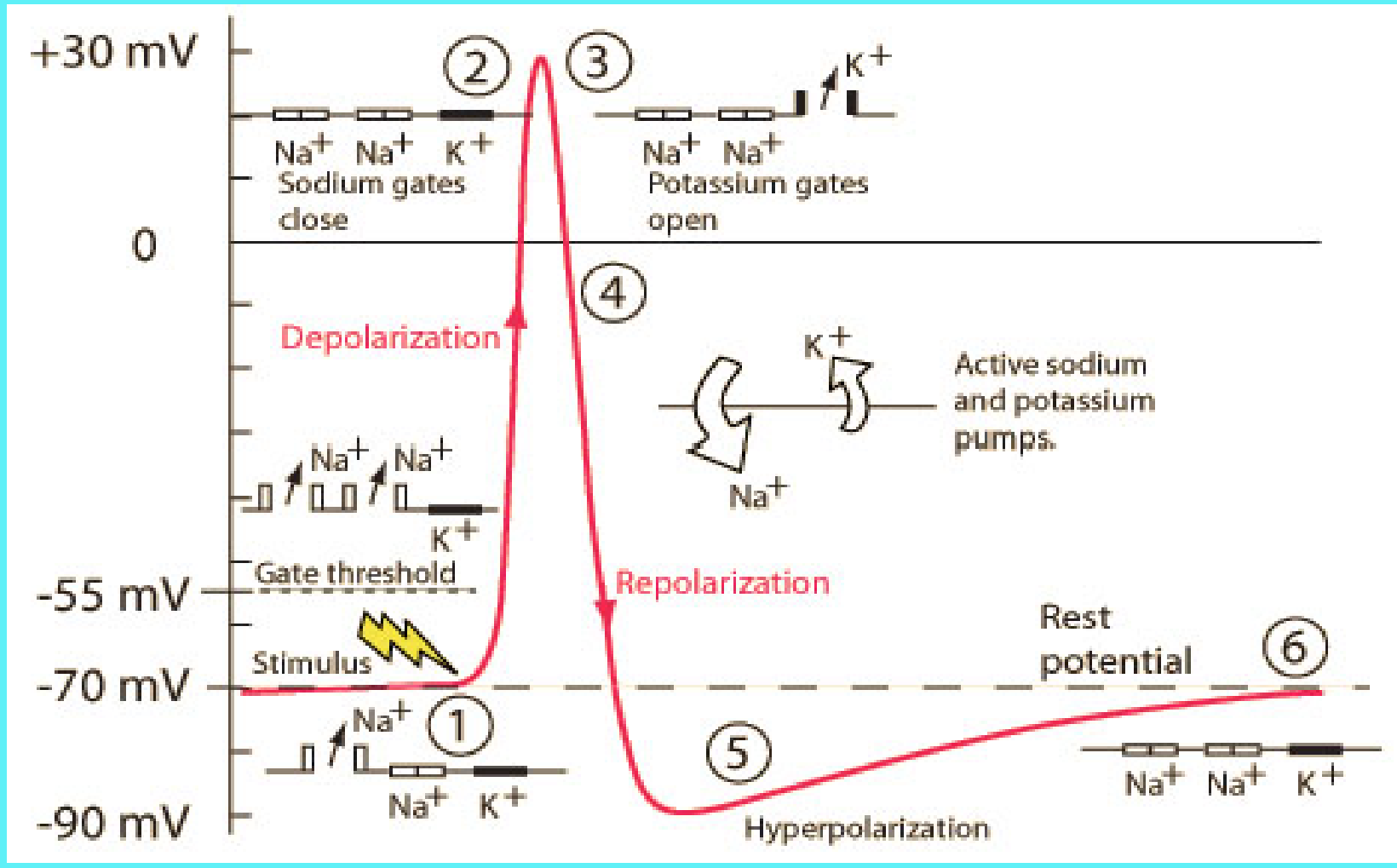
Cellular Mechanisms of Seizure Generation

- Excitation (too much)
  - Ionic-inward Na^{+}, Ca^{++} currents
  - Neurotransmitter: glutamate, aspartate

- Inhibition (too little)
  - Ionic-inward Cl^{-}, outward K^{+} currents
  - Neurotransmitter: GABA



The neuronal excitation



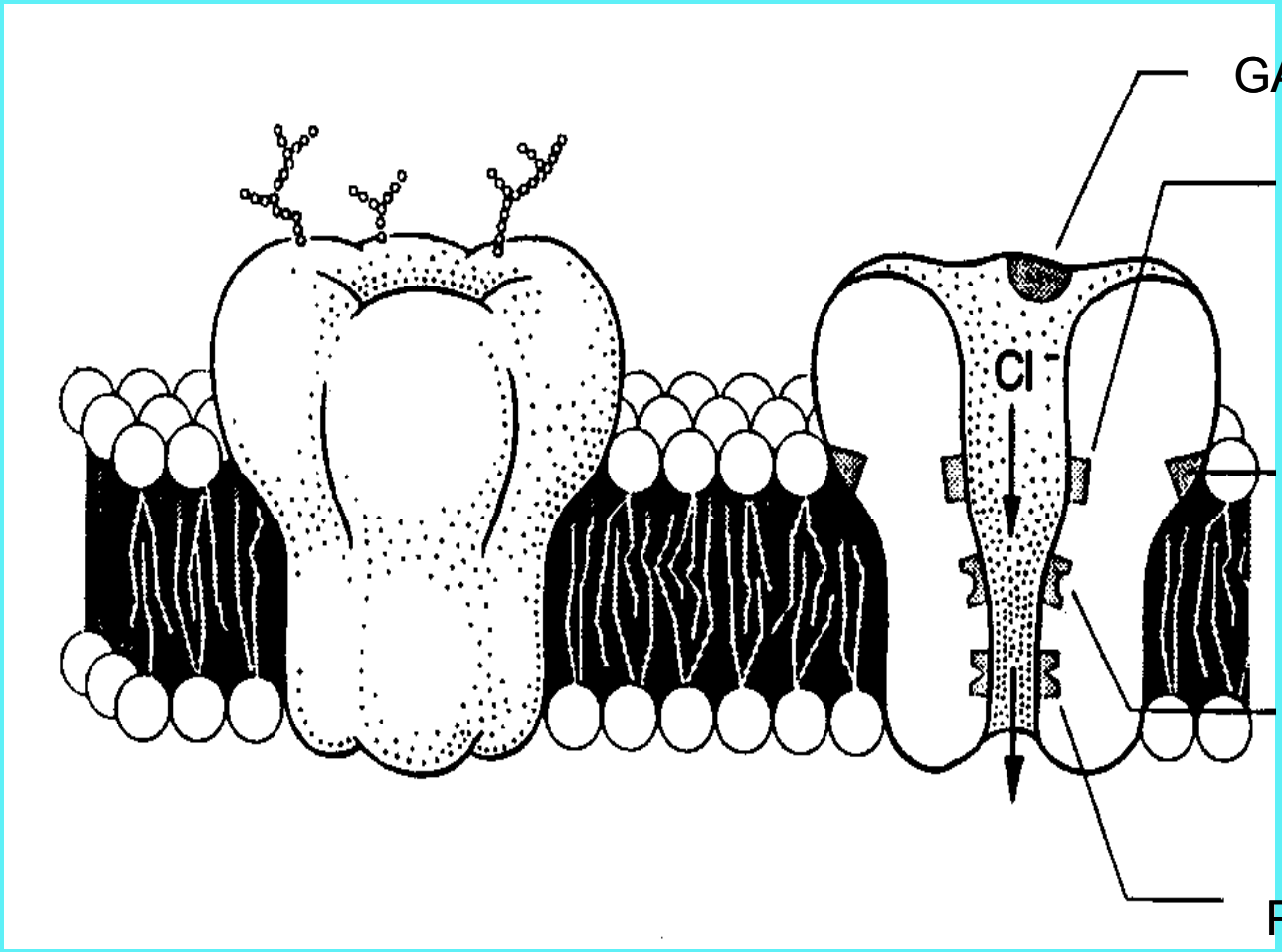
Glutamate

- Brain's major excitatory neurotransmitter
- Two groups of glutamate receptors
  - Ionotropic - 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

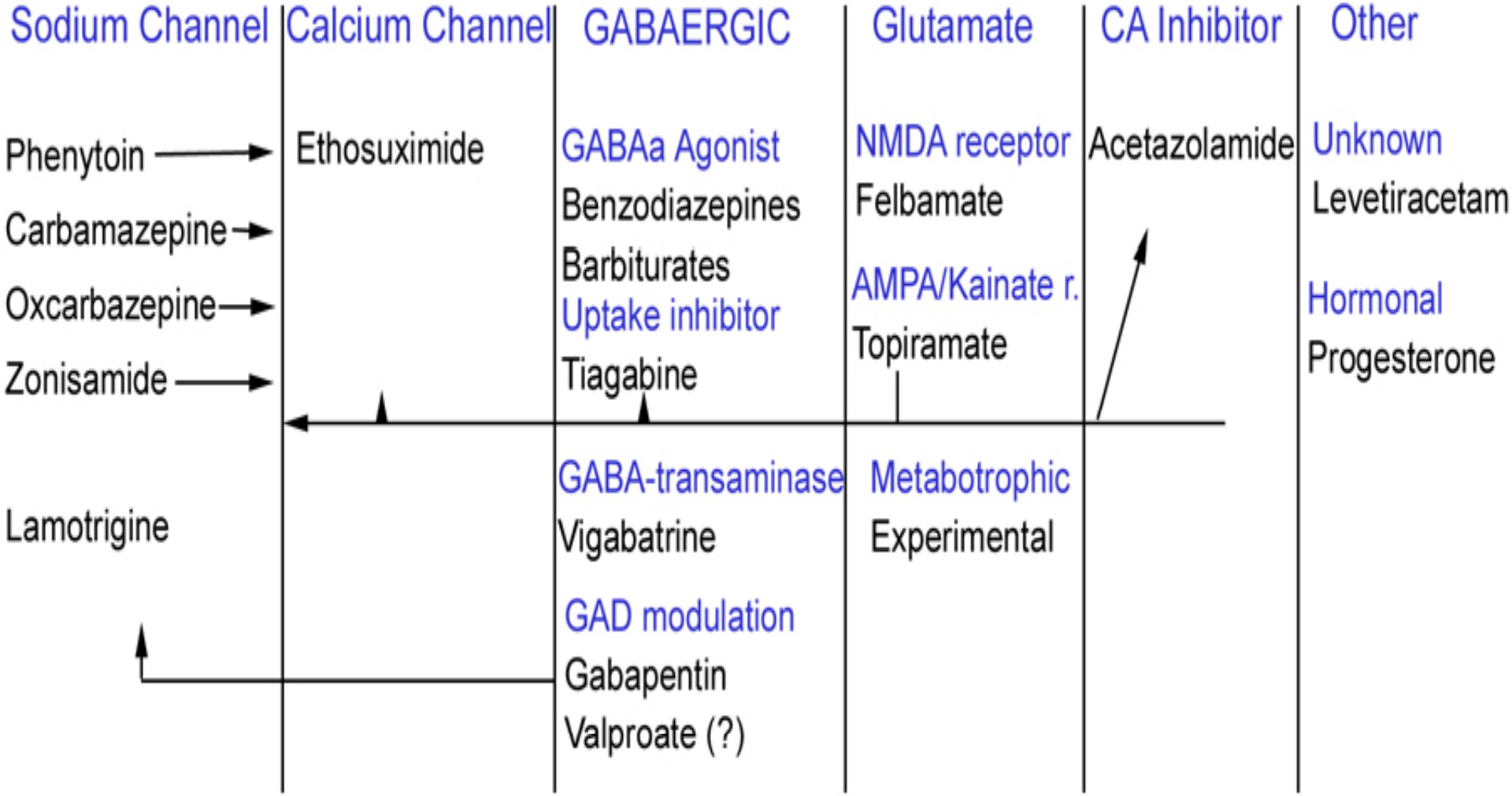
GABA

- 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

Diagram of the $GABA_A$ receptor



Classification



Pharmacokinetic Principles

Absorption: entry of drug into the blood

- Essentially complete for all AEDs
  (*except gabapentin)*
- Timing varies widely by drug, formulation, patient characteristics
- Generally slowed by food in stomach
  (CBZ may be exception)
- Usually takes several hours
  (importance for interpreting blood levels)

Pharmacokinetic Principles

- **Elimination: removal of active drug from the blood by metabolism and excretion**
  - Metabolism/biotransformation — generally hepatic; usually rate-limiting step
  - Excretion — mostly renal
  - Active and inactive metabolites
  - Changes in metabolism over time

    (***Auto-induction with carbamazepine***) or

    with **polytherapy** (***enzyme induction or inhibition***)
  - Differences in metabolism by age, systemic disease

AED Serum Concentrations

- Optimizing AED therapy
- Assessing compliance
- To monitor pharmacodynamic and pharmacokinetic interactions.
- Most often individual patients define their own " therapeutic range" for AEDs.
- For the *new AEDs* there is no clearly defined "therapeutic range".

PHARMACO KINETICS

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	

Antiepileptic Drug Interactions

Induce metabolism of other drugs:

Carbamazepine

Phenytoin

Phenobarbital

Primidone

Inhibit metabolism of other drugs:

Valproate

Felbamate

Topiramate

Neither inducer/inhibitor

Gabapentin

Lamotrigine

Pregabalin

Tiagabine

Levetiracetam

Zonisamide

AEDs that are highly protein bound:

Valproate

Phenytoin

Tiagabine

Carbamazepine

Oxcarbazepine

Topiramate

Adverse Effects

- Acute dose-related—reversible
- Idiosyncratic
  - uncommon
  - potentially serious or life threatening
- Chronic—reversibility and seriousness vary

Adverse effects (dose-related)

- Dizziness , Fatigue , Ataxia, Diplopia : all AEDs
- Irritability : levetiracetam
- Weight loss/anorexia : topiramate, zonisamide, felbamate
- Weight gain :
  valproate
  (also associated with polycystic ovarian syndrome)
  carbamazepine, gabapentin, pregabalin

Adverse Effects of AEDs: Serious

- ***Typically Idiosyncratic:***
- **Renal stones**
  topiramate, zonisamide
- **Anhydrosis, heat stroke**
  topiramate
- **Acute closed-angle glaucoma**
  topiramate
- **Hyponatremia**
  carbamazepine, oxcarbazepine

Used in DI

Adverse Effects of AEDs: Serious

- ***Typically Idiosyncratic:***

- **Aplastic anemia**
  Valproate, Carbamazepine, Felbamate, Zonisamide,

- **Hepatic Failure**
  Valproate, Felbamate, Lamotrigine, Phenobarbital

- **Peripheral vision loss**
  Vigabatrin

- **Rash**
  Phenytoin, Lamotrigine, Zonisamide, Carbamazepine

Risk of "dangerous or even fatal skin reactions" such as **Steven-Johnson Syndrome** and **Toxic epidermal necrolysis** is incrased in patients with **HLA-B*1502 allele**
Estimated absolute risk for those with the allele: **5%**

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LONGTERM ADVERSE EFFECTS

- Endocrine/Metabolic Effects
  - **Osteomalacia, osteoporosis**
    - **Carbamazepine**
    - **Phenobarbital**
    - **Phenytoin**
    - **Oxcarbazepine**
  - **Folate deficiency (anemia, teratogenesis)**
    - **Phenobarbital**
    - **Phenytoin**
    - **Carbamazepine**
    - **Valproate**
  - **Altered connective tissue metabolism or growth**

    (facial coarsening, hirsutism, gingival hyperplasia or contractures)
    - **Phenytoin**
    - **Phenobarbital**

Neurologic

- Neuropathy
- Cerebellar Syndrome

  phenytoin

Starting AEDs

- Discuss likely adverse effects
- Discuss unlikely but important adverse effects
- Discuss likelihood of success
- Discuss recording/reporting seizures, adverse effects, potential precipitants

Choosing Antiepileptic Drugs

- Limited placebo-controlled trials available, particularly of newer AEDs
- Several drugs are commonly used for indications other than those for which they are officially approved/recommended
- For **partial epilepsy** depends on
  drug side-effect profile & patient's preference/concerns
- For **generalized epilepsy** depends on

  predominant seizure type(s) , drug side-effect & patient's preference/concerns

ILAE Summary Guidelines and Summary of AAN evidence-based guidelines

CHOOSING ANTIEPILECTIC DRUGS

	PARTIAL SEIZURES	GTCS	ABSENCE SEIZURES	MYOCLONIC SEIZURES
BEST EVIDENCE	**Carbamazepine Oxcarbamazepine Phenytoin Topiramate**	**Valproate Topiramate**	**Ethosuximide Valproate**	**Valproate Levetiracetam Clonazepam**
alternatives	Lamotrigine Gabapentine Levetiracetam Valproate Phenobarbitol Pregabilin Zonisamide	Phenytoin Carbamazepine Levetiracetam Lamotrigine	Lamotrigine Levetiracetam Clonazepam Topiramate Felbamate	Zonisamide Topiramate

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Antiepileptic Drug: Monotherapy

- Simplifies treatment
- Reduces adverse effects
- Eighty percent of seizures can be controlled with monotherapy
- Monotherapy with different drug should be tried before 2 drugs together
- Conversion to single drug from multiple drugs
    - Eliminate sedative drugs first (barbiturate/benzodiazepine)
    - Withdraw antiepileptic drugs slowly over several months

Discontinuing AEDs

- **Seizure freedom for ≥2 years**

  implies overall >60% chance of success

- **Favorable 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.

Pregnancy and AEDs:

- **EPTOIN** : Fetal Hydantoin Syndrome
- **VALPROATE** : Neural tube defects
- OTHER CONGENITAL MALFORMATIONS
- Cardiac defects
- Genitourinary defects
- Oral clefts

Consensus

- Monotherapy with lowest dose CBZ
- Folate supplementation in all

- 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]

Lactation and AEDs

- ***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

Drug	Dose/ dosing frequency	Remarks	Therapeutic 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
Carbamazepine	600–1800 mg/d (15–35 mg/kg, child); bid-qid	Start low and increase slowly Oral form only	6- 12	Aplastic anemia Leukopenia Hyponatremia
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
levetiracetam	1000–3000 mg/d; bid		20 - 60	Sedation Fatigue Incoordination Psychosis

Thank you