# Outline

- **Definitions**
  - Seizure vs. epilepsy
  - Antiepileptic drugs
- **History of antiepileptic drugs (AEDs)**
- **Cellular mechanisms of seizure generation**
- **Molecular and cellular mechanisms of AEDs**
- **Pharmacokinetic principles**
  - Drug metabolism enzymes
  - AED inducers
  - AED inhibitors
  - AED serum concentrations
  - Definitions: therapeutic index, steady state
- **Comparative pharmacokinetics of old vs. new AEDs**
- **Pharmacokinetics in special populations**
- **Effect of metabolic derangements on AED serum concentrations**
- **AEDs and drug interactions**
- **Pharmacodynamic interactions**
- **Adverse effects**
  - Acute vs. chronic
  - Idiosyncratic
- **Case studies**
Epilepsy is the tendency to have recurrent seizures unprovoked by systemic or acute neurologic insults. Antiepileptic drugs (AEDs) are those which decrease the frequency and/or severity of seizures in people with epilepsy. The older term, anticonvulsant drug, is still sometimes used as a synonym for AED, but is less accurate because many seizures do not involve convulsive movements. There is no convincing evidence that any AED “cures” or alters the natural history of epilepsy. However, many patients whose seizures have been completely controlled for two or more years can be successfully withdrawn from AEDs. The therapeutic goal is maximizing seizure control while minimizing adverse drug effects, thus improving the patient’s quality of life.
Antiepileptic Drug

- An antiepileptic drug (AED) is 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
  - Does not prevent the development of epilepsy in individuals who have acquired a risk for seizures (e.g., after head trauma, stroke, tumor)

- Goal of therapy is to maximize quality of life by eliminating seizures (or diminish seizure frequency) while minimizing adverse drug effects
The first effective AED was potassium bromide, discovered serendipitously in the mid-nineteenth century. Phenobarbital came into use in the early twentieth century, followed by phenytoin in the late 1930s, the latter resulting from systematic investigations by Merritt and Putnam using an animal seizure model. Trimethadione, discovered in 1944, was the first AED specific for the treatment of absence seizures. Many of the early AEDs were modifications of these compounds.
Molecular and Cellular Mechanisms of Seizure Generation
A seizure is the clinical manifestation of a hyperexcitable neuronal network, in which the electrical balance underlying normal neuronal activity is pathologically altered—excitation predominates over inhibition. Effective seizure treatments generally augment inhibitory processes or oppose excitatory processes.
Since the normal resting neuronal membrane potential is intracellularly negative, inhibitory processes make the neuron more electrically negative, hyperpolarizing the membrane, while excitatory processes make the intracellular potential less negative or more positive, depolarizing the cell. On an ionic level, inhibition is typically mediated by inward chloride or outward potassium currents, and excitation by inward sodium or calcium currents. Drugs can directly affect specific ion channels or indirectly influence synthesis, metabolism, or function of neurotransmitters or receptors that control channel opening and closing. The most important central nervous system inhibitory neurotransmitter is gamma-amino-butyric acid (GABA). The most important excitatory neurotransmitter is glutamate, acting through several receptor subtypes.
The GABA system and its associated chloride channel is a target of many old and new AEDs effective against many seizure types. Barbiturates and benzodiazepines act directly on subunits of the GABAA receptor-chloride channel complex. Barbiturates increase the duration of chloride channel openings, while benzodiazepines increase the frequency of these openings. Tiagabine inhibits GABA reuptake from synapses. Vigabatrin elevates GABA levels by irreversibly inhibiting its main catabolic enzyme, GABA-transaminase. Note that gabapentin was designed as a lipophilic GABA analogue, but it does not appear to function as a GABA receptor agonist; its does nevertheless have multiple other sites of action endowing it with AED efficacy.
Excitatory neurotransmission mediated by calcium and sodium currents through glutamate receptors has been a tempting target for new AEDs, because these currents may contribute not only to seizure generation but also to neuronal damage from status epilepticus and stroke. Direct glutamate receptor antagonists are effective against experimental seizures, but frequently cause psychosis and other neuropsychiatric adverse effects, preventing clinical use. However, several newer, better tolerated drugs, including lamotrigine and topiramate, may act on this system indirectly.

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### Glutamate Receptors

- Glutamate is the major excitatory neurotransmitter in the CNS. There are two major categories of glutamate receptors:
  - Ionotropic - fast synaptic transmission
    - AMPA / kainate: channels conduct primarily Na⁺
    - NMDA: channels conduct both Na⁺ and Ca⁺⁺
    - NMDA receptor neuromodulators: glycine, zinc, redox site, polyamine site
  - Metabotropic - slow synaptic transmission
    - 8 subtypes (mGlur 1-8) in 3 subgroups (group I-III)
    - G-protein linked; second messenger-mediated modification of intracellular signal transduction
    - Modulate intrinsic and synaptic cellular activity
Glutamate Receptors

- Group I mGluRs (mGluRs 1 and 5)
  - Primarily postsynaptic/presynaptic
  - Net excitatory effect (ictogenic)
  - Couple to inositol triphosphate
  - Long-lasting effects (epileptogenic)

- Group II (mGluRs 2 & 3) and group III (4,6,7,8)
  - Primarily presynaptic
  - Net inhibitory effect; reduce transmitter release
  - Negatively coupled to adenylate cyclase, reduce cAMP
Glutamate Receptors

Diagram of the various glutamate receptor subtypes and locations

From Takumi et al., 1998
Molecular and Cellular Mechanisms of AEDs
AEDs: Molecular and Cellular Mechanisms Overview

- Blockers of repetitive activation of sodium channels:
  - Phenytoin, carbamazepine, oxcarbazepine, valproate, felbamate, lamotrigine, topiramate, zonisamide, rufinamide, lacosamide

- GABA enhancers (direct or indirect):
  - Barbiturates, benzodiazepines, carbamazepine, valproate, felbamate, topiramate, tiagabine, vigabatrin, ezogabine

- Glutamate modulators:
  - Phenytoin, gabapentin, lamotrigine, topiramate, levetiracetam, felbamate, perampanel

- T-calcium channel blockers:
  - Ethosuximide, valproate, zonisamide
AEDs: Molecular and Cellular Mechanisms

Overview

- N- and L-calcium channel blockers:
  - Lamotrigine, topiramate, zonisamide, valproate

- H-current modulators:
  - Gabapentin, lamotrigine

- Blockers of unique binding sites:
  - Gabapentin, levetiracetam, pregabalin, lacosamide, ezogabine

- Carbonic anhydrase inhibitors:
  - Topiramate, zonisamide
Slides 6 through 19 show chemical structures of several AEDs and their postulated molecular and cellular mechanisms of action. Most older drugs share a 5- or 6-membered heterocyclic ring which includes one or two nitrogen atoms and a wide variety of side chains, sometimes containing other ring structures. The shared heterocyclic ring structure may underlie the allergic reactions in some patients to more than one drug. Structures of the newer drugs possess fewer similarities to the older agents and to each other reflecting perhaps unique mechanisms of drug action. Because AEDs constitute the mainstay of epilepsy therapy, effective treatment requires an understanding of AED pharmacology and pharmacokinetics. Principles of general pharmacology will be reviewed briefly in the specific context of AED use.
AEDs: Molecular and Cellular Mechanisms

oxcarbazepine
- Active metabolite: licarbazepine (10-monohydroxy derivative (MHD))
- Blocks voltage-dependent sodium channels at high firing frequencies
- Exerts effect on K+ channels

eslicarbazepine acetate
- Metabolized primarily to S-isomer of MHD
- Anticonvulsant effects attributable to S-isomer
AEDs: Molecular and Cellular Mechanisms

Both eslicarbazepine acetate (ESL) and oxcarbazepine (OXC) are metabolized to the active MHD metabolite.

AEDs: Molecular and Cellular Mechanisms

**Lamotrigine**
- Blocks voltage-dependent sodium channels at high firing frequencies
- Enhances H current
- Modulates kainate receptors

**Zonisamide**
- Blocks voltage-dependent sodium channels and T-type calcium channels
- Mild carbonic anhydrase inhibitor

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AEDs: Molecular and Cellular Mechanisms

**rufinamide**
- Unclear: Possibly stabilization of the sodium channel inactive state

**lacosamide**
- Enhances slow inactivation of voltage gated sodium channels
AEDs: Molecular and Cellular Mechanisms

topiramate
- Blocks voltage-dependent Na+ 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
- Inhibition of carbonic anhydrase
AEDs: Molecular and Cellular Mechanisms

**Valproic Acid**
- May enhance GABA transmission in specific circuits
- Blocks voltage-dependent sodium channels
- Modulates T-type calcium channels

**Felbamate**
- Blocks voltage-dependent sodium channels at high firing frequencies
- Modulates NMDA receptor (block) and GABA receptors (enhanced)
levetiracetam

- Binding of reversible saturable specific binding site SV2A (a synaptic vesicle protein)
- Modulates kainate receptor activity
- Reverses inhibition of GABA and glycine gated currents induced by negative allosteric modulators
AEDs: Molecular and Cellular Mechanisms

**barbiturates**
- Prolong GABA-mediated chloride channel openings
- Some blockade of kainate receptors

**benzodiazepines**
- Increase frequency of GABA-mediated chloride channel openings
AEDs: Molecular and Cellular Mechanisms

tiagabine
- Interferes with GABA re-uptake

vigabatrin
- Irreversibly inhibits GABA-transaminase (enzyme that breaks down GABA)
AEDs: Molecular and Cellular Mechanisms

**GABAPENTIN**
- Blocks calcium channels
- Enhances H current
- Suppressed presynaptic vesicle release
- Suppresses NMDA receptor at glycine site

**PREGABALIN**
- Increases glutamic acid decarboxylase
- Suppresses calcium currents by binding to the alpha2-delta subunit of the voltage gated calcium channel

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AEDs: Molecular and Cellular Mechanisms

**ezogabine**
- Enhancement of transmembrane potassium current mediated by KCNQ ion channels
- Augmentation of GABA-mediated currents

**perampanel**
- Noncompetitive antagonist of postsynaptic AMPA receptors

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AEDs: Molecular and Cellular Mechanisms

Ethosuximide

- Blocks low threshold, “transient” (T-type) calcium channels in thalamic neurons
## Summary: Mechanisms of Neuromodulation

<table>
<thead>
<tr>
<th>AED</th>
<th>NMDA Channel Blockade</th>
<th>Ca++ Channel Blockade</th>
<th>H-current Enhancement</th>
<th>GABA Receptor Antagonism</th>
<th>GABA Enhancement</th>
<th>Carbonic Anhydrase Inhibition</th>
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<tbody>
<tr>
<td>PHT</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBZ, OXC, ESL</td>
<td>X</td>
<td></td>
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<td>X (GABA, ethanol)</td>
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<td></td>
</tr>
<tr>
<td>VPA</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>FBM</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X (NMDA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LTG</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X (kainate)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPM</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X (AMPA, kainate)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ZNS</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td>LCM</td>
<td>X (slow inact.)</td>
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<tr>
<td>RUF</td>
<td>X</td>
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### Summary: Mechanisms of Neuromodulation

<table>
<thead>
<tr>
<th>AED</th>
<th>Ca⁺⁺ Channel Blockade</th>
<th>Na⁺-current enhancement</th>
<th>Glutamate Receptor Agonism</th>
<th>GABA Enhancement</th>
<th>K⁺ Channel enhancement</th>
</tr>
</thead>
<tbody>
<tr>
<td>barb, benzo</td>
<td>X</td>
<td></td>
<td>X (GABA&lt;sub&gt;a&lt;/sub&gt;)</td>
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<tr>
<td>ESM</td>
<td>X</td>
<td></td>
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<tr>
<td>GBP</td>
<td>X</td>
<td>X</td>
<td>X (NMDA&lt;sub&gt;κ&lt;/sub&gt;, glycine)</td>
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<tr>
<td>TGB</td>
<td></td>
<td></td>
<td>X (reuptake)</td>
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<tr>
<td>LEV</td>
<td></td>
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<td>X (iontoph.)</td>
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<tr>
<td>PCB</td>
<td>X</td>
<td></td>
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<tr>
<td>VGB</td>
<td></td>
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<td>X (metab.)</td>
<td></td>
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<tr>
<td>EZG</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
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<tr>
<td>Patanopet</td>
<td></td>
<td></td>
<td>X (AMPA)</td>
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</tbody>
</table>

Summary: Mechanisms of Neuromodulation


American Ecology Society 2014
Epilepsy Trivia

This epilepsy medication was discovered by accident. It was used as a solvent in studies on a drug that was being investigated as an anticonvulsant. It turned out that similar, substantial improvement was seen in both the placebo group and the "active" drug group.

What drug am I?
Epilepsy Trivia

This epilepsy medication was discovered by accident. It was used as a solvent in studies on a drug that was being investigated as an anticonvulsant. It turned out that similar, substantial improvement was seen in both the placebo group and the "active" drug group.

What drug am I?

valproic acid
Pharmacokinetic Principles
Pharmacokinetics is the quantitative description of what happens to a drug when it enters the body, including drug absorption, distribution, metabolism and elimination/excretion. Absorption is influenced by route of intake. Most AEDs are available for oral administration, although some have formulations that are also available for intravenous, intramuscular or rectal administration. Most AEDs undergo complete or nearly complete absorption when given orally. Most often, administration of AEDs with food slows absorption and can help avert peak dose related side effects. Calcium containing antacids may interfere with phenytoin absorption. Gabapentin is absorbed by a saturable amino acid transport system and does not get absorbed after a certain dose. Intramuscular Administration: Fosphenytoin may be administered intramuscularly if intravenous access cannot be established in cases of frequent repetitive seizures. Rectal administration: Diazepam (available as a rectal gel) has been shown to terminate repetitive seizures and can be administered by family members at home. Intravenous administration is used for emergencies (e.g. status epilepticus). Phenytoin, fosphenytoin, phenobarbital, diazepam, lorazepam, levetiracetam, valproic acid, and lacosamide are available as IV preparations.
Different AEDs either induce or inhibit certain isoenzymes of this system and can result in changes of the pharmacokinetic properties of different medications. Adding an enzyme inducer to a substrate decreases the serum concentration of the substrate, while withdrawing an inducer or adding an enzyme inhibitor has the opposite effect.

<table>
<thead>
<tr>
<th>Pharmacokinetic Principles</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Elimination:</strong> removal of active drug from the blood by metabolism and excretion</td>
</tr>
<tr>
<td>- Metabolism/biotransformation - generally hepatic; usually rate-limiting step</td>
</tr>
<tr>
<td>- Excretion - mostly renal</td>
</tr>
<tr>
<td>- Active and inactive metabolites</td>
</tr>
<tr>
<td>- Changes in metabolism over time (auto induction with carbamazepine) or with polytherapy (enzyme induction or inhibition)</td>
</tr>
<tr>
<td>- Differences in metabolism by age, systemic disease</td>
</tr>
</tbody>
</table>
Drug Metabolizing Enzymes: UDP- Glucuronyltransferase (UGT)

- Important pathway for drug metabolism/inactivation
- Currently less well described than CYP
- Several isozymes that are involved in AED metabolism include:
  - UGT1A9 (VPA)
  - UGT2B7 (VPA, lorazepam)
  - UGT1A4 (LTG, EZG)
Most AEDs are metabolized in the liver by hydroxylation or conjugation. These metabolites are then excreted by the kidney. Some metabolites are themselves active (carbamazepine, oxcarbazepine, primidone). Gabapentin undergoes no metabolism and is excreted unchanged by the kidney. Most AEDs are metabolized by the P450 enzyme system in the liver. Different AEDs either induce or inhibit certain isoenzymes of this system and can result in changes of the pharmacokinetic properties of different medications. In general, enzyme inducers decrease the serum concentrations of other drugs metabolized by the system and enzyme inhibitors have the opposite affect. Valproic acid is metabolized by a combination of conjugation by uridine glucuronate (UDP)-Glucuronyltransferase (UGT) via conjugation and by mitochondrial betaoxidation.

Drug elimination rate is usually expressed as the biological half-life and is defined as the time required for the serum concentration to decrease by 50% following absorption and distribution. This changes for some drugs based on serum concentration e.g. phenytoin has a longer half-life at high serum levels. The half-life also determines the dosing frequency required for a drug to be maintained at a steady state in the serum. Many drugs or their metabolites are eliminated by the kidneys, and dosage adjustments may be required in cases of renal impairment.
## Drug Metabolizing Isozymes and AEDs

<table>
<thead>
<tr>
<th>AED</th>
<th>CYP3A4</th>
<th>CYP2C9</th>
<th>CYP2C19</th>
<th>UGT</th>
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<tbody>
<tr>
<td>CBZ</td>
<td>+</td>
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<tr>
<td>PHT</td>
<td></td>
<td>+</td>
<td>+</td>
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<tr>
<td>VPA</td>
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<td>+</td>
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<td>+</td>
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<td>PB</td>
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<tr>
<td>ZNS</td>
<td>+</td>
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<td>TGB</td>
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<tr>
<td>OXC</td>
<td>+</td>
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# Drug Metabolizing Isozymes and AEDs

<table>
<thead>
<tr>
<th>AED</th>
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<th>CYP2C9</th>
<th>CYP2C19</th>
<th>UGT</th>
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<tbody>
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<td>LTG</td>
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<tr>
<td>TPM</td>
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<tr>
<td>LCM</td>
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<td>1</td>
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<tr>
<td>EZG</td>
<td></td>
<td></td>
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<td>+</td>
</tr>
<tr>
<td>Perampanel</td>
<td>+</td>
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<td></td>
</tr>
<tr>
<td>CLB</td>
<td>+</td>
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</tr>
<tr>
<td>CZP</td>
<td>+</td>
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</table>
AED Inducers: The Cytochrome P-450 Enzyme System

- Increase clearance and decrease steady-state concentrations of other substrates
- Results from synthesis of new enzyme or enhanced affinity of the enzyme for the drug
- Tends to be slower in onset/offset than inhibition interactions
AED Inducers: The Cytochrome P-450 Enzyme System

- Broad Spectrum Inducers:
  - Phenobarbital - CYP1A2, 2A6, 2B6, 2C8/9, 3A4
  - Primidone - CYP1A2, 2B6, 2C8/9, 3A4
  - Phenytoin - CYP2B6, 2C8/9, 2C19, 3A4
  - Carbamazepine - CYP1A2, 2B6, 2C8/9, 2C19, 3A4

- Selective CYP3A Inducers:
  - Oxcarbazepine - CYP3A4 at higher doses
  - Topiramate - CYP3A4 at higher doses
  - Felbamate - CYP3A4

- Tobacco/cigarettes - CYP1A2
AED Inhibitors: The Cytochrome P-450 Enzyme System

- Decrease clearance and increase steady-state concentrations of other substrates
- Competition at specific hepatic enzyme site, decreased production of the enzyme, or decreased affinity of the enzyme for the drug
- Onset typically rapid and concentration (inhibitor) dependent; mirrors time to steady state of inhibitor drug
- Possible to predict potential interactions by knowledge of specific hepatic enzymes and major pathways of AED metabolism
AED Inhibitors: The Cytochrome P-450 Enzyme System

- Topiramate & oxcarbazepine: CYP2C19
  - ↑ plasma concentrations of phenytoin
- Felbamate: CYP2C19
  - ↑ plasma concentrations of phenytoin, phenobarbital
- Clobazam: moderate CYP2D6 inhibitor
- Grapefruit juice: CYP3A4
AED Inhibitors: Other Systems

- **Valproate:**
  - UDP-glucuronosyltransferase (UGT)
    - ↑ plasma concentrations of lamotrigine, lorazepam
  - CYP2C19
    - ↑ plasma concentrations of phenytoin, phenobarbital

- **Ezogabine:**
  - N-acetyl metabolite (NAMR) inhibits p-glycoprotein-mediated clearance of digoxin
  - ↑ plasma concentrations of digoxin
AEDs can have a narrow range within which seizures are controlled without toxicity. This concept is quantified as the “therapeutic index” (TI). TI is the ratio of the drug concentration effective for 50% of subjects (ED50) to the concentration toxic to 50% of subjects (TD50) i.e., TI=ED50/TD50. The “therapeutic range” of AED serum concentration is an attempt to translate the experimental concept of therapeutic index to the clinic. These ranges are broad generalizations which are of limited use and can be misleading when applied to individual patients. Many patients tolerate and need serum concentrations above the usual therapeutic range, while others achieve complete seizure control, or even experience adverse effects, at concentrations below it.
Steady State and Half Life

From Engel, 1989
AED Serum Concentrations

- Serum concentrations are useful when optimizing AED therapy, assessing adherence, or teasing out drug-drug interactions.
- They should be used to monitor pharmacodynamic and pharmacokinetic interactions.
- Should try to measure a serum concentration before the next dose to approximate trough concentration.
AED Serum Concentrations

- Serum concentrations are also useful when documenting positive or negative outcomes associated with AED therapy
- Most often individual patients define their own “therapeutic range” for AEDs
- For the new AEDs there is no clearly defined “therapeutic range”
## Potential Target Range of AED Serum Concentrations

<table>
<thead>
<tr>
<th>AED</th>
<th>Serum Concentration (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>carbamazepine</td>
<td>4 - 12</td>
</tr>
<tr>
<td>ethosuximide</td>
<td>40 - 100</td>
</tr>
<tr>
<td>phenobarbital</td>
<td>20 - 40</td>
</tr>
<tr>
<td>phenytoin</td>
<td>5 - 25 (10-20)</td>
</tr>
<tr>
<td>valproic acid</td>
<td>50 - 100</td>
</tr>
<tr>
<td>primidone</td>
<td>5 - 12</td>
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# Potential Target Range of AED Serum Concentrations

<table>
<thead>
<tr>
<th>AED</th>
<th>Serum Concentration (µg/ml)</th>
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<tbody>
<tr>
<td>gabapentin</td>
<td>4 - 16</td>
</tr>
<tr>
<td>lamotrigine</td>
<td>2 - 20</td>
</tr>
<tr>
<td>levetiracetam</td>
<td>20 - 60</td>
</tr>
<tr>
<td>oxcarbazepine</td>
<td>5 - 50 (MHD)</td>
</tr>
<tr>
<td>pregabalin</td>
<td>5 - 10</td>
</tr>
<tr>
<td>tiagabine</td>
<td>5 - 70</td>
</tr>
<tr>
<td>topiramate</td>
<td>2 - 25</td>
</tr>
<tr>
<td>zonisamide</td>
<td>10 - 40</td>
</tr>
<tr>
<td>felbamate</td>
<td>40 - 100</td>
</tr>
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# Admixture and Administration of Injectable AEDs

<table>
<thead>
<tr>
<th>AED</th>
<th>Dosage/Rate of Infusion</th>
</tr>
</thead>
</table>
| fosphenytoin (Cerebyx®) | Status epilepsy: Loading Dose: 15-20 mg PE/kg IV (PE = phenytoin equivalent)  
Not-emergent: Loading Dose: 10-20 mg PE/kg IV or IM; MD: 4-6 mg PE/kg/day IV or IM  
Infusion Rate: Should not exceed 150 mg PE/minute  |
| levetiracetam (Keppra®) | >16 y/o: No Loading Dose. 1000 mg/day in 2 divided doses. Dose can be increased by 1000 mg/day over 2 weeks up to a maximum dose of 1000 mg/day  
Infusion Rate: Dilute in 100 ml of normal saline (NS), lactated ringer (LR) or dextrose 5% and infuse over 15 minutes  |
| phenytoin (Dilantin®)    | Loading Dose: 10-15 mg/kg; up to 25 mg/kg has been used clinically  
Maintenance Dose: 300 mg/day or 5-6 mg/kg/day in 3 divided doses, IM not recommended, use within 4 hrs. Use saline 0.22-5 micron filter  
Infusion Rate: Should not exceed 50 mg/min; elderly/debilitated should not exceed 20 mg/min |
| valproic acid (Depakote®)| No Loading Dose: 1000-2500 mg/day in 1-3 divided doses  
Infusion Rate: Administer over 60 minutes (< = 20 mg/min); rapid infusion over 5-10 minutes as 1.5-3 mg/kg/min |
| lacosamide (Vimpar®)     | No Loading Dose; maintenance dose 200-600 mg/day in 2 divided doses  
Infusion Rate: IV formulation is 10 mg/ml, can be administered with or without additives over 30-60 minutes |
# Comparative Pharmacokinetics of Traditional AEDs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Absorption</th>
<th>Binding %</th>
<th>Elimination</th>
<th>t ½ (hrs)</th>
<th>Cause Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ</td>
<td>80</td>
<td>75-85</td>
<td>100% H*</td>
<td>6-15</td>
<td>Yes</td>
</tr>
<tr>
<td>PB</td>
<td>100</td>
<td>50</td>
<td>75% H</td>
<td>72-124</td>
<td>Yes</td>
</tr>
<tr>
<td>PHT</td>
<td>95</td>
<td>90</td>
<td>100% H**</td>
<td>12-60</td>
<td>Yes</td>
</tr>
<tr>
<td>VPA</td>
<td>100</td>
<td>75-95</td>
<td>100% H</td>
<td>6-18</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Problems with traditional AEDs:
- Poor water solubility
- Extensive protein binding
- Extensive oxidative metabolism
- Multiple drug-drug interactions

* autoinduction
** non-linear
H = hepatic
R = renal
**Pharmacokinetics of Newer AEDs**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Absorption</th>
<th>Binding</th>
<th>Elimination</th>
<th>T ½ (hrs)</th>
<th>Cause Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>GBP</td>
<td>≤ 60%</td>
<td>0%</td>
<td>100% R</td>
<td>5-9</td>
<td>No</td>
</tr>
<tr>
<td>LTG</td>
<td>100%</td>
<td>55%</td>
<td>100% H</td>
<td>18-30</td>
<td>No</td>
</tr>
<tr>
<td>LEV</td>
<td>~100%</td>
<td>&lt;10%</td>
<td>66% R</td>
<td>4-8</td>
<td>No</td>
</tr>
<tr>
<td>TGB</td>
<td>~100%</td>
<td>95%</td>
<td>100% H</td>
<td>3-13</td>
<td>No</td>
</tr>
<tr>
<td>TPM</td>
<td>≥80%</td>
<td>15%</td>
<td>30-55% R</td>
<td>20-30</td>
<td>Yes/No</td>
</tr>
</tbody>
</table>

Potential advantages of newer AEDs:
- Improved water solubility...predictable bioavailability
- Negligible protein binding...no need to worry about hypoalbuminemia
- Less reliance on CYP metabolism...perhaps less variability over time

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Pharmacokinetics of Newer AEDs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Absorption</th>
<th>Binding</th>
<th>Elimination</th>
<th>T 1/2 (hrs)</th>
<th>Cause Interactions?</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZNS</td>
<td>80-100%</td>
<td>40-60%</td>
<td>50-70% H</td>
<td>50-80</td>
<td>No</td>
</tr>
<tr>
<td>OXC</td>
<td>100%</td>
<td>40%</td>
<td>100% H</td>
<td>5-11</td>
<td>Yes/No</td>
</tr>
<tr>
<td>LCM</td>
<td>100%</td>
<td>&lt;15%</td>
<td>60% H</td>
<td>13</td>
<td>No</td>
</tr>
<tr>
<td>RUF</td>
<td>85%</td>
<td>35%</td>
<td>100% H</td>
<td>6-10</td>
<td>Minor</td>
</tr>
<tr>
<td>VGB</td>
<td>100%</td>
<td>0%</td>
<td>R</td>
<td>7-8</td>
<td>Yes/No</td>
</tr>
</tbody>
</table>
# Pharmacokinetics of Newer AEDs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Absorption</th>
<th>Binding</th>
<th>Elimination</th>
<th>T 1/2 (hrs)</th>
<th>Cause Interactions?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perampanel</td>
<td>100%</td>
<td>95-96%</td>
<td>100% H</td>
<td>105</td>
<td>No</td>
</tr>
<tr>
<td>EZG</td>
<td>60%</td>
<td>80%</td>
<td>85% R</td>
<td>7-11</td>
<td>No</td>
</tr>
<tr>
<td>CLB</td>
<td>100%</td>
<td>80-90%</td>
<td>100% H</td>
<td>36-42</td>
<td>No</td>
</tr>
</tbody>
</table>
Pharmacokinetics in special populations
C. Patient influences on drug effects
Age and systemic conditions can influence pharmacokinetic and pharmacodynamic parameters. Elimination of many drugs is slower in the elderly, mainly because of reduced hepatic and renal blood flow, which lengthens drug half-life above published values based on young adults. In addition, albumin levels fall with age; this increases the free fraction of drugs that are highly protein bound, thus increasing risk of toxicity, especially for highly protein-bound drugs. Further, older people are often more sensitive to drug effects at a given free level. In the elderly, AEDs should usually be started at a lower dose and increased at a slower rate than in younger patients.
Drug metabolism and disposition in children can differ significantly from that in adults. Beyond the neonatal period, when protein binding and drug metabolic rates are low, children usually have faster drug elimination rates and reduced serum half-lives relative to adults. Some children require almost twice the adult mg/kg dosage, particularly if combination therapy with enzyme-inducers is employed. Furthermore, because of shorter pediatric half-lives, many AEDs require at least 3 times daily administration in children 1-10 years of age.

Despite frequent drug administration, large swings in peak-to-peak concentrations are possible, especially in young children, because of their fast elimination rates. Solid oral dosage forms overcome this problem by providing a longer absorption phase that reduces peak and increases trough concentrations. Crushed tablets are preferable to liquids in younger children for similar reasons. Rapid gastrointestinal transit times in children may, however, impede absorption.
Pregnancy increases the volume of distribution and the rate of drug metabolism, and decreases protein binding. For many AEDs, the optimal dose increases as pregnancy progresses; this is particularly true for lamotrigine, which often requires at least a doubling of the dose to maintain serum concentrations. Total and free drug concentrations are helpful guides to adjusting doses in pregnancy.
Pharmacokinetics in Pregnancy

<table>
<thead>
<tr>
<th>AED</th>
<th>Increase in clearance (%)</th>
<th>Decrease in total concentrations (%)</th>
<th>Changes in clearance or free level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>19-150</td>
<td>60-70</td>
<td>Free PHT level decreased by 16-40% (3rd trimester)</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>11-27</td>
<td>0-12</td>
<td>No change</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>60</td>
<td>55</td>
<td>Decrease in free level by 50%</td>
</tr>
<tr>
<td>Primidone</td>
<td>Inconsistent</td>
<td>Inconsistent</td>
<td>Decrease in PB level, lower PB:primidone ratio</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Increased by 2nd and 3rd trimesters</td>
<td>No reports</td>
<td>No change in clearance of free VPA</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>Inconsistent</td>
<td>Inconsistent</td>
<td>Inconsistent</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>65-230</td>
<td>No reports</td>
<td>89% increase in clearance of free LTG</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>No reports</td>
<td>36-61 (active metabolite)</td>
<td>No reports</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>243</td>
<td>60 (by. 3rd trimester)</td>
<td>No reports</td>
</tr>
</tbody>
</table>
Fever can increase the metabolic rate, resulting in more rapid drug elimination and lower serum concentrations. Febrile illnesses may also elevate serum proteins that bind AEDs, resulting in decreased free levels.

Severe hepatic disease impairs metabolism, increasing serum levels and risk of toxicity of many drugs. However, complex interactions among hepatic blood flow, biliary excretion, and hepatocellular function make the net effect of hepatic disease on drug levels difficult to predict.

<table>
<thead>
<tr>
<th>Effect of Metabolic Derangements on AED Serum Concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Febrile Illnesses</td>
</tr>
<tr>
<td>⚫ ↑ metabolic rate and ↓ serum concentrations</td>
</tr>
<tr>
<td>⚫ ↑ serum proteins that can bind AEDs and ↓ free levels of AED serum concentrations</td>
</tr>
<tr>
<td>• Severe Hepatic Disease</td>
</tr>
<tr>
<td>⚫ Impairs metabolism and ↑ serum levels of AEDs</td>
</tr>
<tr>
<td>⚫ ↓ serum proteins and ↑ free levels of AED serum concentrations</td>
</tr>
<tr>
<td>⚫ Often serum levels can be harder to predict in this situation</td>
</tr>
</tbody>
</table>

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Renal disease reduces elimination of some drugs such as gabapentin. In chronic renal disease where there is protein loss, one commonly can see a higher free fraction of highly protein bound AEDs which then are more susceptible to elimination potentially resulting in lower total serum concentration of the drug. More frequent doses may need to be given. Effects of dialysis differ among AEDs. Some, such as phenobarbital, are significantly removed. Serum concentrations can be measured before and after dialysis, and appropriate boluses given.
Effects of Dialysis

- Serum concentrations pre/post dialysis can be beneficial in this patient population
- Bolus dosing of AEDs is sometimes recommended in this situation
AEDs and Drug Interactions
Hepatic Drug Metabolizing Enzymes and Specific AED Interactions

- Phenytoin: CYP2C9/CYP2C19
  - Inhibitors: valproate, ticlopidine, fluoxetine, topiramate, fluconazole

- Carbamazepine: CYP3A4/CYP2C8/CYP1A2
  - Inhibitors: ketoconazole, fluconazole, erythromycin, diltiazem

- Lamotrigine: UGT 1A4
  - Inhibitor: valproate

- Important note about oral contraceptives (OCPs).
  - OCP efficacy is decreased by inducers: phenytoin, phenobarbital, primidone, carbamazepine, and higher doses of topiramate, oxcarbazepine, perampanel
  - OCPs and pregnancy significantly decrease serum levels of lamotrigine
## Isozyme Specific Drug Interactions

<table>
<thead>
<tr>
<th>Category</th>
<th>CYP3A4</th>
<th>CYP2C9</th>
<th>CYP2C19</th>
<th>UGT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibitor</td>
<td>erythromycin, clarithromycin, dilazep, fluconazole, itraconazole, ketoconazole, cimetidine, propoxyphene, grapefruit juice</td>
<td>VPA, fluconazole, metronidazole, sulindac, paroxetine, trimethoprim/sulfa</td>
<td>ticlopidine, felbamate, OXC/MHD, omeprazole</td>
<td>VPA</td>
</tr>
<tr>
<td>Inducer</td>
<td>CBZ, PH1, PB, felbamate, rifampin, OXC/MHD</td>
<td>CR7, PH1, PB, rifampin</td>
<td>CR7, PH1, PB, rifampin</td>
<td>CBZ, PH1, PB, OXC/MHD, LTG (?)</td>
</tr>
</tbody>
</table>

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AEDs and Drug Interactions

- Although many AEDs can cause pharmacokinetic interactions, several agents appear to be less problematic.

- AEDs that do not appear to be either inducers or inhibitors of the CYP system include:
  - gabapentin
  - lamotrigine
  - pregabalin
  - tiagabine
  - levetiracetam
  - zonisamide
  - lacosamide
  - ezogabine
  - perampanel
Pharmacokinetic Interactions: Possible Clinical Scenarios

Be aware that drug interactions may occur with:

- Addition of a new medication when an inducer/inhibitor is present
- Addition of inducer/inhibitor to an existing medication regimen
- Removal of an inducer/inhibitor from chronic medication regimen
Drug interactions based on pharmacokinetics, or what the body does to the drug, must be distinguished from those based on pharmacodynamics, or “what the drug does to the body.” Pharmacodynamic effects include both wanted and unwanted drug effects on the brain and other organs. Gabapentin, for example, has no important pharmacokinetic interactions with other AEDs. Because gabapentin and many other drugs can cause sedation and dizziness, however, pharmacodynamic interactions can occur. Ideally, drug combinations should produce additive or synergistic (supra-additive) therapeutic effects and subadditive toxicities. Drug combinations with different mechanisms of action may help achieve this goal.
Adverse Effects
As mentioned previously, most AEDs have a narrow therapeutic window—a small range of serum concentrations within which seizure prevention is achievable without significant toxicity or side effects. This concept applies primarily to dose-related, reversible, short-term side effects. However, risk of idiosyncratic effects such as allergic reactions and organ damage must also be considered. Serious idiosyncratic effects are rare but can be life-threatening. They generally occur within several weeks or months of starting the drug, tend to be dose-independent (except possibly for skin rash with lamotrigine), and unpredictable.
Acute, Dose-Related Adverse Effects of AEDs

- Neurologic/psychiatric: most common
- Sedation, fatigue
  - All AEDs, except unusual with LTG and FBM
  - More pronounced with traditional AED
- Unsteadiness, incoordination, dizziness
  - Mainly traditional AEDs, perampanel
  - May be sign of toxicity with many AEDs
- Tremor
  - Valproic acid
Acute, Dose-Related Adverse Effects of AEDs (cont.)

- Parasthesia
  - Topiramate, zonisamide
- Diplopia, blurred vision, visual distortion
  - Carbamazepine, lamotrigine
- Mental/motor slowing or impairment
  - Topiramate
- Mood or behavioral changes
  - Levetiracetam, ezogabine, perampanel
- Changes in libido or sexual function
  - Carbamazepine, phenytoin, phenobarbital
Acute, Dose-Related Adverse Effects of AEDs (cont.)

- Gastrointestinal (nausea, heartburn)
- Mild to moderate laboratory changes
  - Hyponatremia: carbamazepine, oxcarbazepine
  - Increases in ALT or AST
  - Leukopenia
  - Thrombocytopenia
Acute, Dose-Related Adverse Effects of AEDs (cont.)

- Weight gain/appetite changes
  - Valproic acid
  - Gabapentin
  - Pregabalin
  - Vigabatrin
  - Perampanel

- Weight loss
  - Topiramate
  - Zonisamide
  - Felbamate
Intermittent or frequent monitoring of biochemical (e.g., liver functions such ALT, AST) or hematologic (e.g., CBC) laboratory tests may not detect changes in time to alter prognosis. In addition, frequent monitoring may detect changes or abnormalities which are not clinically significant (e.g., usually transient alterations in liver function tests associated with valproate therapy or commonly-observed, usually transient reductions in leukocyte counts associated with carbamazepine). Education of patients or caregivers to promptly report relevant symptoms of possibly serious idiosyncratic effects accompanied by appropriate laboratory follow-up are currently regarded as mainstays of detection.

Many idiosyncratic reactions likely result from inherited genetic susceptibilities to a particular drug or metabolite. The most common target organs are skin, liver, bone marrow, and occasionally pancreas. Skin rashes are common, immunologically mediated, and usually minor and reversible. Skin rashes, can however, progress to Stevens-Johnson syndrome. The more serious organ toxicities occur in less than 1 in 10,000-100,000 treated patients. Felbamate-related aplastic anemia appears to occur more commonly (approximately 1:5,000). For some AEDs, the presence of predisposing risk factors may increase the risk of serious idiosyncratic reactions. Valproate-related hepatotoxicity is more common in very young children receiving multiple AEDs; lamotrigine-induced skin rashes are more common in patients receiving valproate and/or who are treated with aggressively-titrated lamotrigine doses.
Stevens-Johnson Syndrome

- Early symptoms: abdominal pain, vomiting, jaundice
- Hepatic damage
- Laboratory monitoring probably not helpful in early detection
- Fever and mucus membrane involvement
- Importance of patient education
AED Hypersensitivity Syndrome

- Characterized by rash, systemic involvement
- Arene oxide intermediates - aromatic ring
- Lack of epoxide hydrolase
- Cross-reactivity
  - Phenytoin
  - Carbamazepine
  - Phenobarbital
  - Oxcarbazepine
- Relative cross reactivity
  - Lamotrigine
AED Hypersensitivity

Idiosyncratic Adverse Effects of AEDs

- Hematologic damage
  - Marrow aplasia, agranulocytosis
  - Early symptoms: abnormal bleeding, acute onset of fever, symptoms of anemia
  - Laboratory monitoring probably not helpful in early detection
  - Felbamate aplastic anemia approx. 1:5,000 treated patients
  - Patient education
The third type of adverse drug effect is cumulative toxicity, usually occurring over years of treatment. Because most AEDs other than phenobarbital and phenytoin have been in use for less than 25 years, data regarding these types of adverse effects are limited.
17 yo boy with h/o generalized tonic clonic seizures for 4 years on phenytoin 300mg/day for 2 years WITHOUT SUPERVISION.

Found to have severe gingival hyperplasia and cerebellar ataxia.
After Withdrawal of Phenytoin

Trabecular Bone
Long-Term Adverse Effects of AEDs

- Ophthalmologic effects
  - Retinal pigment changes with ezogabine
    • Associated with blue discoloration of skin, sclera, nails
    • May lead to vision loss, unknown if reversible upon drug discontinuation
    • Need eye exam every six months
  - Irreversible concentric visual loss with vigabatrin
    • Risk factors include high cumulative dosage, male gender, old age
    • Need visual field testing every six months
Teratogenic effects

- Dose dependent effects demonstrated with valproic acid, carbamazepine, phenobarbital, lamotrigine
- Polytherapy increases risk compared to monotherapy regimens
- Valproic acid
  - Oral cleft, neural tube defects, hypospadias, cardiac malformations, polydactyly, craniosynostosis
- Carbamazepine
  - Neural tube defects
- Phenobarbital
  - Cardiac malformations
- Oral cleft
  - Phenytoin, phenobarbital, carbamazepine, topiramate


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# Timing of Congenital Malformations

<table>
<thead>
<tr>
<th>Tissues</th>
<th>Malformations</th>
<th>Postconceptional age (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>Neural tube defect</td>
<td>28</td>
</tr>
<tr>
<td>Heart</td>
<td>Ventricular septal defect</td>
<td>42</td>
</tr>
<tr>
<td>Face</td>
<td>Cleft lip</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>Cleft palate</td>
<td>47-70</td>
</tr>
</tbody>
</table>

*Continuum. 2013:19:697.*
Teratogenic effects

- Cognitive outcomes in children of women with epilepsy
  - Children of untreated mothers do not have worse outcomes
  - Worse outcomes with valproic acid, phenytoin, phenobarbital, and polytherapy
  - Preliminary data shows association between autism spectrum disorder and valproic acid

Epilepsy Trivia

This famous person with epilepsy held the papal throne from 1846 thru 1878.

Who am I?
Epilepsy Trivia

This famous person with epilepsy held the papal


diocese from 1834 to 1878.

Who am I?

Pope Pius IX
Pharmacology Resident Case Studies
American Epilepsy Society
Medical Education Program
Case #1 - Pediatric

- Tommy is a 4 year old child with a history of intractable seizures and developmental delay since birth.

- He has been tried on several anticonvulsant regimens (i.e., carbamazepine, valproic acid, ethosuximide, phenytoin, and phenobarbital) without significant benefit.
Case #1 – Pediatric Con’t

- Tommy’s seizures are characterized as tonic seizures and atypical absence seizures and has been diagnosed with a type of childhood epilepsy known as Lennox-Gastaut Syndrome.
Case #1 – Pediatric Con’t

1. Briefly describe what characteristics are associated with Lennox-Gastaut Syndrome.

2. What anticonvulsants are currently FDA approved for Lennox-Gastaut Syndrome?
Case #1 – Pediatric Con’t

3. Tommy is currently being treated with ethosuximide 250 mg BID and valproic acid 250 mg BID. The neurologist wants to add another anticonvulsant onto Tommy’s current regimen and asks you for your recommendations. (Hint: Evaluate current anticonvulsants based on positive clinical benefit in combination therapy and adverse effect profile.)
Case #1 – Pediatric Con’t

4. Based on your recommendations above, what patient education points would you want to emphasize?