Incidence: 0.5% - 1.0% of U.S. population

Peak incidence of onset: first 2 years of life, ages 5-7 years, early puberty and elderly.

125,000 new cases/year

- 30% in patients < 18 year  Generalized > partial seizures
- 25% in patients > 65 year  Partial > Generalized

Epilepsy: not a simple disease, but a symptom of disturbed electrical activity in the brain caused by a wide variety of disorders

Seizure: results from an excessive discharge of neurons and is characterized by changes in electrical activity as measured by electroencephalogram (EEG). In addition, there may be disturbances in consciousness, sensory symptoms, subjective well-being and objective behavior.

10% of population will have a seizure during their lifetime: identifiable insult vs. idiopathic causes.

Factors predisposing to epilepsy

1. genetics
2. head trauma
3. brain tumors
4. cerebrovascular disease
5. infection
6. alcohol and drug withdrawal
7. idiopathic (70%)

SEIZURES IN THE ELDERLY

A. Etiology

1. idiopathic 48.9%
2. vascular (eg. stroke) 32.4%
3. degenerative (eg. Alzheimer’s) 11.5%
4. traumatic (eg. subdural hematomas) 3.3%
5. neoplastic 2.7%
6. metabolic/chemical
B. Disease/Organ failures that may increase susceptibility to seizures in the elderly

1. Atherosclerotic cardiovascular disease
2. Cancer of various organs
3. Metastatic disease to the CNS
4. Systemic hypercoagulability
5. Renal failure
6. Diabetes mellitus

C. Difficulties with Diagnosis

1. Seizures misdiagnosed as TIAs or dementia
2. Intermittent confusion/stereotyped movements common in the elderly and misdiagnosed as seizures

C. Consequences

1. Loss of independence and self-esteem
2. Falls and fractures secondary to seizures

SEIZURE TYPES

1. Generalized Seizures
   a. Tonic-Clonic Seizures (grand mal)
      - Aura
      - Tonic/clonic
      - Post ictal
   b. Absence (petit mal)
   c. Atonic/Akinetic
   d. Myoclonic
   e. Infantile spasms

2. Partial Seizures
   a. Simple
   b. Complex
   c. Simple and complex partial seizures that can secondarily generalize
3. STATUS EPILEPTICUS

2 or more repetitive seizures without consciousness or single seizure over 30 minutes long. Medical emergency to prevent brain damage.

10 – 30% of elderly patients present with tonic-clonic SE as first episode

FIRST SEIZURES: DECISION TO TREATMENT

1. Rule out and treat underlying cause if possible

2. Treat only if seizures recur
   67% to 83% recurrence in elderly

3. Abnormal EEG

4. History of previous cerebral insult

PRINCIPLES OF ANTIEPILEPTIC THERAPY

1. Select proper medication for type of epilepsy

2. Use one antiepileptic medication until therapeutic effect is achieved or toxic signs occur.

3. Monitor blood levels of antiepileptic drugs: phenytoin, phenobarbital carbamazepine, valproate, ethosuximide,

4. If inadequate control is achieved with primary medication, add second drug and decrease first

5. Monotherapy best, however polytherapy is sometimes necessary.
   a. drug interactions
   b. side effects

6. Epilepsy is not a commitment to life long drug therapy with young; however with elderly patients, relapses are common if AEDs are withdrawn.
POST STROKE SEIZURES

A. POSSIBLE CEREBROVASCULAR MECHANISMS

1. Hypoxia-hypoperfusion

2. Cerebrovascular hemorrhage
   a. usually produces seizures at onset
   b. cortical involvement predisposes to seizures

3. Cerebral Infarction
   majority of seizures occur at onset or within 24 hours of infarction

4. Late Neuronal changes
   a. persistence of underperfused tissue
   b. development of epileptogenic structural changes in cortical neurons

B. INCIDENCE OF POST-STROKE SEIZURES

1. one seizure: = 5-10% of patients with stroke
   recurrent seizures (epilepsy) ≤ 8%

2. Risk factors for seizures
   a. cortical involvement
   b. hemorrhagic instead of infarct
   c. lesions involving more than one lobe

3. Risk factors for epilepsy

   Berges et al. Seizures and Epilepsy following Strokes: recurrence Factors
   *Eur Neurol* 2000;43:3-8

   n = 3,206 patients admitted for stroke over 10 year period

   159 first-ever seizures (5%)
   Early onset ≤ 14 days: (1.8%)
   Late onset: > 14 days    (3.2%)

   Recurrence:
   Early onset ≤ 14 days: 34%
   Late onset: > 14 days    72%

   No effect of treatment with AEDs

Conclusion:
   a. late onset of 1st seizure ( > 14 days)
   b. hemorrhagic component
   c. occipital involvement
C. APPROACH TO POST-STROKE AED TREATMENT

1. Control of persistent or recurrent seizures (ie, status epilepticus)
2. Prevention of seizures within the first 24-48 hours of stroke
3. Prevention of seizures within the first 2 weeks of stroke
4. Prevention of recurrence of seizures ≥ 2 weeks after stroke, or the appearance of late onset seizures
5. Treatment after early seizure??


N=61 patients with early stroke seizure
Group 1: 35 treated (CBZ = 24, VPA =9, PHT=2) for 2 years
Group 2: No treatment

Results:
Seizure free rate during 2 years of treatment: Group 1: 81%  Group 2: 61%  (p=0.042)
Seizure rate during next 2 years:  Group 1: 4.8%  Group 2: 6.2%  (p=0.605)

USE OF AEDS IN ELDERLY


Methods: Computerized evaluation of medical records throughout the US
N = 43,757 and N = 41,386

Results:

a. 10.5% of residents received an AED
   age 65-84: 15% received AED
   age > 85: 6% received AED
b. Gender effect: Males: 13.4%  Females 9.4%
c. Most common AEDs:
   Phenytion > Carbamazepine > Phenobarbital > Clonazepam > Valproic acid
d. Average number of meds: If taking an AED: n = 5.6  No AED: n = .6
AGE RELATED CHANGES IN PHARMACOKINETICS/PHARMACODYNAMICS

Pharmacodynamic: possible changes in receptor sensitivity and altered response to drugs
(no data for AEDs)

Pharmacokinetic: Physiologic changes that may alter drug disposition: absorption, distribution, excretion and metabolism

**ABSORPTION**

1. ↑ gastric pH
2. ↓ GI motility
3. ↓ absorptive surface
4. ± splanchnic blood flow

No changes in extent of absorption with age of AEDs

**DISTRIBUTION**

1. ↑ percentage of body fat
2. protein binding changes:
   a. ↓ albumin concentrations (phenytoin, carbamazepine, valproic acid)
   b. ± alpha-1-acid glycoprotein (carbamazepine)
      (disease vs. age effect no clear)

**METABOLISM**
1. ↓ hepatic mass
2. ↓ hepatic metabolism capacity (primarily phase I), smaller effects of glucuronidation
3. Will affect drugs that are eliminated by CYP450 metabolism:
   - Phenytoin, carbamazepine, valproic acid, phenobarbital, felbamate, tiagabine
4. Phenytoin example

<table>
<thead>
<tr>
<th>AGE (years)</th>
<th>$V_{\text{max}}$ (mg/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5-3</td>
<td>18.3</td>
</tr>
<tr>
<td>4-6</td>
<td>18.5</td>
</tr>
<tr>
<td>7-9</td>
<td>10.1</td>
</tr>
<tr>
<td>10-18</td>
<td>11.8</td>
</tr>
<tr>
<td>20-39</td>
<td>7.5</td>
</tr>
<tr>
<td>40-59</td>
<td>6.6</td>
</tr>
<tr>
<td>69-79</td>
<td>6.0</td>
</tr>
</tbody>
</table>

$V_{\text{max}}$ measure of enzymatic capacity of the liver

EXCRETION

1. ↓ renal blood flow
2. ↓ tubular secretion
3. ↓ Glomerular filtration rate

   Gabapentin is only AED almost 100% really excreted
   Levetiracetam, oxcarbazepine, phenobarbital, oxcarbazepine (MDH metabolite) are both renal and hepatic cleared and doses need to be reduced in elderly.

DOSAGE TITRATION IN THE ELDERLY: “Start low and go slow”

1. Loading doses usually not different
2. Maintenance doses may be similar
3. Adjust doses to patient response, not to arbitrary “therapeutic range”
   do to changes in protein binding, total plasma concentrations will not reflect unbound or active plasma concentrations in the elderly.
DOSING CONSIDERATIONS IN THE ELDERLY

PHENYTOIN

1. 90% bound to serum albumin  
   a. ↓ protein binding results in change in ratio of unbound phenytoin to total phenytoin  
   b. use unbound phenytoin concentrations if available  
   c. equation to predict effects of low albumin on total phenytoin measurement  
      \[ C_{\text{calc}} = \frac{C_{\text{obs}}}{0.25 \cdot ALB + 0.1} \]

Anderson et al. Ann Pharmacotherapy 1997;31:279-284

N=37 nursing home patients  
Measured albumin, total and unbound phenytoin plasma concentrations  
Therapeutic range: Total phenytoin 10 – 20 mg/ml  
unbound phenytoin 1 -2 mg/ml  
Results:  
Of the 37 nursing home patients evaluated  
Albumin concentration ranged from 2.7 to 3.4 gm/dl  
5 patients had total phenytoin concentration > 20mg/ml  
However 11 patients had unbound phenytoin concentrations > 2.0mg/ml  

2. Maximum rate of metabolism (Vmax) declines gradually with age  
   metabolism because saturable at lower concentrations in the elderly  
3. Broad spectrum inducers of CYP450s and UGT enzymes  
4. Toxicity: Common dose related toxicity is ataxia – dangerous for elderly patient  
5. a. Loading doses: 18-20 mg/kg  
      If given P.O.: saturable absorption > 400 mg divide doses and give q 3h  
      b. Maintenance doses: 4-5mg/kg/day (young adults: 300 - 400 mg/day)  
      Smaller maintenance doses for elderly  
      Relatively small changes in dose (< 10%) are recommended  
      c. PHOSPHENYTOIN: injectable form of phenytoin can be used IV push or IM  
         i) Can be safely mixed with all diluents  
         ii) Neutral pH  
         iii) Puritis

CARBMAZEPINE

1. Both carbamazepine and its active metabolite, carbamazepine epoxide are 68-85% bound to albumin and α₁-acid glycoprotein  
2. Broad spectrum hepatic inducer and autoinduction requires slow titration  
3. Hepatic metabolism is reduced by as much as 40% in elderly
4. Total carbamazepine plasma concentrations do not reflect the same unbound carbamazepine concentrations as found in younger adults due to ↓ protein binding.

5. Efficacy: seizure disorders, as well as pain and manic-depression.

6. Adverse effects: Rash and blood dyscrasias (leukopenia) incidence may be higher in elderly. Mild diplopia or blurred vision usually precedes ataxia as typical dose-related toxicity in elderly.

7. Dosing: young adults
   a) Start at 200 mg BID
      a. due to autoinduction, N/V
      b. increase 200 mg daily every 3-5 days until seizure control or toxicity
   b) Max = 800-1200mg per day
      a. some have used up to 1800mg/day
   c) Usually need tid to qid dosing except with sustained release formulations.
   d) Once daily is not tolerated and associated with large fluctuations in plasma levels
   e) Dosage requirements reduced by as much as 40%

**OXCARBAZEPINE**

1. Indication: Monotherapy and adjunctive therapy for partial seizures

2. A pro-drug analogue of carbamazepine:

3. Rapidly converted to a monohydroxy derivative (MHD) by a non-CYP metabolism (active). MHD is 50% glucuronide conjugated and 50% excreted unchanged.

4. No autoinduction, but does induce CYP3A4 and UGT (less than CBZ) and inhibits CYP219.

5. Adverse effects: Decreased incidence or rash compared to carbamazepine, but may have higher incidence of hyponatremia.

7. Dosing:
   a. Adults: 300 - 600 mg BID (1.5 x CBZ)
      Increase weekly as needed
   b. Decrease renal clearance in elderly expected, so reduce target dose by 50% for estimated CrCl ≤ 30 ml/min.
      - When switching CBZ to OXC, in young adults, OXC doses are 50% higher.
      It is recommended to use 20% for the elderly

**VALPROIC ACID**

1. Highly protein bound to albumin (>90%) and saturable

2. No change in total clearance with increasing age; increase in protein binding due decreased albumin offsets decrease in intrinsic clearance:
   a. Total plasma concentrations do not reflect the same unbound valproic acid concentrations found in younger adults due to decreased albumin
   b. Neurotoxicity has been reported with total valproate concentrations within the
therapeutic range in patients with hypoalbuminemia
3. No major drug interactions with other non-AED meds
4. Toxicity: primarily GI, minimal CNS, weight gain, Dose-limiting toxicity maybe lethargy, fatigue and tremor (can be hard to recognize in elderly patient)
5. Efficacy in seizure disorders.
7. Dosing
   Valproic acid - Depakene capsules, syrup (Na+ salt)
   Depakox sodium = Depakote capsules.
   equal mix of Na+ VPA and VPA acid in enteric coated capsules
   (250mg,500mg VPA equivalence) slow absorption, possibly less GI upset
   Generics: Na valporate
   Adults: 15-45 mg/kg/d bid-tid
   Start 25-30% target dose to avoid GI side effects and drowsiness
   Increase 25-30% every 7 days until target dose is reached

PHENOBARBITAL

1. Not extensively bound to plasma proteins
2. Both renal and hepatic elimination
3. Elimination maybe reduced in the elderly
4. Lower initial maintenance doses recommended, if used at all.
5. High incidence of CNS adverse effects in elderly patients including paradoxical hyperactivity

LAMOTRIGINE

1. Monotherapy and adjunctive therapy for partial seizures w and w/o 2° generalization
2. Not extensively bound to plasma proteins
3. Eliminated by hepatic glucuronide conjugation (phase II)
4. Half-life in elderly is similar to young adults
5. Toxicity: High incidence of skin rash in combination therapy with valproic acid
   Minor visual adverse effects are usually first signs of dose-related toxicity preceding ataxia
6. Brodie et al. 150 elderly patients
   - LTG vs. CBZ in newly diagnosed epilepsy
   - Rash rate: LTG 3% vs. CBZ 19%
   - Somnolence: LTG 12% vs. CBZ 29%
   - Drop-out rate adverse effects:
     LTG 18% vs. CBZ 42%
   - Efficacy
     No difference in time to first seizure
     Pts. seizure free for 16 wks. LTG 39% CBZ 21%
     Patients continued on therapy: LTG 71% CBZ 42%
8. Dosing: Start very low and go very very slow, if used.
a. Start at initial dose at 50-100 mg/day; then titrate to maintenance dose of 100-400 mg/d given qd or bid.
b. For patients on concurrent valproic acid: start at an initial dose of 25 mg/d; then titrate to maintenance dose of 50-200 mg/d given qd or bid.
c. Dosage adjustments not necessary in the elderly

9. Advantage: broad spectrum AED similar to valproic acid
   - Patients often report improved alertness and a feeling of well-being
   - Lack of total sedating properties
   - Lack of drug interactions on other drugs

GABAPENTIN

1. Indication: Adjunctive therapy for partial seizures
2. More patients on gabapentin for “pain” than for seizures
3. Toxicity: dizziness, somnolence or fatigue, usually mild
4. Completely eliminated by the kidneys
5. Clearance highly correlated with creatinine clearance
6. Not protein bound
7. May need to start with lower doses in elderly due to decreased GFR
8. Advantages: No drug interactions and low toxicity
9. Gabapentin Withdrawal syndrome has been reported on rapid withdrawal of therapy.

<table>
<thead>
<tr>
<th>Creatinine Clearance (ml/min)</th>
<th>Total Daily Dose (mg)</th>
<th>Dosage Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60</td>
<td>1200</td>
<td>400 mg TID</td>
</tr>
<tr>
<td>30-60</td>
<td>600</td>
<td>300 mg BID</td>
</tr>
<tr>
<td>15-30</td>
<td>300</td>
<td>300 mg daily</td>
</tr>
<tr>
<td>&lt; 15</td>
<td>150</td>
<td>300 mg QOD</td>
</tr>
</tbody>
</table>

TOPIRAMATE

1. Indication: Adjunctive therapy for adults with partial onset seizures
2. Eliminated by both hepatic metabolism and renal excretion of unchanged topiramate
3. Minimal protein binding
4. Relationship between plasma concentrations and effect/toxicity not clear
5. One of the more potent new AEDs in refractory partial-onset seizures
6. 8% increase in concentration/dose ratio per 10 years of life
7. Toxicity: High incidence of cognitive adverse effects; slowed thinking, fatigue, slowed speech and memory complaints are common.
8. Dosing needs to start low and go very very slow to avoid CNS side effects
   a. start on 25 mg qD, increase weekly by 25-50 mg/day until maximum of 200-600 mg/day
**TIAGABINE**

1. Eliminated by hepatic metabolism
2. Highly protein bound to albumin
3. Relationship between plasma concentrations and effect/toxicity not clear
4. Toxicity: fatigue, headache and dizziness
5. Tiagabine pharmacokinetics is not different between young and elderly patients
6. Dosing needs to start low and go very very slow to avoid CNS side effects
   - Initiate therapy: 5 mg/d given TID, increase q week by 5 mg/d to decrease CNS effects.

**LEVETIRACETAM**

1. Indication: Adjunctive therapy for partial seizures
2. Adverse effects in clinical trials: All within first month
   - CNS: somnolence and fatigue (15%)
   - Coordination difficulties
   - Behavioral abnormalities
   - Of 347 elderly subjects in clinical trials, there were no differences between toxicity in young and old
3. Predominately renal elimination (66%) with non CYP or UGT enzymatic hydrolysis
4. No drug interactions
5. Pharmacokinetics determined in 16 elderly subjects (61-88 yrs) with CrCl from 39-74 ml/min
   - total clearance decreased by 38% and T1/2 increased correlated with CrCl
   - Adjust doses if decreased renal function with age only
6. Dosing: Initiate at 500 mg bid, increase as needed q 2 weeks to max of 3000 mg/day

**ZONISAMIDE**

1. Indication: Adjunctive therapy for partial onset seizures
2. Adverse effects in clinical trials:
   - CNS: somnolence, headache and fatigue
   - GI: N/V, anorexia
   - Renal calculi (3%) all males in study
   - Need to maintain adequate fluid intake
   - Rash: Zonisamide is a sulfonamide: avoid in patients with sulfonamide allergy
3. Eliminated by combination of renal and hepatic metabolism. CYP3A4
4. Drug Interactions
   - Zonisamide does not affect other drugs
   - Enzyme inducers (PHT, CBZ, PB) will decrease Zonisamide plasma concentrations.
5. Single dose pharmacokinetics were similar in young and elderly subjects
6. Dosing: Initiate at 50-100 mg qd or bid, increase as needed q 1-2 weeks to
max of 600 mg/day

**Adverse Effects of Antiepileptic Drugs: Traditional**

<table>
<thead>
<tr>
<th>AED</th>
<th>Dose-Dependent</th>
<th>Non-Dose Dependent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>Nystagmus</td>
<td>Gingival Hyperplasia</td>
</tr>
<tr>
<td></td>
<td>Ataxia</td>
<td>Increase in body hair</td>
</tr>
<tr>
<td></td>
<td>Cognitive Impairment</td>
<td>Coarsening of facial Features</td>
</tr>
<tr>
<td></td>
<td>Lethargy</td>
<td>Acne</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Folate Deficiency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Skin Rash</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td>Ataxia</td>
<td>Fluid retention (hyponatremia)</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Blurred or double vision</td>
<td>Leukopenia</td>
</tr>
<tr>
<td></td>
<td>Lethargy</td>
<td>Bone marrow depression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Skin Rash</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GI irritation</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>GI upset</td>
<td>Weight Gain</td>
</tr>
<tr>
<td></td>
<td>Lethargy</td>
<td>Alopecia</td>
</tr>
<tr>
<td></td>
<td>Tremor</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperammonemia</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>GI upset</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Drowsiness</td>
<td>Skin Rash</td>
</tr>
<tr>
<td></td>
<td>Hiccups</td>
<td></td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Sedation</td>
<td>Hyperactivity</td>
</tr>
<tr>
<td></td>
<td>Cognitive impairment</td>
<td>Sleep problems</td>
</tr>
<tr>
<td></td>
<td>Hyperactivity</td>
<td>Skin rashes</td>
</tr>
<tr>
<td></td>
<td>Behavioral difficulties</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ataxia</td>
<td>Hepatotoxicity</td>
</tr>
</tbody>
</table>
### Adverse Effects of Antiepileptic Drugs: New Agents

<table>
<thead>
<tr>
<th>AED</th>
<th>Dose-dependent</th>
<th>Non-Dose dependent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Felbamate</td>
<td>GI upset</td>
<td>Aplastic anemia</td>
</tr>
<tr>
<td></td>
<td>Anorexia/Weight loss</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Insomnia</td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Ataxia</td>
<td>Weight gain</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nystagmus</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Ataxia</td>
<td>Skin Rash</td>
</tr>
<tr>
<td></td>
<td>Blurred or double vision</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GI upset</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Insomnia</td>
<td></td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Dizziness</td>
<td>Hyponatremia</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>Skin Rash</td>
</tr>
<tr>
<td></td>
<td>Sedation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sedation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diplopia</td>
<td></td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>GI upset</td>
<td>Weight loss</td>
</tr>
<tr>
<td></td>
<td>Sedation</td>
<td>Acute myopia and secondary angle closure glaucoma</td>
</tr>
<tr>
<td></td>
<td>Diplopia</td>
<td></td>
</tr>
<tr>
<td>Tiagabine</td>
<td>Dizziness</td>
<td>Exacerbation of generalized seizures</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Difficulty w/ concentration</td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>Sedation</td>
<td>Weight loss</td>
</tr>
<tr>
<td></td>
<td>Confusion</td>
<td>Acute myopia and secondary angle closure glaucoma</td>
</tr>
<tr>
<td></td>
<td>Mental slowing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Word finding difficulties</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anorexia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Parasthesias</td>
<td></td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Somnolence</td>
<td>Renal stones/Calculi</td>
</tr>
<tr>
<td></td>
<td>Ataxia</td>
<td>Liver toxicity</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>Leukopenia</td>
</tr>
<tr>
<td></td>
<td>Anorexia</td>
<td>Oligohidrosis/hyperthermia (peds)</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td></td>
</tr>
</tbody>
</table>
Effects of Traditional AEDs on Hepatic Enzymes

<table>
<thead>
<tr>
<th>AED</th>
<th>Effect on Hepatic Enzymes</th>
<th>Enzymes Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Inducer</td>
<td>CYP2C, CYP3A4, UGT</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Inducer</td>
<td>CYP2C, CYP3A4, UGT</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Inducer</td>
<td>CYP2C, CYP3A4, UGT</td>
</tr>
<tr>
<td>Valproate</td>
<td>Inhibitor</td>
<td>CYP2C9, UGT, Epoxide Hydrolase</td>
</tr>
</tbody>
</table>

Effects of New AEDs on Hepatic Enzymes

<table>
<thead>
<tr>
<th>AED</th>
<th>Effect on Hepatic Enzymes</th>
<th>Enzymes Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Felbamate</td>
<td>Inhibitor, Inducer</td>
<td>CYP2C19, β-oxidation, CYP3A4</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Weak Inducer</td>
<td>UGT</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Inducer, Inhibitor</td>
<td>CYP3A4, UGT, CYP2C19</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>Inducer, Inhibitor</td>
<td>β-oxidation, CYP2C19</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Zonisamide</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>