



Epilepsy

Definitions

- ♦ Seizure: the clinical manifestation of an abnormal, excessive excitation and synchronization of a population of cortical neurons
- ♦ Epilepsy: two or more recurrent seizures unprovoked by systemic or acute neurologic insults

Epidemiology of Seizures and Epilepsy

◆ Seizures

- Incidence: 80/100,000 per year
- Lifetime incidence: 9%
(1/3 febrile convulsions)

◆ Epilepsy

- Incidence: 45/100,000 per year
- Point prevalence: 0.5-1%
- Cumulative lifetime incidence: 3%

Etiology of Seizures and Epilepsy

- ◆ **Infancy and childhood**
 - Prenatal or birth injury
 - Inborn error of metabolism
 - Congenital malformation
- ◆ **Childhood and adolescence**
 - Idiopathic/genetic syndrome
 - CNS infection
 - Trauma

Etiology of Seizures and Epilepsy

◆ Adolescence and young adult

- Head trauma
- Drug intoxication and withdrawal*

◆ Older adult

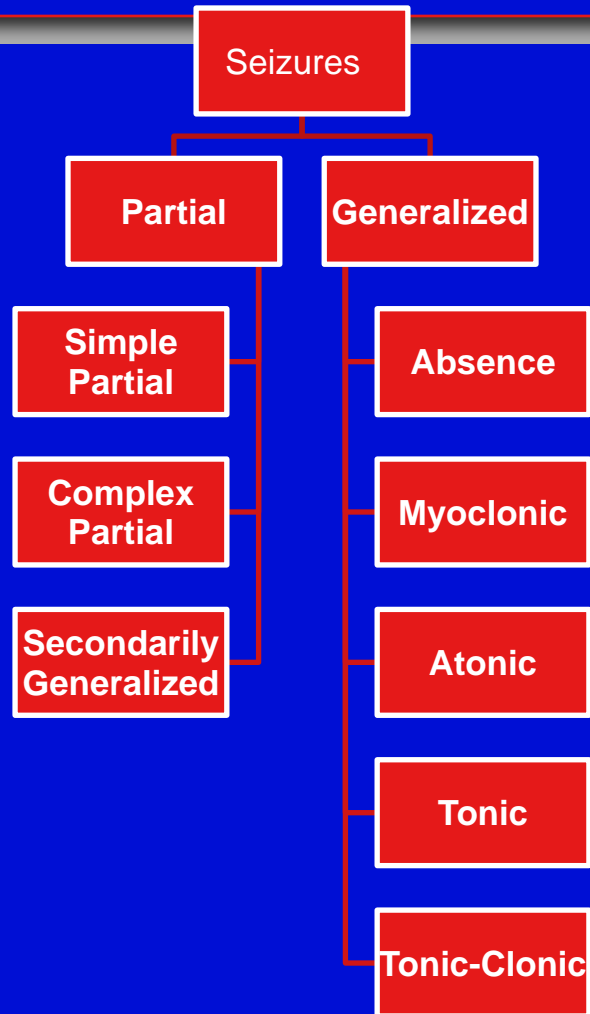
- Stroke
- Brain tumor
- Acute metabolic disturbances*
- Neurodegenerative

*causes of acute symptomatic seizures, not epilepsy

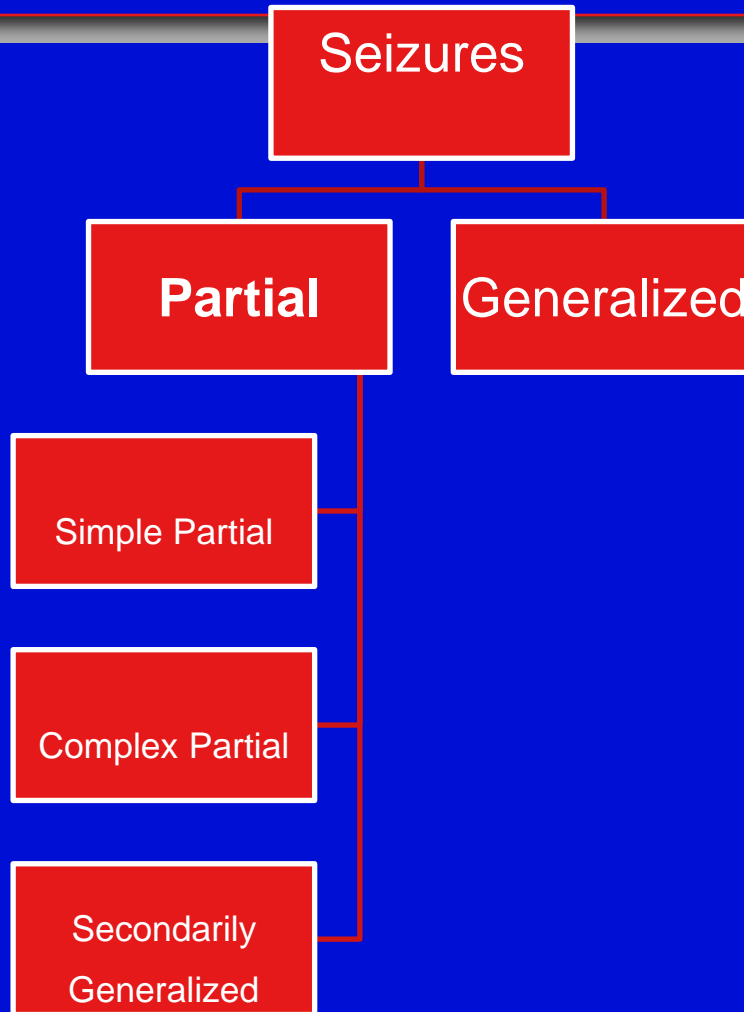
Pathophysiology

- neurons undergo prolonged depolarizations associated with the rapid firing of repeated action potentials.
- Seizures may then spread to involve adjacent areas of the brain or through established anatomic pathways to other distant areas.

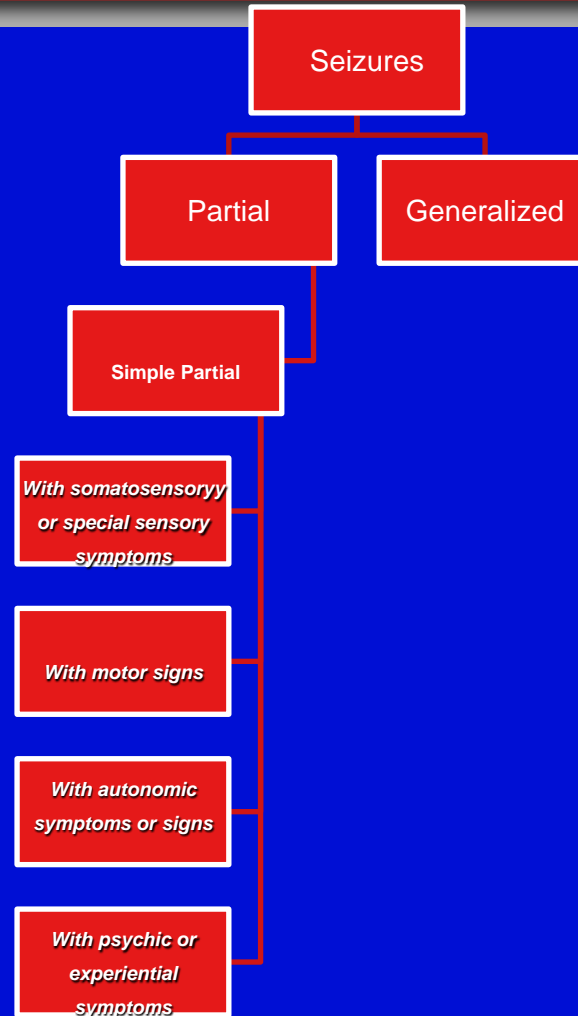
Classification of Seizures



Classification of Seizures

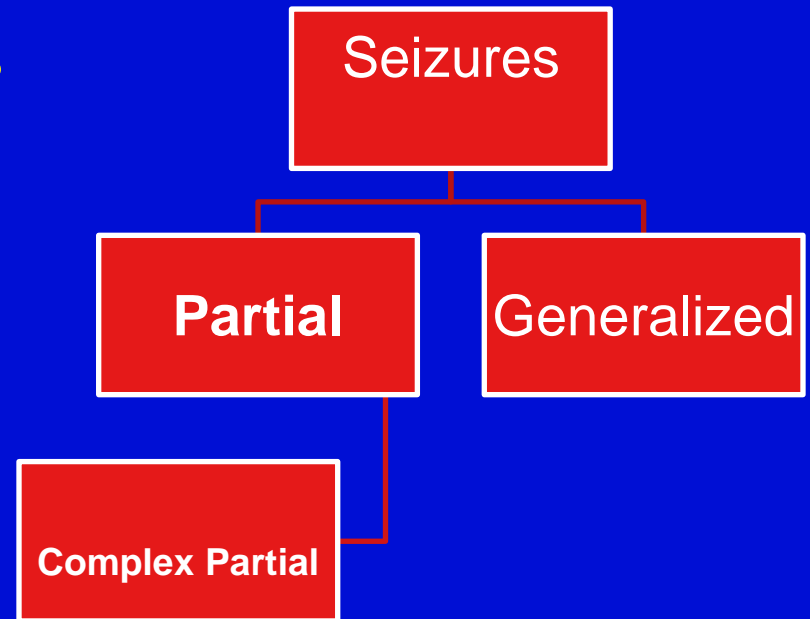


Classification of Seizures



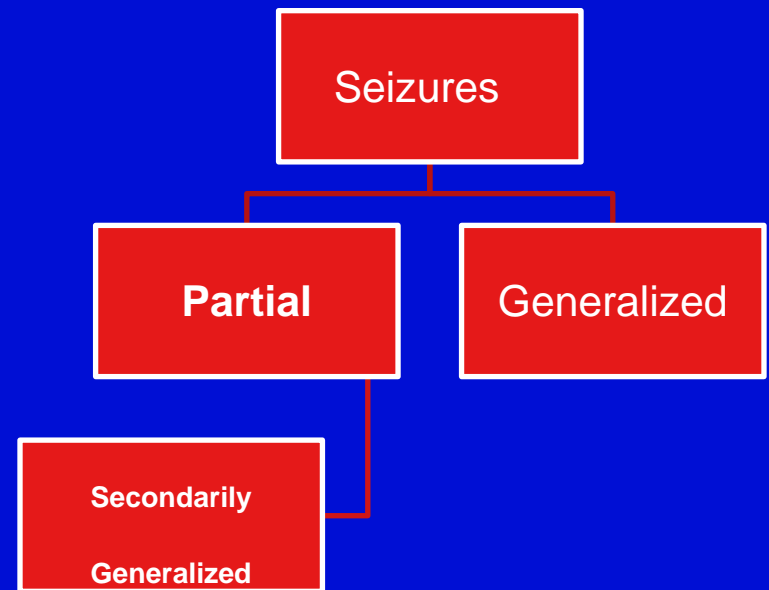
Complex Partial Seizures

- ◆ Impaired consciousness
- ◆ Clinical manifestations vary with site of origin and degree of spread
 - Presence and nature of aura
 - Automatisms
 - Other motor activity
- ◆ Duration typically < 2 minutes

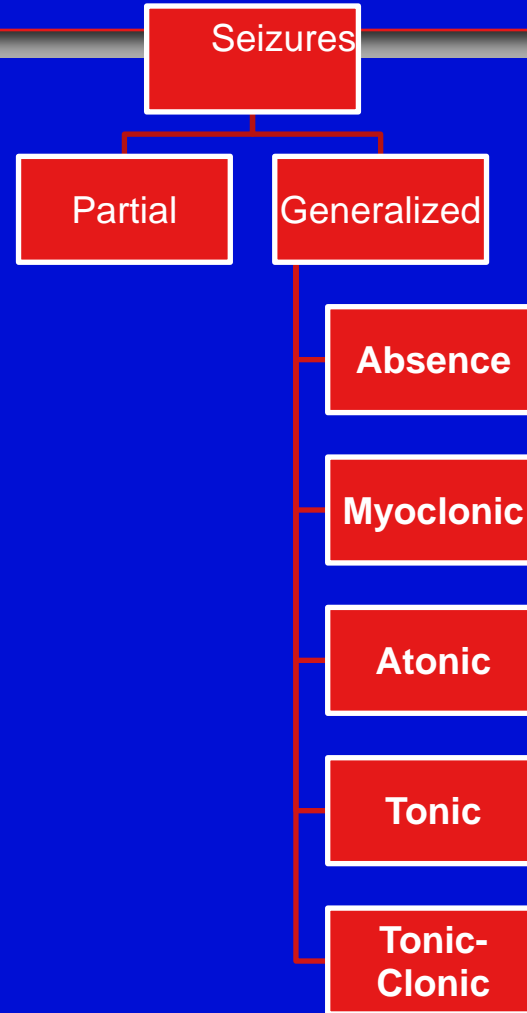


Secondarily Generalized Seizures

- ◆ Begins focally, with or without focal neurological symptoms
- ◆ Variable symmetry, intensity, and duration of tonic (stiffening) and clonic (jerking) phases
- ◆ Typical duration 1-3 minutes
- ◆ Postictal confusion, somnolence, with or without transient focal deficit

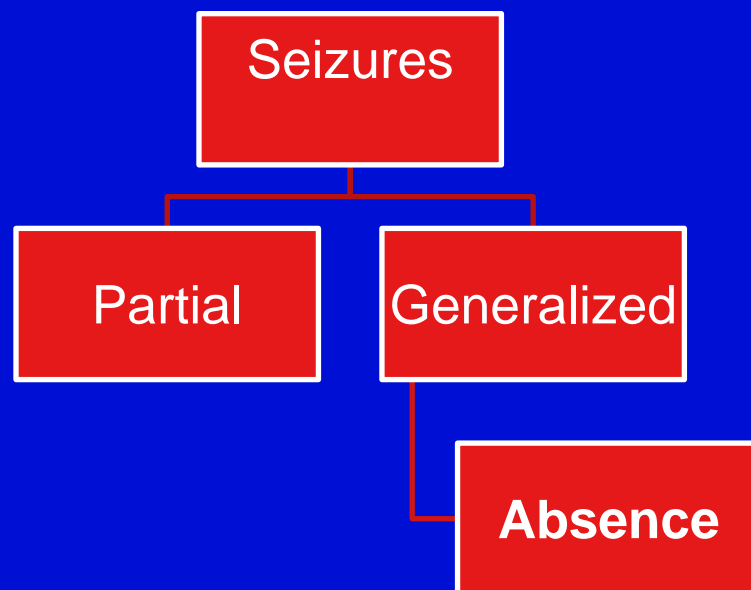


Classification of Seizures



Typical Absence Seizures

- ♦ Brief staring spells (“petit mal”) with impairment of awareness
 - ♦ 3-20 seconds
 - ♦ Sudden onset and sudden resolution
 - ♦ Often provoked by hyperventilation
 - ♦ Onset typically between 4 and 14 years of age
 - ♦ Often resolve by 18 years of age
- ♦ Normal development and intelligence
- ♦ EEG: Generalized 3 Hz spike-wave discharges

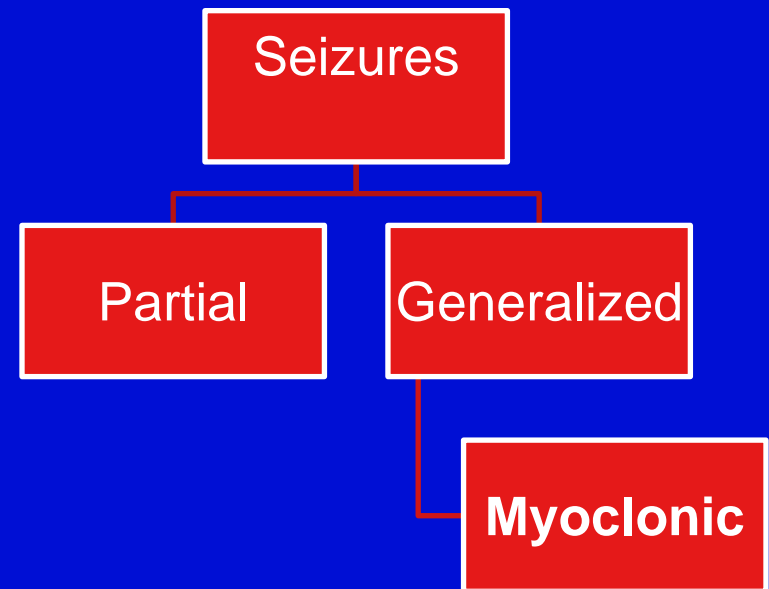


Atypical Absence Seizures

- ◆ Brief staring spells with variably reduced responsiveness
 - ◆ 5-30 seconds
 - ◆ Gradual (seconds) onset and resolution
 - ◆ Generally not provoked by hyperventilation
 - ◆ Onset typically after 6 years of age
- ◆ Often in children with global cognitive impairment
- ◆ EEG: Generalized slow spike-wave complexes (<2.5 Hz)
- ◆ Patients often also have Atonic and Tonic seizures

Myoclonic Seizures

- ◆ Brief, shock-like jerk of a muscle or group of muscles
- ◆ Epileptic myoclonus
 - ◆ Typically bilaterally synchronous
 - ◆ Impairment of consciousness difficult to assess (seizures <1 second)
 - ◆ Clonic seizure – repeated myoclonic seizures (may have impaired awareness)
- ◆ Differentiate from benign, nonepileptic myoclonus (e.g., while falling asleep)
- ◆ EEG: Generalized 4-6 Hz polyspike-wave discharges



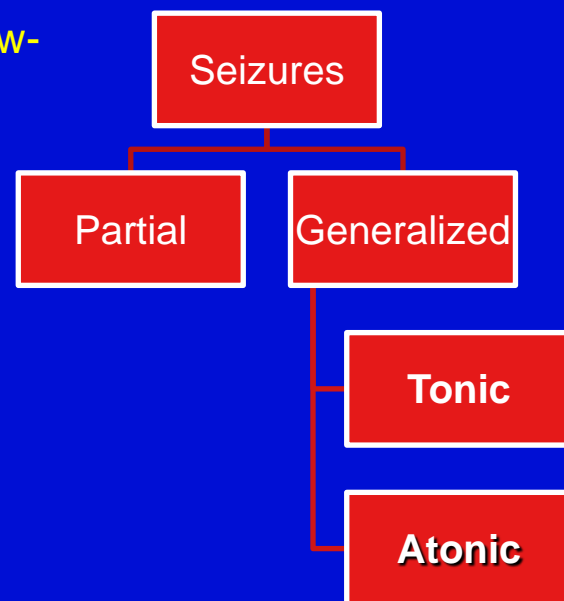
Tonic and Atonic Seizures

Tonic seizures

- Symmetric, tonic muscle contraction of extremities with tonic flexion of waist and neck
- Duration - 2-20 seconds.
- EEG – Sudden attenuation with generalized, low-voltage fast activity (most common) or generalized polyspike-wave.

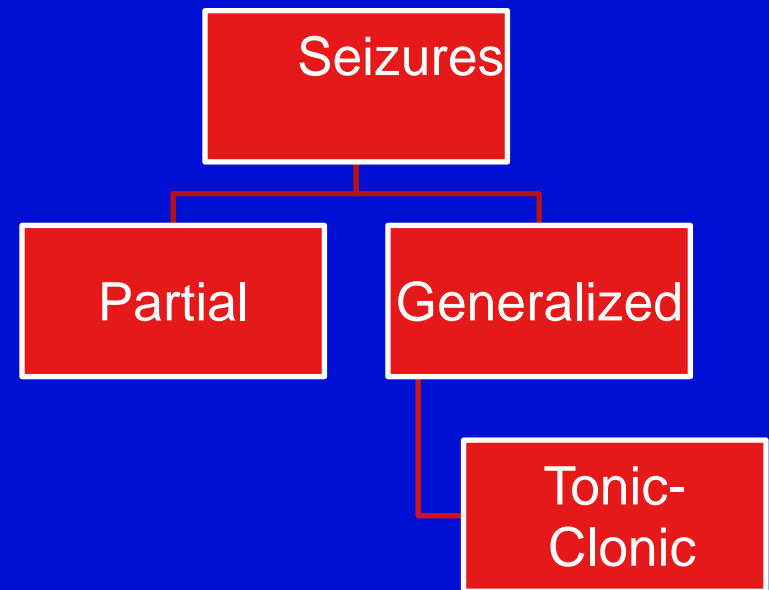
Atonic seizures

- Sudden loss of postural tone
 - When severe often results in falls
 - When milder produces head nods or jaw drops.
- Consciousness usually impaired
- Duration - usually seconds, rarely more than 1 minute
- EEG – sudden diffuse attenuation or generalized polyspike-wave



Generalized Tonic-Clonic Seizures

- ♦ Associated with loss of consciousness and post-ictal confusion/lethargy
- ♦ Duration 30-120 seconds
- ♦ Tonic phase
 - ♦ Stiffening and fall
 - ♦ Often associated with ictal cry
- ♦ Clonic Phase
 - ♦ Rhythmic extremity jerking
- ♦ EEG – generalized polyspikes



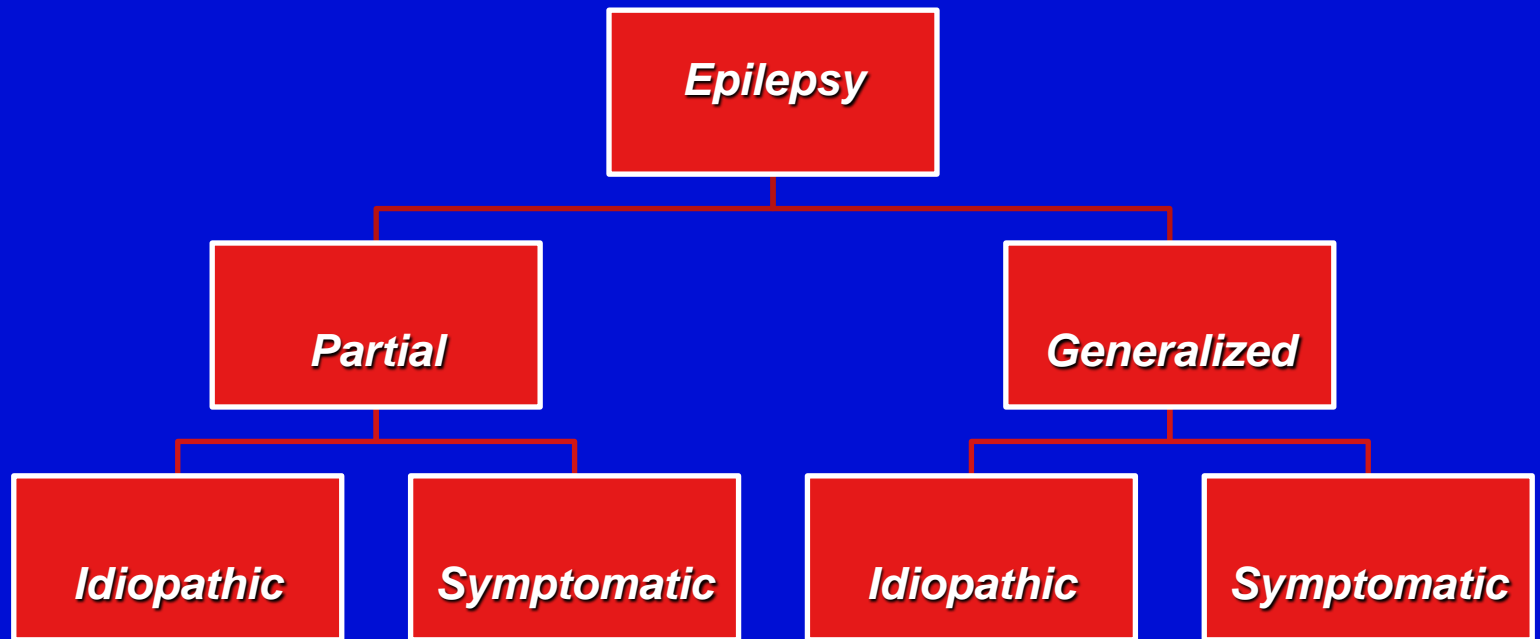
Epilepsy Syndromes

Epilepsy Syndrome

Grouping of patients that share similar:

- Seizure type(s)
- Age of onset
- Natural history/Prognosis
- EEG patterns
- Genetics
- Response to treatment

Epilepsy Syndromes



THERAPEUTIC CONSIDERATIONS

- **Goal - no seizures, but ↓ drug side effects (60-80% patients obtain good seizure control)**
- **Diagnosis - drug selection (for seizure type)**
- **Clinical evaluation - drug trial period**
- **Plasma drug levels - narrow therapeutic range – monitor**
- **Compliance difficult - chronic disorder**
- **Withdrawing medication - weeks → months**

Seizure Precipitants

- ◆ Metabolic and Electrolyte Imbalance
- ◆ Stimulant/other proconvulsant intoxication
- ◆ Sedative or ethanol withdrawal
- ◆ Sleep deprivation
- ◆ Antiepileptic medication reduction or inadequate AED treatment
- ◆ Hormonal variations
- ◆ Stress
- ◆ Fever or systemic infection
- ◆ Concussion and/or closed head injury

Seizure Precipitants (cont.)

Metabolic and Electrolyte Imbalance

- ◆ Low blood glucose
(or high glucose, esp. w/ hyperosmolar state)
- ◆ Low sodium
- ◆ Low calcium
- ◆ Low magnesium

Seizure Precipitants (cont.)

Stimulants/Other Pro-convulsant Intoxication

- ◆ IV drug use
- ◆ Cocaine
- ◆ Ephedrine
- ◆ Other herbal remedies
- ◆ Medication reduction

Choosing Antiepileptic Drugs

- ◆ Seizure type
- ◆ Epilepsy syndrome
- ◆ Pharmacokinetic profile
- ◆ Interactions/other medical conditions
- ◆ Efficacy
- ◆ Expected adverse effects
- ◆ Cost

Choosing Antiepileptic Drugs

- ♦ Limited placebo-controlled trials available, particularly of newer AEDs
- ♦ In practice, several drugs are commonly used for indications other than those for which they are officially approved/recommended
- ♦ Choice of AED for partial epilepsy depends largely on drug side-effect profile and patient's preference/concerns
- ♦ Choice of AED for primary generalized epilepsy depends on predominant seizure type(s) as well as drug side-effect profile and patient's preference/concerns

Choosing Antiepileptic Drugs

Broad-Spectrum Agents

Valproate
Felbamate
Lamotrigine
Topiramate
Zonisamide
Levetiracetam
Rufinamide*

Narrow-Spectrum Agents

Partial onset seizures

Phenytoin
Carbamazepine
Oxcarbazepine
Gabapentin
Pregabalin
Tiagabine
Lacosamide*

Absence

Ethosuximide

* New AEDs (approved 2008) categorization may change

Antiepileptic Drug

- ◆ 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
- ◆ Currently no “anti-epileptogenic” drugs available

Current Pharmacotherapy

- n **Just under 60% of all people with epilepsy can become seizure free with drug therapy**
- n **In another 20% the seizures can be drastically reduced**
- n **~ 20% epileptic patients, seizures are refractory to currently available AEDs**

Choosing Antiepileptic Drugs

- ◆ **Seizure type**
- ◆ **Epilepsy syndrome**
- ◆ **Pharmacokinetic profile**
- ◆ **Interactions/other medical conditions**
- ◆ **Efficacy**
- ◆ **Expected adverse effects**
- ◆ **Cost**

General Facts About AEDs

- n **Good oral absorption and bioavailability**
- n **Most metabolized in liver but some excreted unchanged in kidneys**
- n **Classic AEDs generally have more severe CNS sedation than newer drugs (except ethosuximide)**
- n **Because of overlapping mechanisms of action, best drug can be chosen based on minimizing side effects in addition to efficacy**
- n **Add-on therapy is used when a single drug does not completely control seizures**

Classification of AEDs

Classical

- n **Phenytoin**
- n **Phenobarbital**
- n **Primidone**
- n **Carbamazepine**
- n **Ethosuximide**
- n **Valproate (valproic acid)**
- n **Trimethadione (not currently in use)**

Newer

- n **Lamotrigine**
- n **Felbamate**
- n **Topiramate**
- n **Gabapentin**
- n **Tiagabine**
- n **Vigabatrin**
- n **Oxycarbazepine**
- n **Levetiracetam**
- n **Fosphenytoin**

In general, the newer AEDs have less CNS sedating effects than the classical AEDs

History of Antiepileptic Drug Therapy in the U.S.

- ◆ **1857 - Bromides**
- ◆ **1912 - Phenobarbital**
- ◆ **1937 - Phenytoin**
- ◆ **1954 - Primidone**
- ◆ **1960 - Ethosuximide**

History of Antiepileptic Drug Therapy in the U.S.

- ◆ **1974 - Carbamazepine**
- ◆ **1975 – Clonazepam (benzodiazapine)**
- ◆ **1978 - Valproate**
- ◆ **1993 - Felbamate, Gabapentin**
- ◆ **1995 - Lamotrigine**
- ◆ **1997 - Topiramate, Tiagabine**
- ◆ **1999 - Levetiracetam**
- ◆ **2000 - Oxcarbazepine, Zonisamide**
- ◆ **Vigabatrin—not approved in US**

Cellular Mechanisms of Seizure Generation

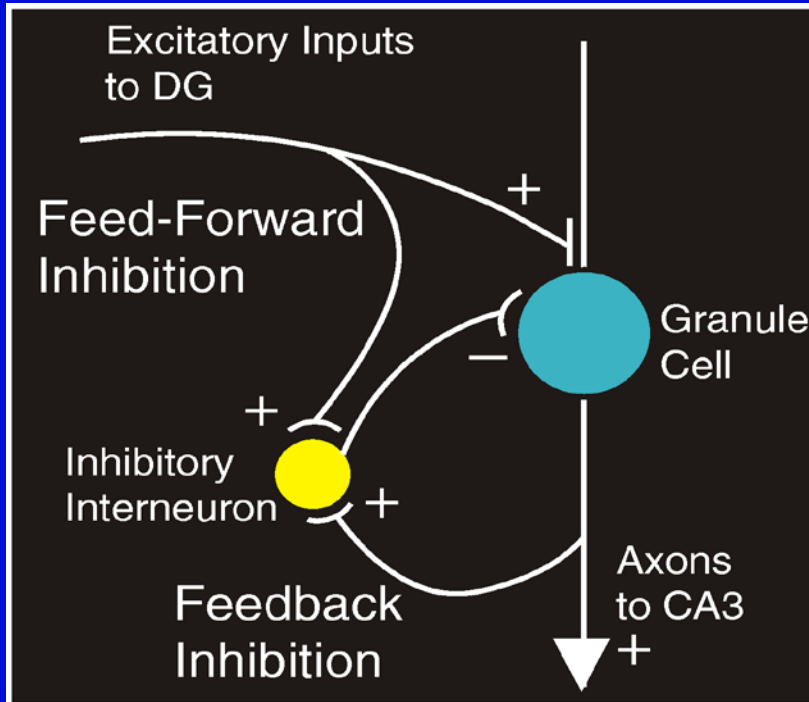
◆ **Excitation (too much)**

- Ionic—inward Na^+ , Ca^{++} currents
- Neurotransmitter—glutamate, aspartate

◆ **Inhibition (too little)**

- Ionic—inward Cl^- , outward K^+ currents

Basic Mechanisms Underlying Seizures and Epilepsy



- ◆ **Feedback and feed-forward inhibition, illustrated via cartoon and schematic of simplified hippocampal circuit**

Babb TL, Brown WJ. Pathological Findings in Epilepsy. In: Engel J. Jr. Ed. Surgical Treatment of the Epilepsies. New York: Raven Press 1987: 511-540.

Neuronal (Intrinsic) Factors Modifying Neuronal Excitability

- ♦ **Ion channel type, number, and distribution**
- ♦ **Biochemical modification of receptors**
- ♦ **Activation of second-messenger systems**
- ♦ **Modulation of gene expression (e.g., for receptor proteins)**

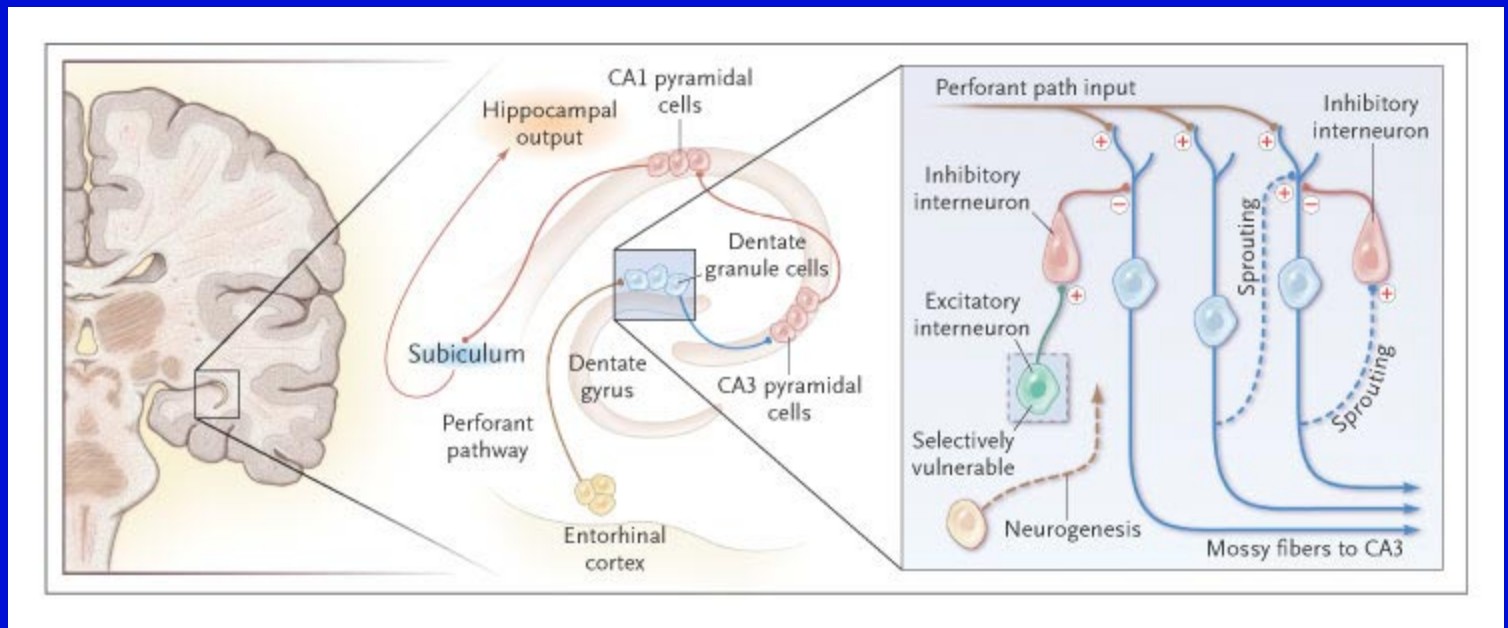
Extra-Neuronal (Extrinsic) Factors Modifying Neuronal Excitability

- ◆ **Changes in extracellular ion concentration**
- ◆ **Remodeling of synapse location or configuration by afferent input**
- ◆ **Modulation of transmitter metabolism or uptake by glial cells**

Mechanisms of Generating Hyperexcitable Networks

- ◆ **Excitatory axonal “sprouting”**
- ◆ **Loss of inhibitory neurons**
- ◆ **Loss of excitatory neurons “driving” inhibitory neurons**

Hippocampal Circuitry and Seizures



Targets for AEDs

- n Increase inhibitory neurotransmitter system—GABA**
- n Decrease excitatory neurotransmitter system—glutamate**
- n Block voltage-gated inward positive currents—Na⁺ or Ca⁺⁺**
- n Increase outward positive current—K⁺**
- n Many AEDs pleiotropic—act via multiple mechanisms**

Epilepsy—Glutamate

- ◆ **The 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**
 - Quisqualate
 - Regulation of second messengers (cAMP and Inositol)
 - Modulation of synaptic activity
- ◆ **Modulation of glutamate receptors**

Epilepsy—Glutamate

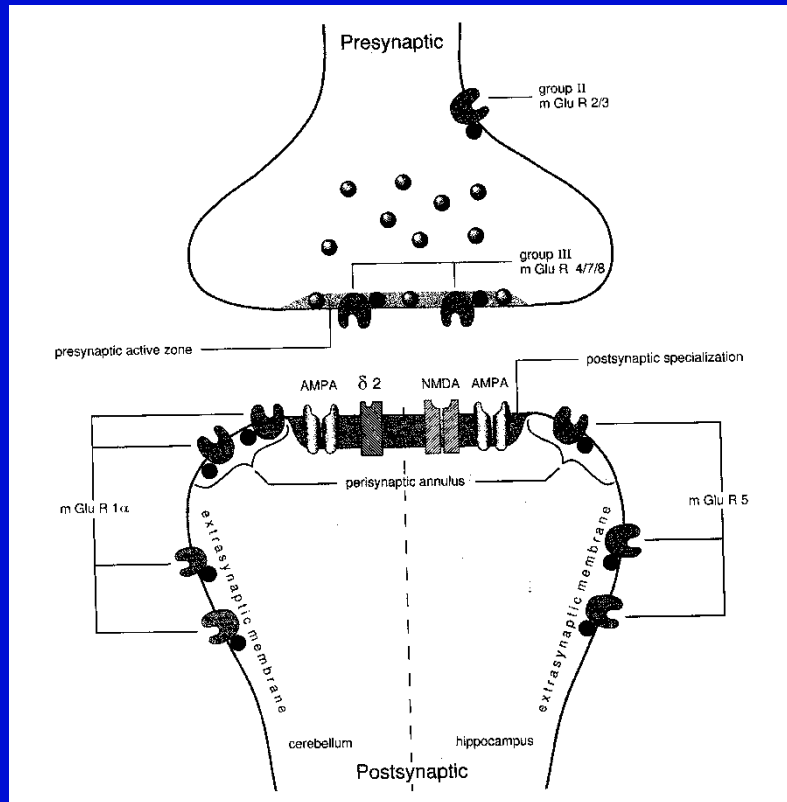


Diagram of the various glutamate receptor subtypes and locations

From Takumi et al, 1998

Glutamate Receptors as AED Targets

n NMDA receptor sites as targets

- Ketamine, phencyclidine, dizocilpine block channel and have anticonvulsant properties but also dissociative and/or hallucinogenic properties; open channel blockers.
- Felbamate antagonizes strychnine-insensitive glycine site on NMDA complex

n AMPA receptor sites as targets

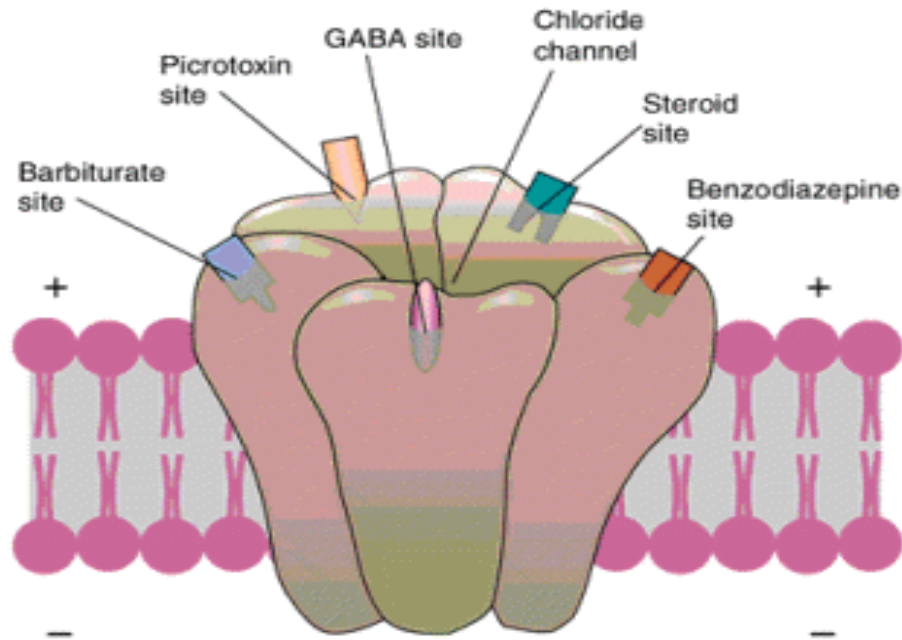
- Topiramate antagonizes AMPA site

Epilepsy—GABA

- ◆ Major inhibitory neurotransmitter in the CNS
- ◆ Two types of receptors
 - GABA_A—post-synaptic, specific recognition sites, linked to Cl⁻ channel
 - GABA_B—presynaptic autoreceptors, mediated by K⁺ currents

GABA_A Receptor

► Schematic Illustration of a GABA_A Receptor, with Its Binding Sites



AEDs That Act Primarily on GABA

Benzodiazepines (diazepam, clonazepam)

- Increase frequency of GABA-mediated chloride channel openings

Barbiturates (phenobarbital, primidone)

- Prolong GABA-mediated chloride channel openings
- Some blockade of voltage-dependent sodium channels

AEDs That Act Primarily on GABA

Gabapentin

- May modulate amino acid transport into brain
- May interfere with GABA re-uptake

Tiagabine

- Interferes with GABA re-uptake

Vigabatrin (not currently available in US)

- elevates GABA levels by irreversibly inhibiting its main catabolic enzyme, GABA-transaminase

Na⁺ Channels as AED Targets

- n Neurons fire at high frequencies during seizures**
- n Action potential generation is dependent on Na⁺ channels**
- n Use-dependent or time-dependent Na⁺ channel blockers reduce high frequency firing without affecting physiological firing**

AEDs That Act Primarily on Na⁺ Channels

Phenytoin, Carbamazepine

- Block voltage-dependent sodium channels at high firing frequencies—use dependent

Oxcarbazepine

- Blocks voltage-dependent sodium channels at high firing frequencies
- Also effects K⁺ channels

Zonisamide

- Blocks voltage-dependent sodium channels and T-type calcium channels

Ca²⁺ Channels as Targets

- n **Absence seizures are caused by oscillations between thalamus and cortex that are generated in thalamus by T-type (transient) Ca²⁺ currents**
- n **Ethosuximide is a specific blocker of T-type currents and is highly effective in treating absence seizures**

What about K⁺ channels?

n **K⁺ channels have important inhibitory control over neuronal firing in CNS—repolarize membrane to end action potentials**

n **K⁺ channel agonists would decrease hyperexcitability in brain**

n **So far, the only AED with known actions on K⁺ channels is valproate**

n **Retiagabine is a novel AED in clinical trials that acts on a specific type of voltage-dependent K⁺ channel**

Pleiotropic AEDs

Felbamate

- Blocks voltage-dependent sodium channels at high firing frequencies
- May modulate NMDA receptor via strychnine-insensitive glycine receptor

Lamotrigine

- Blocks voltage-dependent sodium channels at high firing frequencies
- May interfere with pathologic glutamate release
- Inhibit Ca⁺⁺ channels?

Pleiotropic AEDs

Topiramate

- Blocks voltage-dependent sodium channels at high firing frequencies
- Increases frequency at which GABA opens Cl⁻ channels (different site than benzodiazepines)
- Antagonizes glutamate action at AMPA/kainate receptor subtype?

Valproate

- May enhance GABA transmission in specific circuits
- Blocks voltage-dependent sodium channels
- May also augment K⁺ channels
- T-type Ca²⁺ currents?

The Cytochrome P-450 Isozyme System

- ◆ The enzymes most involved with drug metabolism
- ◆ Enzymes have broad substrate specificity, and individual drugs may be substrates for several enzymes
- ◆ The principle enzymes involved with AED metabolism include CYP2C9, CYP2C19, CYP3A

Enzyme Inducers/Inhibitors: General Considerations

- ◆ **Inducers: Increase clearance and decrease steady-state concentrations of other drugs**
- ◆ **Inhibitors: Decrease clearance and increase steady-state concentrations of other drugs**

The Cytochrome P-450 Enzyme System

Inducers

phenobarbital

primidone

phenytoin
(CYP2C19)

carbamazepine

felbamate (CYP3A)

topiramate (CYP3A)

Inhibitors

valproate

topiramate (CYP2C19)

oxcarbazepine

felbamate (CYP2C19)

*(increase phenytoin,
phenobarbital)*

AEDs and Drug Interactions

- ◆ Although many AEDs can cause pharmacokinetic interactions, several newer agents appear to be less problematic.
- ◆ AEDs that do not appear to be either inducers or inhibitors of the CYP system include:
 - Gabapentin
 - Lamotrigine
 - Tiagabine
 - Levetiracetam
 - Zonisamide



Classic AEDs

Phenytoin

First line drug for partial seizures

Inhibits Na⁺ channels—use dependent

**Prodrug fosphenytoin for IM or IV administration.
Highly bound to plasma proteins.**

Half-life: 22-36 hours

Adverse effects: CNS sedation (drowsiness, ataxia, confusion, insomnia, nystagmus, etc.), gum hyperplasia, hirsutism

Interactions: carbamazepine, phenobarbital will decrease plasma levels; alcohol, diazepam, methylphenidate will increase. Valproate can displace from plasma proteins. Stimulates cytochrome P-450, so can increase metabolism of some drugs.

Carbamazapine

- n **First line drug for partial seizures**
- n **Inhibits Na⁺ channels—use dependent**
- n **Half-life: 6-12 hours**
- n **Adverse effects: CNS sedation. Agranulocytosis and aplastic anemia in elderly patients, rare but very serious adverse. A mild, transient leukopenia (decrease in white cell count) occurs in about 10% of patients, but usually disappears in first 4 months of treatment. Can exacerbate some generalized seizures.**
- n **Drug interactions: Stimulates the metabolism of other drugs by inducing microsomal enzymes, stimulates its own metabolism. This may require an increase in dose of this and other drugs patient is taking.**

Phenobarbital

n

Partial seizures, effective in neonates

n

Second-line drug in adults due to more severe CNS sedation

n

Allosteric modulator of GABA_A receptor (increase open time)

n

Absorption: rapid

n

Half-life: 53-118 hours (long)

n

Adverse effects: CNS sedation but may produce excitement in some patients. Skin rashes if allergic. Tolerance and physical dependence possible.

n

Interactions: severe CNS depression when combined with alcohol or benzodiazepines. Stimulates

systemic enzymes

Primidone

n

Partial seizures

n

Mechanims—same as phenobarbital

n

Absorption: Individual variability in rates. Not highly bound to plasma proteins.

n

Metabolism: Converted to phenobarbital and phenylethyl malonamide, 40% excreted unchanged.

n

Half-life: variable, 5-15 hours. PB ~100, PEMA 16 hours

n

Adverse effects: CNS sedative

n

Drug interactions: enhances CNS depressants, drug metabolism, phenytoin increases conversion to PB

Benzodiazapines (Diazepam and clonazepam)

Status epilepticus (IV)

Allosteric modulator of GABA_A receptors—increases frequency

Absorption: Rapid onset. Diazepam—rectal formulation for treatment of SE

Half-life: 20-40 hours (long)

Adverse effects: CNS sedative, tolerance, dependence. Paradoxical hyperexcitability in children

Drug interactions: can enhance the action of other CNS depressants

Valproate (Valproic Acid)

n Partial seizures, first-line drug for generalized seizures.
n Enhances GABA transmission, blocks Na⁺ channels, activates K⁺ channels

n Absorption: 90% bound to plasma proteins

n Half-life: 6-16 hours

n Adverse effects: CNS depressant (esp. w/ phenobarbital), anorexia, nausea, vomiting, hair loss, weight gain, elevation of liver enzymes. Hepatotoxicity is rare but severe, greatest risk <2 Yrs. May cause birth defects.

n Drug interactions: May potentiate CNS depressants, displaces phenytoin from plasma proteins, inhibits metabolism of phenobarbital, phenytoin, carbamazepine (P450 inhibitor).

Ethosuximide

- n **Absence seizures**
- n **Blocks T-type Ca^{++} currents in thalamus**
- n **Half-life: long—40 hours**
- n **Adverse effects: gastric distress—pain, nausea, vomiting. Less CNS effects than other AEDs, transient fatigue, dizziness, headache**
- n **Drug interactions: administration with valproate results in inhibition of its metabolism**



Newer Drugs

Oxcarbazepine

n Approved for add-on therapy, monotherapy in partial seizures that are refractory to other AEDs

n Activity-dependent blockade of Na⁺ channels, may also augment K⁺ channels

n Half-life: 1-2 hours, but converted to 10-hydroxycarbamazepine 8-12 hours

n Adverse effects: similar to carbamazepine (CNS sedative) but may be less toxic.

n Drug interactions: less induction of liver enzymes, but can stimulate CYP3A and inhibit CYP2C19

Gabapentin

- n **Add-on therapy for partial seizures, evidence that it is also effective as monotherapy in newly diagnosed epilepsies (partial)**
- n **May interfere with GABA uptake**
- n **Absorption: Non-linear. Saturable (amino acid transport system), no protein binding.**
- n **Metabolism: none, eliminated by renal excretion**
- n **Half-life: 5-9 hours, administered 2-3 times daily**
- n **Adverse effects: less CNS sedative effects than classic AEDs**

Lamotrigine

n **Add-on therapy, monotherapy for refractory partial seizures. Also effective in Lennox Gastaut Syndrome and newly diagnosed epilepsy. Effective against generalized seizures.**

n **Use-dependent inhibition of Na⁺ channels, glutamate release, may inhibit Ca⁺⁺ channels**

n **Half-life—24 hours**

n **Adverse effects: less CNS sedative effects than classic AEDs, dermatitis potentially life-threatening in 1-2% of pediatric patients.**

n **Drug interactions: levels increased by valproate, decreased by carbamazepine. PB. phenytoin**

Felbamate

- n **Third-line drug for refractory partial seizures**
- n **Frequency-dependent inhibition of Na⁺ channels, modulation of NMDA receptor**
- n **Adverse effects: aplastic anemia and severe hepatitis restricts its use (black box)**
- n **Drug interactions: increases plasma phenytoin and valproate, decreases carbamazepine. Stimulates CYP3A and inhibits CYP2C19**

Levetiracetam

n **Add-on therapy for partial seizures**

n **Binds to synaptic vesicle protein SV2A, may regulate neurotransmitter release**

n **Half-life: 6-8 hours (short)**

n **Adverse effects: CNS depression**

n **Drug interactions: minimal**

Tiagabine

- n **Add-on therapy for partial seizures**
- n **Interferes with GABA reuptake**
- n **Half-life: 5-8 hours (short)**
- n **Adverse effects: CNS sedative**
- n **Drug interactions: minimal**

Zonisamide

- n **Add-on therapy for partial and generalized seizures**
- n **Blocks Na⁺ channels and T-type Ca⁺⁺ channels**
- n **Half-life: 1-3 days (long)**
- n **Adverse effects: CNS sedative**
- n **Drug interactions: minimal**

Topimera

n Add-on for refractory partial or generalized seizures. Effective as monotherapy for partial or generalized seizures, Lennox-Gastaut syndrome.

n Use-dependent blockade of Na⁺ channels, increases frequency of GABA_A channel openings, may interfere with glutamate binding to AMPA/KA receptor

n Half-life: 20-30 hours (long)

n Adverse effects: CNS sedative

n Drug interactions: Stimulates CYP3A and inhibits CYP2C19, can lessen effectiveness of birth control pills

Vigabatrin

- n Add-on therapy for partial seizures, monotherapy for infantile spasms. (Not available in US).
- n Blocks GABA metabolism through actions on GABA-transaminase
- n Half-life: 6-8 hours, but pharmacodynamic activity is prolonged and not well-coordinated with plasma half-life.
- n Adverse effects: CNS sedative, ophthalmologic abnormalities
- n Drug interactions: minimal

Treatment of Epilepsy

n First consideration is efficacy in stopping seizures

n Because many AEDs have overlapping, pleiotropic actions, the most appropriate drug can often be chosen to reduce side effects. Newer drugs tend to have less CNS depressant effects.

n Potential of long-term side effects, pharmacokinetics, and cost are other considerations

Partial Onset Seizures

n With secondary generalization

- First-line drugs are carbamazepine and phenytoin (equally effective)
- Valproate, phenobarbital, and primidone are also usually effective

n Without generalization

- Phenytoin and carbamazepine may be slightly more effective

n Phenytoin and carbamazepine can be used together (but both are enzyme inducers)

Partial Onset Seizures—New Drugs

- n **Adjunctive (add-on) therapy where monotherapy does not completely stop seizures—newer drugs felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, and zonisamide**
- n **Lamotrigine, oxcarbazepine, felbamate approved for monotherapy where phenytoin and carbamazepine have failed.**
- n **Topirimate can effective against**

Generalized Onset Seizures

- n **Tonic-clonic, myoclonic, and absence seizures—first line drug is usually valproate**
- n **Phenytoin and carbamazepine are effective on tonic-clonic seizures but not other types of generalized seizures**
- n **Valproate and ethosuximide are equally effective in children with absence seizures, but only valproate protects against the tonic-clonic seizures that sometimes develop. Rare**

should not be used in children under 2

Generalized Onset Seizures

n Clonazepam, phenobarbital, or primidone can be useful against generalized seizures, but may have greater sedative effects than other AEDs

n Tolerance develops to clonazepam, so that it may lose its effectiveness after ~6 months

n Carbamazepine may exacerbate absence and myoclonic, underscoring the importance of appropriate seizure classification

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Status Epilepticus

- n **More than 30 minutes of continuous seizure activity**
- n **Two or more sequential seizures spanning this period without full recovery between seizures**
- n **Medical emergency**

Status Epilepticus

n Treatment

- **Diazepam, lorazepam IV (fast, short acting)**
- **Followed by phenytoin, fosphenytoin, or phenobarbital (longer acting) when control is established**

Alternative Uses for AEDs

- n **Gabapentin, carbamazepine—
neuropathic pain**
- n **Lamotrogine, carbamazepine—bipolar
disorder**
- n **Leviteracitam, valproate, topirimate,
gabapentin, migroline**

Drugs Used According to Type of Seizure and Epileptic Syndrome

Type of Seizure and Epileptic Syndrome	First Line Drug (Generally, the first drug tried)	Second Line or Add-on Drug (Those tried when first-line drugs fail) Note: some of these agents are used as second-line agents but have not yet been FDA approved.
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Primary Generalized Seizures

Absence (petit mal) seizures	Ethosuximide in children and adults, valproic acid (divalproex sodium may be better tolerated). Note: Carbamazepine and phenytoin are contradicted. Others under investigation include levetiracetam.	Valproic acid (or divalproex sodium), Others under investigation include clonazepam and lamotrigine.
Myoclonic seizures	Valproic acid (or divalproex sodium) Note: Carbamazepine and phenytoin can actually aggravate these seizures. Others under investigation include levetiracetam.	Acetazolamide, clonazepam, Others under investigation include zonisamide, lamotrigine, topiramate, primidone (for juvenile myoclonic epilepsies).
Tonic-clonic (grand mal) seizures	Valproic acid (or divalproex sodium), carbamazepine, phenytoin.	Phenobarbital, primidone Topiramate (including in children two and over) Other under investigation include lamotrigine
Infantile spasms (West's syndrome)	Corticotropin, vigabatrin. Zonisamide and tiagabine under investigation.	Clonazepam, valproic acid (or divalproex sodium),
Lennox-Gastaut	Valproic acid (or divalproex sodium).	Carbamazepine. clonazepam (absence

Drugs Used According to Type of Seizure and Epileptic Syndrome		
Type of Seizure and Epileptic Syndrome	First Line Drug (Generally, the first drug tried)	Second Line or Add-on Drug (Those tried when first-line drugs fail) Note: some of these agents are used as second-line agents but have not yet been FDA approved.

Partial Seizures

Partial seizures, secondarily generalized tonic-clonic seizures, and partial epileptic syndromes	Carbamazepine in children and adults, phenytoin. A 2002 analysis of evidence comparing carbamazepine and phenytoin found no significant differences between the two. Newer drugs, including gabapentin and lamotrigine, are showing promise as first line agents but not yet approved for this.	<p>Add-on drugs approved for adults include gabapentin, lamotrigine, zonisamide, tiagabine, topiramate levetiracetam, and oxcarbazepine Felbamate is approved only as monotherapy in adults. They appear to be similar in effectiveness, and to date none has shown clear superiority over others. Some, such as lamotrigine, may have fewer adverse effects than others.</p> <p>Topiramate is approved for children over two and oxcarbazepine for those over four. Gabapentin and tiagabine approved for children over 12 and are being studied for younger children. (A French study found no additional benefits for gabapentin in this younger group.) Other add-ons are also being studied for children.</p> <p>Older add-on agents sometimes used include valproate, phenobarbital, primidone.</p>
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Original data from a table in Patients with Refractory Seizures, *The New England Journal of Medicine*, Vol. 340, No. 20, May 20, 1999. By permission of the author Orrin Devinsky, MD. Updated data from American Epilepsy Society and various studies.

Drugs of Choice for Specific Seizure Types

Seizure Type	First-Line Drugs	Second-Line Drugs	Others Alternatives
Simple or Complex Partial	Carbamazepine	Gabapentin	Phenobarbital
	Phenytoin	Valproic Acid	Primidone
		Lamotrigine	Tiagabine
			Topiramate
			Clonazepam
			Felbamate
Primary or Secondarily Generalized Tonic-Clonic	Carbamazepine	Gabapentin ⁺	Topiramate ⁺
	Valproic Acid	Lamotrigine ⁺	Tiagabine ⁺
	Phenytoin	Phenobarbital	Clonazepam
		Primidone	Felbamate ⁺
Absence	Ethosuximide	Lamotrigine*	
	Valproic Acid	Clonazepam	
Atypical Absence, Atonic, Myoclonic	Valproic Acid	Lamotrigine*	Felbamate*
		Clonazepam	Ethosuximide
			Ketogenic Diet

Characteristics of Antiepileptic Drug

Drug	Mechanism of Action	Dose	Pharmacokinetic Parameters	Usual Serum Concentration Range	Dose-Related Adverse Effects
Carbamazepine	Modulate sodium channels	<p><i>Loading dose:</i> Not recommended due to excessive dose-related toxicity</p> <p><i>Maintenance dose:</i> Titrate dosage to target over 3–4 weeks</p> <p>Adults: 10–20 mg/kg per day as a divided dose</p> <p>Children: 20–30 mg/kg per day as a divided dose</p>	<p><i>Half-life:</i> 10–25 hours with chronic dosing</p> <p><i>Apparent volume of distribution:</i> 0.8–1.9 L/kg</p> <p><i>Protein binding:</i> 67–81%</p> <p><i>Primary elimination route:</i> Hepatic</p>	4–12 mcg/mL (17–51 μmol/L)	Diplopia, drowsiness, nausea, sedation
Clonazepam	Enhance GABA activity	<p><i>Loading dose:</i> Not recommended due to increased adverse effects</p> <p><i>Maintenance dose:</i> Initiate at 0.5 mg one to three times daily, titrate dose to effectiveness usually 3–5 mg daily in 2 to 3 divided doses</p>	<p><i>Half-life:</i> 30–40 hours</p> <p><i>Apparent volume of distribution:</i> 3.2 L/kg</p> <p><i>Protein binding:</i> 47–80%</p> <p><i>Primary elimination route:</i> Hepatic</p>	Not established	Ataxia, memory impairment, sedation, slowed thinking
Ethosuximide	Modulate calcium channels	<p><i>Loading dose:</i> Not recommended due to increased adverse effects</p> <p><i>Maintenance dose:</i> Initiate at 250 mg twice daily and titrate to 500–1000 mg twice daily</p>	<p><i>Half-life:</i> 60 hours</p> <p><i>Apparent volume of distribution:</i> 0.6–0.7 L/kg</p> <p><i>Protein binding:</i> None</p> <p><i>Primary elimination route:</i> Hepatic</p>	40–100 mcg/mL (283–708 μmol/L)	Ataxia, sedation
Felbamate	Inhibit glutamate activity	<p><i>Loading dose:</i> Not recommended due to increased adverse effects</p> <p><i>Maintenance dose:</i> 1200–3600 mg/day in 3–4 divided doses</p>	<p><i>Half-life:</i> Monotherapy: 20 hours Concurrent enzyme inducers: 11–16 hours</p> <p><i>Apparent volume of distribution:</i></p>	Not established	Anxiety, insomnia, nausea