Seizures in the Elderly
Achieving Control

Objectives

• Review the epidemiology, etiology, and pathophysiology of epilepsy.
• Describe current and emerging pharmacological approaches for the management of epilepsy to include adjunctive therapy for those patients where monotherapy does not control seizures.
• Outline the pharmacist’s role in counseling epilepsy patients and caregivers on the array of challenges to daily living, seizure control, range of available resources, and non-pharmacological therapy available to improve quality of life.

Faculty Disclaimer

• Dr. Saffel currently provides consulting services to:
  – Astellas Pharmaceuticals
  – Acadia Pharmaceuticals
  – Avanir Pharmaceuticals
  – Sun Pharmaceutical Technologies, LTD
  – Sunovion Pharmaceuticals
• Dr. Saffel is on the speaker’s bureau for:
  – Acadia Pharmaceuticals
  – Avanir Pharmaceuticals
  – Sunovion Pharmaceuticals
Epilepsy is the Fourth Most Common Neurological Condition

Nearly 3 million people in the United States have active epilepsy.

Prevalence in North America falls between 5 and 10 of every 1000 people.

Self Assessment Question

When the cause of epilepsy is known, what is the most common cause of new-onset epilepsy beyond 65 years of age?

A. Stroke  
B. Traumatic Brain Injury  
C. Neurodegenerative Disease  
D. Tumors

Epilepsy in the Elderly

- Epilepsy in the elderly is potentially life threatening
  - 2 to 3 times greater mortality than in the general population
  - Status epilepticus has a 50% mortality rate
  - Frequently results in physical injury

Causes of Epilepsy in the Elderly

- 30% - 75%
- 10% - 20%
- 20%
- 50%

References:
Types of Epilepsy

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

A seizure is a symptom of epilepsy

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

Types of Seizures


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


<table>
<thead>
<tr>
<th>Self Assessment Question</th>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>What is the most common type of seizure in the elderly?</td>
<td>A. Generalized Onset</td>
<td>B. Simple Partial Onset</td>
<td>C. Complex Partial Onset</td>
</tr>
</tbody>
</table>

Partial Onset Seizures

- Simple: No loss of consciousness
  - Simple Partial Seizures are often interchanged with the term “aura”
- Complex: Impaired consciousness
  - Most common seizure in epileptic adults
  - Auras are less likely to be reported
  - Most common aura is “dizziness”
  - Atypical presentation
    - Altered mental status
    - Periods of staring
    - Unresponsiveness
    - Brief loss of consciousness
    - Inattention
    - Memory lapses or confusion
  - Post-ictal periods may be more prolonged, sometimes for several days

Diagnosis of epilepsy in the elderly is difficult and may be incorrect.
Common comorbidities can mimic epilepsy:
- Mechanical falls
- Syncope
- Confusional states
- Memory problems
- Sleep disorders

Partial Onset Seizures

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  - Auras are less likely to be reported
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    - Unresponsiveness
    - Brief loss of consciousness
    - Inattention
    - Memory lapses or confusion
  - Post-ictal periods may be more prolonged, sometimes for several days
Differential Diagnosis of Seizures in the Elderly

Cardiovascular
- Reflex (vasovagal) syncope (including micturition and cough syncope)
- Carotid sinus hypersensitivity (a variant of reflex syncope)
- Orthostatic hypotensive syncope (autonomic failure or vasodilator medication)
- Cardiac arrhythmogenic syncope (especially scar-related ventricular tachycardia)
- Structural heart disease

Medications
- Hypotensive agents (β-blockers and calcium channel antagonists) causing orthostatic hypotension
- Alcohol (especially alcohol withdrawal) causing acute symptomatic seizures

Neurological
- Limb-shaking TIA
- Movement disorders
- Migraine
- Transient global amnesia

Endocrine & Metabolic
- Hypoglycemia
- Hypocalcemia
- Hypomagnesemia

Sleep Disorders
- Hypnic jerks
- Obstructive sleep apnea
- Periodic leg movements of sleep
- Rapid eye movement sleep behavior disorder

Psychological
- Psychological nonepileptic attacks (panic disorder or dissociative disorder)
- Factitious disorder

Antiepileptic Drugs (AED)

Self Assessment Question
Which of the following statements is true?
A. Older AEDs are more effective than newer AEDs
B. All commonly used AEDs have similar efficacy in the elderly
C. Newer AEDs are more effective than older AEDs
D. Efficacy of AEDs changes with age
Management of Epilepsy in the Elderly

• Multidisciplinary approach should be used
• Antiepileptic drugs (AED) are the mainstay of therapy
• Characteristics of an ideal AED
  – Achieves seizure control
  – Well tolerated
  – Limited side-effect profile
  – Easy dosing
  – Free of drug-drug interactions
• All commonly used AEDs appear similarly effective for seizure control in the elderly
  – Choice of AED depends primarily on tolerability
  – Newer AEDs having inert metabolites and limited drug interactions should be considered over older AEDs

Pharmacokinetic and Pharmacodynamic Alteration in the Elderly

<table>
<thead>
<tr>
<th>Physiology</th>
<th>Changes in the Elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Absorption</td>
<td>• Decreased absorption</td>
</tr>
<tr>
<td></td>
<td>• Delayed esophageal emptying</td>
</tr>
<tr>
<td></td>
<td>• Altered gastric pH</td>
</tr>
<tr>
<td>Drug Distribution</td>
<td>• Decreased albumin and degree of protein binding</td>
</tr>
<tr>
<td>Metabolism and Excretion</td>
<td>• Decreased hepatic metabolism</td>
</tr>
</tbody>
</table>

Considerations for AED selection in the elderly

• Adjust renally-cleared AED dose based on CrCl
• Select AEDs that have little or no protein binding
• Select AEDs that do not require metabolism for therapeutic effect
• Select AEDs that have limited drug interactions
• Start low and go slow

Summary of Common Older AEDs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Main clinical benefit</th>
<th>Cautionary note in elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td>Acute use</td>
<td>Idiosyncratic reactions, psychosis and sedation</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Effective in partial onset seizures</td>
<td>Enzyme inducer interacts with other AEDs, some antibiotics and warfarin Hyponatremia can occur, especially with diuretics</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Acute use</td>
<td>Zero-order kinetics, no care is needed in making dose changes Enzyme inducer Interacts with digoxin and warfarin</td>
</tr>
<tr>
<td>Vaziproate</td>
<td>Effective in generalized onset seizures Few interactions</td>
<td>Absence and tonic may be troublesome Can cause reversible EPS</td>
</tr>
</tbody>
</table>
Summary of Common Newer AEDs

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<thead>
<tr>
<th>Drug</th>
<th>Main clinical benefit</th>
<th>Cautionary note in elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>Used for neuropathic pain. Limited efficacy in epilepsy</td>
<td>Can cause dizziness, sedation and weight gain</td>
</tr>
<tr>
<td>Esticarbazine</td>
<td>Few interactions, rapid metabolism, lack of drug interactions</td>
<td>Hyponatremia can occur</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>Current use as an add-on AED</td>
<td>Increased risk of PR interval prolongation on ECG, contraindicated in 2nd and 3rd degree AV block</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Effective in partial onset seizures</td>
<td>Requires slow dose titration to avoid serious adverse effects, especially in patients already taking valproate</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Inert metabolite</td>
<td>Motor and behavior disturbances occur occasionally</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Few interactions, rapid metabolism, lack of drug interactions</td>
<td>Hyponatremia can occur, especially with thiazide diuretics</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Used for neuropathic pain. Limited drug interactions</td>
<td>Can cause dizziness and weight gain</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Also approved for migraine prophylaxis</td>
<td>Can cause weight loss and cognitive problems</td>
</tr>
</tbody>
</table>


Benzodiazepines

<table>
<thead>
<tr>
<th>Drug Type: Not for</th>
<th>Benzodiazepines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Select Drug Intervention: (AED)</td>
<td>(Gabapentin, lamotrigine, oxcarbazepine)</td>
</tr>
<tr>
<td>Comment:</td>
<td>Hyponatremia and seizures associated with antiepileptic use</td>
</tr>
</tbody>
</table>

Carbamazepine

<table>
<thead>
<tr>
<th>Dose Type: Used for</th>
<th>Carbamazepine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Select Drug Intervention: (Mood stabilizer, anticonvulsant, proconvulsant drug)</td>
<td>(Carbamazepine)</td>
</tr>
<tr>
<td>Comment:</td>
<td>Hyponatremia and seizures associated with antiepileptic use</td>
</tr>
</tbody>
</table>


Eslicarbazepine

- **Adverse Effects**
  - GI: Nausea, vomiting
  - CNS: Dizziness, somnolence
  - Dose-dependent: Aminoglycosides, amphotericin (intravenous only), calcium channel blockers
  - Drug interactions: CYP3A4 inhibitors (e.g., clarithromycin, itraconazole) may reduce levels of eslicarbazepine, requiring higher doses or additional monitoring
  - Adverse effects: Sialorrhea, peripheral edema

- **Contraindications**
  - Pregnancy class C
  - Lactation: Use with caution

- **Drug Interactions**
  - CYP3A4 inhibitors: Reduce levels of eslicarbazepine, may require dose adjustment
  - Avoid concomitant use with amphotericin B (intravenous only)
  - Use with caution with other drugs that are metabolized by CYP3A4

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Ethosuximide

- **Adverse Effects**
  - CNS: Nervous system depression
  - Dizziness
  - Drowsiness
  - Somnolence

- **Contraindications**
  - Pregnancy class B
  - Lactation: Use with caution

- **Drug Interactions**
  - CYP3A4 inhibitors: May reduce ethosuximide levels

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Ezogabine

- **Adverse Effects**
  - CNS: Nervous system depression
  - Somnolence
  - Sedation

- **Contraindications**
  - Pregnancy class C
  - Lactation: Use with caution

- **Drug Interactions**
  - CYP3A4 inhibitors: May reduce ezogabine levels

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**Felbamate**

<table>
<thead>
<tr>
<th>Category</th>
<th>Use in</th>
<th>Contraindications/Warnings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tmax</td>
<td>Absence tonic-clonic (lost tone), simple or complex partial with or without secondary generalized tonic-clonic seizures</td>
<td></td>
</tr>
<tr>
<td>Tmax</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tmax</td>
<td>Adverse Effects</td>
<td></td>
</tr>
<tr>
<td>Tmax</td>
<td>Subjective: headache, dizziness, nausea, anorexia, dyspepsia, and vomiting</td>
<td></td>
</tr>
<tr>
<td>Tmax</td>
<td>Objective: no significant changes</td>
<td></td>
</tr>
<tr>
<td>Tmax</td>
<td>Drug Interactions (Use in drug-drug interaction)</td>
<td></td>
</tr>
<tr>
<td>Tmax</td>
<td>Subjective: CYP3A4 inhibition, CYP2C9 inhibition</td>
<td></td>
</tr>
<tr>
<td>Tmax</td>
<td>Objective: no significant changes</td>
<td></td>
</tr>
<tr>
<td>Tmax</td>
<td>Comments</td>
<td></td>
</tr>
<tr>
<td>Tmax</td>
<td>Generic available</td>
<td></td>
</tr>
<tr>
<td>Tmax</td>
<td>Requires laboratory monitoring. See our chart. Lab monitoring for Common Adverse Events</td>
<td></td>
</tr>
<tr>
<td>Tmax</td>
<td>Requires oral dose adjustment. Cautioned to patients with a history of hepatic dysfunction or blood dyscrasia</td>
<td></td>
</tr>
</tbody>
</table>

**Gabapentin**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Tmax</td>
<td>Simple or complex partial with or without secondary generalized seizures</td>
<td></td>
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<tr>
<td>Tmax</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tmax</td>
<td>Adverse Effects</td>
<td></td>
</tr>
<tr>
<td>Tmax</td>
<td>Subjective: nausea, dizziness, somnolence, fatigue, weakness, paresthesia, tremor, dysgeusia, weight gain, edema</td>
<td></td>
</tr>
<tr>
<td>Tmax</td>
<td>Objective: no significant changes</td>
<td></td>
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<tr>
<td>Tmax</td>
<td>Drug Interactions (Use in drug-drug interaction)</td>
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<td>Requires laboratory monitoring. See our chart. Lab monitoring for Common Adverse Events</td>
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<tr>
<td>Tmax</td>
<td>Requires oral dose adjustment.</td>
<td></td>
</tr>
<tr>
<td>Tmax</td>
<td>Associated with behavioral changes, mainly in children</td>
<td></td>
</tr>
<tr>
<td>Tmax</td>
<td>Other uses: prophylactic treatment, reflex leg syndromes, fibromyalgia, leg cramps, epicondylitis lateral</td>
<td></td>
</tr>
<tr>
<td>Tmax</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Lacosamide**

<table>
<thead>
<tr>
<th>Category</th>
<th>Use in</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Tmax</td>
<td>Simple or complex partial</td>
<td></td>
</tr>
<tr>
<td>Tmax</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tmax</td>
<td>Adverse Effects</td>
<td></td>
</tr>
<tr>
<td>Tmax</td>
<td>Subjective: dizziness, diplopia, headache, vertigo, insomnia, drowsiness, fatigue, nausea, vomiting, weight gain</td>
<td></td>
</tr>
<tr>
<td>Tmax</td>
<td>Objective: no significant changes</td>
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<tr>
<td>Tmax</td>
<td>Drug Interactions (Use in drug-drug interaction)</td>
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</tr>
<tr>
<td>Tmax</td>
<td>Comments</td>
<td></td>
</tr>
<tr>
<td>Tmax</td>
<td>Requires dose adjustment for renal and/or hepatic impairment</td>
<td></td>
</tr>
<tr>
<td>Tmax</td>
<td>Common side effects: dizziness, diplopia, headache, nausea</td>
<td></td>
</tr>
</tbody>
</table>
Lamotrigine

**Use**: Mono- or polytherapy in the treatment of partial seizures (with or without secondary generalization).

**Dosage**: Initial: 25 mg once/day; may be doubled weekly up to 200 mg/day. Maintenance: 100 to 200 mg/day.

**Adverse Effects**: Rash, headache, dizziness, nausea, vomiting, ataxia, diplopia, diplopia, blurred vision, fatigue, drowsiness, dizziness, and balance disruption.

**Interactions**: None significant.

**Comments**: Need for close monitoring. May cause drowsiness and dizziness.

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Levetiracetam

**Use**: Primary generalized tonic-clonic seizures, secondarily generalized tonic-clonic, simple or complex partial.

**Dosage**: Initial: 500 mg/day; may be increased to 1000 mg/day.

**Adverse Effects**: No significant drug interactions.

**Interactions**: None significant.

**Comments**: May cause drowsiness and dizziness.

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Oxcarbazepine

**Use**: Primary or polytherapy in the treatment of partial seizures (with or without secondary generalization).

**Dosage**: Initial: 200 mg once/day; may be doubled weekly up to 1200 mg/day.

**Adverse Effects**: Rash, headache, dizziness, nausea, vomiting, ataxia, diplopia, diplopia, blurred vision, fatigue, drowsiness, dizziness, and balance disruption.

**Interactions**: None significant.

**Comments**: Need for close monitoring. May cause drowsiness and dizziness.
**Perampanel**

*Indicated for:* Partial onset seizures with or without secondary generalization (adult and pediatric patients).

**Side Effects:**
- Central nervous system disturbances
- Dizziness
- Somnolence

**Drug Interactions:**
- Lowered plasma levels: carbamazepine, lamotrigine, zonisamide
- Increased plasma levels: valproic acid

**Common:**
- Common side effects: nausea, vomiting, rash, abdominal pain, edema, hypotension, decreased sodium, weight gain
- Intracranial hypertension: not related to co-administered medications
- Rare: death in a 3-month-old infant

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**Phenobarbital/Primidone**

*Indicated for:* Seizures in adults and children 6 months of age and older

**Side Effects:**
- Drowsiness
- Somnolence
- Nystagmus
- Hypotonia

**Drug Interactions:**
- Increased plasma levels: ethosuximide, carbamazepine, phenytoin, lamotrigine

**Common:**
- Gastrointestinal disturbances
- CNS: drowsiness, dizziness, sleep disturbances
- Neurologic: tremors, ataxia
- Hepatobiliary: jaundice

---

**Phenytoin/Fosphenytoin**

*Indicated for:* Seizures in adults and children 6 months of age and older

**Side Effects:**
- Gastrointestinal disturbances
- CNS: drowsiness, dizziness, sleep disturbances
- Neurologic: tremors, ataxia
- Hepatobiliary: jaundice

**Drug Interactions:**
- Increased plasma levels: ethosuximide, carbamazepine, phenytoin, lamotrigine

**Common:**
- Gastrointestinal disturbances
- CNS: drowsiness, dizziness, sleep disturbances
- Neurologic: tremors, ataxia
- Hepatobiliary: jaundice

---

**Combination of Antiepileptic Drugs**

**Phenobarbital/PHT**

- Lowered plasma levels: lamotrigine

**Phenobarbital/Primidone**

- Increased plasma levels: ethosuximide, carbamazepine, phenytoin, lamotrigine

**Phenytoin/Fosphenytoin**

- Increased plasma levels: ethosuximide, carbamazepine, phenytoin, lamotrigine
Phenytoin/Fosphenytoin (Con’t)

- Drug information:
  - Phenytoin/fosphenytoin is a medication used to treat seizures. It is available in both oral and intravenous forms.
  - Fosphenytoin is a prodrug of phenytoin and is used in the emergency treatment of seizures. It is converted to phenytoin in the body.
  - Phenytoin can be given to adults and children, while fosphenytoin is primarily used in emergency situations.
  - Side effects of phenytoin include drowsiness, dizziness, blurred vision, and rash. Fosphenytoin may cause headache and vomiting.

Pregabalin

- Drug information:
  - Pregabalin is a medication used to treat nerve pain caused by diabetes, shingles, and certain types of arthritis. It is also used to treat anxiety disorders.
  - Common side effects of pregabalin include dizziness, sedation, dry mouth, diarrhea, blurred vision, weight gain, and cognitive impairment.
  - Other side effects include tingling in the arms and legs, loss of coordination, and changes in body temperature.

Rufinamide

- Drug information:
  - Rufinamide is a medication used to treat seizures in people who have not responded well to other antiepileptic drugs. It is available in oral form.
  - Common side effects of rufinamide include sedation, dizziness, fatigue, constipation, and confusion.
  - Rufinamide may also cause changes in behavior and mood, and can rarely cause more serious side effects such as liver problems.
### Tiagabine

<table>
<thead>
<tr>
<th>Side Effects/Adverse Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Nausea, dizziness, headache, insomnia, fatigue, suicidal ideation</td>
<td>Infrequent</td>
</tr>
<tr>
<td>- Less sedation and weight changes than gabapentin</td>
<td>Infrequent</td>
</tr>
<tr>
<td>- May cause a decrease in plasma levels with concomitant use of cytochrome P450 (CYP) inhibitors</td>
<td>Infrequent</td>
</tr>
<tr>
<td>- Intestinal bowel syndrome (IBS)</td>
<td>Infrequent</td>
</tr>
<tr>
<td>- Sinus bradycardia</td>
<td>Infrequent</td>
</tr>
<tr>
<td>- Possibly reduces efficacy if taken with valproate</td>
<td>Infrequent</td>
</tr>
</tbody>
</table>

### Topiramate

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### Valproic Acid/Valproate/Divalproex

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<td>- Possibly reduces efficacy if taken with valproate</td>
<td>Infrequent</td>
</tr>
</tbody>
</table>

These drugs may also interact with other medications, so it is important to consult with a healthcare provider before making any changes to your medication regimen.
Zonisamide

**Seizure Efficacy**
- Single or complete partials with or without secondary generalization (infantile) 1

**Seizure Adverse Effects**
- Nausea 2
- Multi-organ hypersensitivity 3
- Rhabdomyolysis/damage to kidneys 4
- Metabolic acidosis 5
- Hypotension and hypothermia (tends to diminish) 6

**Selected Drug Interactions**

<table>
<thead>
<tr>
<th>Drug Interaction</th>
<th>Use Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td>- Typically activating meds</td>
</tr>
<tr>
<td>TCAs</td>
<td>- Use caution in hepatic impairment</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>- Typical &gt; atypical?</td>
</tr>
<tr>
<td>Sympathomimetics</td>
<td>- Theophylline, pseudoephedrine, caffeine, Ritalin</td>
</tr>
<tr>
<td>- Many others implicated</td>
<td>- Risk not assessed</td>
</tr>
<tr>
<td>- Muscle relaxants, albuterol, EIOH, anticholinergics, ondansetron, Pitocin, lithium (elev.conc)</td>
<td></td>
</tr>
</tbody>
</table>

**Evaluate for Medications that Lower Seizure Threshold**

- When possible, avoid the use of medications that lower seizure threshold. If the medication is necessary, may need to adjust AED dose. Counsel patient and caregivers that breakthrough seizures may occur.

- Medications that lower seizure threshold include:
  - Antibiotics
  - Beta-lactams; Quinolones
  - Antidepressants
  - Typically activating meds
  - TCAs
  - Antipsychotics (typical > atypical?)
  - Sympathomimetics
  - Theophylline, pseudoephedrine, caffeine, Ritalin
  - Many others implicated (risk not assessed)
  - Muscle relaxants, albuterol, EIOH, anticholinergics, ondansetron, Pitocin, lithium (elev.conc)

**Non-drug treatment**

- Ketogenic diet – aka "Johns Hopkins Diet"
  - Complete seizure remission ~ 15%, reduction in occurrence ~ 90%
  - 4:1 ratio of fats to protein
  - Mechanism unknown; children may have stunted growth and early hyperlipidemia

- Yoga
  - Pranayama, Dhyana, Asanas

- EEG Biofeedback

- Neutraceuticals – Valerian root, kava kava

- Accupuncture
Summary

- Epilepsy is the most common serious neurological disorder in the elderly after stroke and dementia
- Old age is the time of life when seizures, unprovoked or associated with acute illness, are most common
- Epilepsy in the elderly is potentially life threatening
- Stroke is the leading cause of new-onset epilepsy beyond 65 years of age
- There is little research to underpin best epilepsy management in the elderly
- Overall goals of management are:
  - Maintenance of seizure freedom without medication side effects
  - Maintenance of a normal lifestyle
  - Unchanged or improved quality of life

Summary (Con’t)

- Ideal AED
  - Achieves seizure control
  - Well-tolerated
  - Few side effects
  - Easy dosing
  - Free of drug-drug interactions
- All commonly used AEDs have similar efficacy in the elderly
- Newer AEDs with benefits of inert metabolites and limited drug interactions should be considered first-line
- Elderly people with epilepsy are equally, if not more, vulnerable than younger patients to the psychological and psychosocial consequences

Thank You!