Neurology and The Older Adult
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Learning Objectives
At the conclusion of this application-based activity, participants should be able to:
1. List the common causes of mental status changes seen in older adults with delirium.
2. Select appropriate treatment for targeted symptoms in delirium.
3. Identify the key monitoring parameters for antiepileptic drugs.
4. Evaluate a given antiepileptic regimen in an older adult for efficacy and toxicity.

The 3 D’s of Geriatric Psychiatry

- Delirium
- Dementia
- Depression

Delirium
- Present in up to 50% of hospitalized elderly
- On admission present in 8-17% of all elderly and 40% of nursing home (NH) residents
- Associated with poor outcomes
  - Increased length of stay
  - Functional decline
  - Dementia
  - Nursing home/rehab placement
  - Mortality
  - Increased healthcare cost
  - ~$164 billion per year in United States

Delirium Prevalence Increases with Age

Prevalence of Delirium Increases with Age

Delirium Prevalence by Age
Duration and Caues of Delirium

- Prospective 2 year study in a 650 bed extended-stay geriatric medical center in N = 322 patients
- Delirium found in 34% (n = 109)
- Causes
  - 58% infection
  - 36% metabolic
  - 18% drug-induced
- Duration
  - Mean 16 days; Range 2 to 96 days

Predictors of Duration of Delirium

- Prospective 2 year study in a 650 bed extended-stay geriatric medical center in N = 322 patients; delirium found in 34% (n = 109)
- Duration
  - Mean 16 days; Range 2 to 96 days
- Predicting variables of duration:
  - Female
  - Infection
  - Number of comorbidities (especially presence of congestive heart failure)
  - W/o stroke
  - Advanced age
  - elevated BUN
  - BUN/SCr ratio (in US units)
  - Hypoalbuminemia

Outcomes in Delirium

- Prospective 2 year study in a 650 bed extended-stay geriatric medical center in N = 322 patients; delirium found in 34% (n = 109)
- Outcomes (n = 92)
  - Resolution 33%
  - Persistence 12%
  - Unchanged 8%
  - Mortality 48%
  - Infection related – 70%

Differentiating the 3 D’s

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Delirium</th>
<th>Depression</th>
<th>Anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute, rapid, sudden; hours to days</td>
<td>Acute, rapid, sudden; hours to days</td>
<td>Acute, rapid, sudden; hours to days</td>
<td></td>
</tr>
<tr>
<td>Fluctuates, waves and wanes</td>
<td>Fluctuates, waves and wanes</td>
<td>Fluctuates, waves and wanes</td>
<td></td>
</tr>
<tr>
<td>Confused, disoriented, with lucid periods</td>
<td>Confused, disoriented, with lucid periods</td>
<td>Confused, disoriented, with lucid periods</td>
<td></td>
</tr>
<tr>
<td>Present, often visual</td>
<td>Present, often visual</td>
<td>Present, often visual</td>
<td></td>
</tr>
<tr>
<td>Distracted, incorrect answers, concrete, language changes</td>
<td>Distracted, incorrect answers, concrete, language changes</td>
<td>Distracted, incorrect answers, concrete, language changes</td>
<td></td>
</tr>
<tr>
<td>Changes - disturbed, &quot;sundowning&quot;</td>
<td>Changes - disturbed, &quot;sundowning&quot;</td>
<td>Changes - disturbed, &quot;sundowning&quot;</td>
<td></td>
</tr>
<tr>
<td>Usually reversible</td>
<td>Usually reversible</td>
<td>Usually reversible</td>
<td></td>
</tr>
<tr>
<td>Prolonged hospitalization, increased mortality</td>
<td>Prolonged hospitalization, increased mortality</td>
<td>Prolonged hospitalization, increased mortality</td>
<td></td>
</tr>
<tr>
<td>Reverse cause if identified; antipsychotics</td>
<td>Reverse cause if identified; antipsychotics</td>
<td>Reverse cause if identified; antipsychotics</td>
<td></td>
</tr>
</tbody>
</table>

Delirium

- Symptoms: Acute, rapid, sudden; hours to days
- Symptom onset: Acute, rapid, sudden; hours to days
- Alertness: Fluctuates, waves and wanes
- Duration: Hours to weeks
- Orientation: Confused, disoriented, with lucid periods
- Hallucinations: Present, often visual
- Disabilities: Prolonged hospitalization, increased mortality
- Treatment: Reverse cause if identified; antipsychotics

Subtypes of Delirium

- Hyperactive: Pulling out lines, agitated, restless
- Hypoactive: Obtunded, withdrawal, flat affect, apathy, lethargy, reduced responsiveness
- Mixed

www.icudelirium.org/docs/CAM_ICU_training.pdf
Delirium Diagnosis

DSM-5
- Attention disturbance
- Develops over a short period of time
- Fluctuates over the course of the day
- A change from baseline
- Evidence suggests it is a consequence of another medical condition or substance intoxication/withdrawal

ICD-10
- Impaired consciousness and attention
- Global cognitive disturbance
- Psychomotor changes
- Sleep-wake cycle changes
- Emotional Distress

Confused Assessment Method (CAM)
Diagnosis requires BOTH A and B
A. Acute onset and fluctuating course
   Evidence of an acute change from baseline?
   OR
   Fluctuated during the previous 24 hours?
   If NO
   - Negative
   If Yes
   - go to question 2
B. Inattention
   Squeeze my hand when I say the letter “A”
   S A V E A A R T
   0 – 2 errors
   - Negative
   > 2 errors
   - go to question 3
C. Disorganized thinking
   Thinking disorganized or incoherent?
   Examples: rambling speech, irrelevant conversation?
   Unpredictably switches subjects
   Illogical flow
   AND either C or D
D. Altered level of consciousness
   Current RASS or SAS level
   Any RASS other than 0 or SAS other than 4 positive
   Continue to question 4
E. Altered level of consciousness
   Ask: Will a stone float on water?
   Are there fish in the sea?
   Does one pound weigh more than two?
   Can you use a hammer to pound a nail?
   Set up this many fingers (hold up 2 fingers)
   Instruct them to “do the same with the other hand” without demonstrating
   • 1 error – suggestive of delirium
   • 0-1 error - Negative

CAM-ICU
1. Acute onset and fluctuating course
   Evidence of an acute change from baseline?
   OR
   Fluctuated during the previous 24 hours?
   If NO
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   If Yes – go to question 2
2. Inattention
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RASS = Richmond Agitation-Sedation Scale
SAS = Riker Sedation-Agitation Scale

Confusion Assessment Method - ICU

Duration and Causes of Delirium
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Causes of Altered Mental Status
***Often multi-factorial***
**Infection**

**Urinary Tract Infection**
- Know your local sensitivities
- Increasing resistance to SMZ/TMP and fluoroquinolones
- Psychiatric adverse effects of antibiotics
- Nitrofurantoin updated on Beers list

**Respiratory Infection**

**Wound Infection**

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**Case Vignette**

A 90+ year old female with dementia is referred from her NH for increasingly agitated behavior over the last week. She has developed a cough and is complaining of back pain. She was hospitalized within the last week for syncope. What do you recommend?

A. Chest X-ray and urinalysis to rule out infection
B. Initiate an antibiotic
C. Start scheduled ibuprofen
D. Start scheduled acetaminophen
E. Start olanzapine 2.5 mg at bedtime

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**Respiratory Infection**

This patient was transferred with an rx for levofloxacin 250 mg daily for pneumonia. She weighs ~ 45 kg; her SCr is 0.87 mg/dL (76.9 umol/L) and Cr/Cl 26 mL/min. Allergy to sulfa.

Which is the MOST appropriate dosing recommendation?

A. Levofloxacin 250 mg daily
B. Levofloxacin 500 mg daily
C. Levofloxacin 750 mg daily
D. Levofloxacin 500 mg every other day
E. Levofloxacin 750 mg every other day

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**Urinary Tract Infection + Pneumonia**

<table>
<thead>
<tr>
<th>Etest Susceptibility</th>
<th>Urine Culture</th>
<th>MIC&lt;br&gt;interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>S (= sensitive)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R (= resistant)</td>
<td>Med-Terp.</td>
<td></td>
</tr>
<tr>
<td>H (High Level Synergy)</td>
<td>N (not synergistic)</td>
<td></td>
</tr>
<tr>
<td>L (Low Level Synergy)</td>
<td>S (= sensitive)</td>
<td></td>
</tr>
</tbody>
</table>

What do you recommend?

A. Amoxicillin 500 mg every 8 hours
B. Amox/Clavulanate 500 mg every 12 hours
C. Amox/Clavulanate 875 mg every 12 hours
D. Vancomycin 1 G every 12 hours
E. Vancomycin 750 mg every 48 hours

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**Dehydration**

Look for symptoms of dehydration
- Reduced urination or urine output
- Dry cracked lips
- Skin tenting

In US units the BUN:SCr ratio of > 20:1 is considered pre-renal and can be associated with dehydration; however at baseline elderly may have an elevated BUN:Cr ratio secondary to reduced muscle mass

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**Electrolyte/Metabolic Imbalances**

- Hypercalcemia
- Hyperglycemia (Diabetic ketoacidosis)
- Hyperparathyroidism
- Hyperkalemia
- Hypernatremia
- Metabolic acidosis
- Hypoglycemia
- Hypokalemia
- Hyponatremia

Case Vignette – Hyponatremia and Altered Mental Status (AMS)

An 80+ year old patient with a history of schizoaffective disorder on an antipsychotic + mood stabilizer.

Alcohol Withdrawal Time Course

6-8 hrs
• Mild withdrawal – Mental status not altered
• Tremor, anxiety, nausea, tachycardia

6-48 hrs
• Seizures

12-48 hrs
• Moderate withdrawal - Hallucinations: visual, auditory and/or tactile
• Orientation still intact

48-96 hrs
• Severe withdrawal - Delirium tremens
• Confusion, tachycardia, agitation, hypertension, fever, diaphoresis

Alcohol Withdrawal

For elderly patients
• Lorazepam is preferred
• Chlordiazepoxide and diazepam are more likely to accumulate with their long t1/2 and active metabolites
  • These agents have ↓ in clearance by at least 50% and a 4-9x ↑ in half-life elimination
• Role of Thiamine?

Benzodiazepine Withdrawal

• Benzodiazepine withdrawal depends on the half-life of the medication
• Some present as early as 3 days after discontinuation others up to 2 weeks later
• Case Example – A 63 yo male presented as a Trauma – his home diazepam 5 mg TID PRN did not have this restarted on admission.
  • On ~ day 10 or 11 started exhibiting agitated intrusive behaviors, increased anxiety, 0-2 hours of sleep. Was very disoriented and wandering in hall. Noted to be having auditory, visual, and tactile hallucinations.
  • Agitation and orientation improved with lorazepam
  • Diazepam half-life is 44-48 hours; metabolite ~ 100 hours
  • Time to get out of system – 10 to 20 days and symptoms of withdrawal to begin

Delirium-inducing Medications

Case Vignette - Drug toxicity

75+ year old female with history of Neurocognitive disorder, depression, DM2, HTN, and chronic pain brought to ED for Altered Mental Status. Over last 2 weeks has had major changes including staying in bed all the time, poor sleep, appears confused intermittently, + auditory hallucinations of hearing angels, + visual hallucinations of seeing birds in the room and people in the room.

Symptoms appear even worse over the last 2 days. Other complaints include back pain (from arthritis) and a recent fall (X-ray negative for fracture). Denies constipation.

Labs: SCr 1.28 mg/dL [113.2 umol/L]; CrCl 28 mL/min; TSH 1.01 µU/mL; glucose 208 mg/dL [11.5 mmol/L]
Medication Reconciliation

Stable Home Medications

- Sertraline 150 mg daily
- Insulin 70/30 (Canada insulin 30/70) - 45 units in AM and 30 units HS
- Amlodipine 10 mg daily
- Oxycodone/Acetaminophen 5/325 – 2 tablets every 6 hours PRN pain
- Esomeprazole 20 mg daily
- Memantine 10 mg BID
- Gabapentin 100 mg TID
- Levothyroxine 50 mcg daily
- Lisinopril 40 mg daily

Recent Changes

21 days Prior to Admission:
- Fentanyl 50 mcg transdermal every 3 days
- Bupropion 75 mg BID
- Oxycodone/Acetaminophen 5/325 – 2 tablets every 6 hours PRN pain
- Memantine 10 mg BID
- Gabapentin 100 mg TID
- Lisinopril 40 mg daily

Anticholinergic Medications

Group Activity

List as many medications as you can with anticholinergic properties

Anticholinergic Medications

Anticholinergics

- Antihistamines
- H1 and H2 Antagonists
- Antispasmodics
- Antipsychotics
- Tricyclic Antidepressants

Anticholinergic Burden

- Salahudeen MS, et al. completed a systematic review of Anticholinergic Burden/Scoring Scales
- Identified 7 Anticholinergic Burden/Scoring Scales from 4 different countries
  - USA - Carnahan 2006 Anticholinergic Drug Scale identifies 117 anticholinergic medications
  - Reviewed consistency between scoring of each scale
  - Example quetiapine was rated high n = 1, moderate n = 1, low n = 2 scales

Beers List Delirium

- Meds that are potentially inappropriate:
- Antipsychotics (APs), anticholinergics, sedative/hypnotics (benzodiazepines and nonbenzodiazepines), meperidine, H1 receptor antagonists, H2 receptor antagonists, corticosteroids

- Rationale: May worsen delirium
- Recommendation: Avoid in older adults with or at high risk of delirium

Other Delirium Risk Factors

- Sleep deprivation
- Immobilization
- Pain
  - Untreated
  - Vs. side effects of narcotics
- Sensory deficits (e.g. provide hearing aids, eye glasses)
- History of delirium
- Environmental factors including external light, noise
Delirium Management Strategies

SCCM Guidelines 2013

- Does haloperidol treatment reduce duration of delirium?  
  No Evidence

- Does SGA treatment reduce duration of delirium?  
  Small (n=36), prospective, randomized, double-blind study – quetiapine  
  Reduced duration of delirium [Evidence Level C]

- Should cholinesterase inhibitors be used in delirium?  
  No Evidence

SCCM = Society of Critical Care Medicine; SGA = Second Generation Antipsychotic

Meta-Analysis of Antipsychotics in Delirium

- Meta-Analysis of 19 studies (n = number of trials)  
  - N = 7 Post-op prevention with antipsychotic vs placebo  
    Haloperidol (n = 4) 1 – 7.5 mg/day  
    Risperidone (n = 4) 1 mg/day  
    Olanzapine (n = 1) 1.5 mg/day
  
  - N = 12 Treatment Intervention (medical or surgical admissions; ICU [n = 5])  
    Haloperidol (n = 9) 0.75 mg – 20 mg/day  
    Ziprasidone (n = 3) 40 mg every 6 hrs  
    Risperidone (n = 2) 0.25 – 4mg/day  
    Quetiapine (n = 2) 25 – 400 mg/day
  
- Limited evidence to support routine use of antipsychotics (Evidence Level 2C)

Meta-Analysis Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Results</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-Operative Prevention (n = 170)</td>
<td>No significant association with antipsychotic (AP) administration and incidence of delirium</td>
<td>OR 0.55, CI= 0.23 – 1.34, P=93%</td>
</tr>
<tr>
<td>Duration (n = 581)</td>
<td>AP administration not associated with a difference in duration or severity - Mean difference in severity (-0.11)</td>
<td>CI= -1.59-0.29, I²=80%</td>
</tr>
<tr>
<td>ICU LOS (n = 1454)</td>
<td>Hospital mean difference -0.01 days - ICU mean difference -0.46 days</td>
<td>CI= -0.16-0.14, P=42% CI= -0.15-0.24, P=91%</td>
</tr>
<tr>
<td>N = number of participants; OR = Odds Ratio; CI = 95% confidence interval; LOS = length of stay; ICU = intensive care unit</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Role of Antipsychotics?

- Severe agitation risking patient safety
- Example post op and not following movement restrictions
- Pulling out essential lines
- Psychotic symptoms causing severe distress
- If indicated
  - Lowest possible dose
  - Short therapy (days)

Case Vignette

78 yr female with osteoporosis and hypertension admitted following a fall requiring hip replacement surgery. Day 3 post-op develops “confusion” and is tearing out IV lines and keeps trying to get out of bed and stand on hip.


Do you suggest?

A. Lorazepam 0.5 mg IV
B. Quetiapine 25 mg PO
C. Ziprasidone 10 mg IM
D. Risperidone 0.5 mg IM
E. Haloperidol 0.25 mg IV

Anticholinergic Activity of Antipsychotics

<table>
<thead>
<tr>
<th>Medication</th>
<th>Anticholinergic Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>Moderate</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>High</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Low</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>None</td>
</tr>
<tr>
<td>Risperidone</td>
<td>None</td>
</tr>
</tbody>
</table>

Antipsychotic Dosing PRN Delirium

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage Form</th>
<th>Route</th>
<th>Onset/Time to peak</th>
<th>Initial</th>
<th>PRN Frequency</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>Tab, PO</td>
<td>PO</td>
<td>30 – 60 mins</td>
<td>PO/IM/IV</td>
<td>0.25 mg</td>
<td>Every 4 – 6 hrs</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Injection</td>
<td>IM</td>
<td>0.5 mg</td>
<td>0.5-2 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Tab, SR</td>
<td>PO</td>
<td>≤ 60 mins</td>
<td>PO: 0.25-0.5 mg</td>
<td>Every 6 hrs</td>
<td>**Do not combine with benzos</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Cap, Injection</td>
<td>PO with food</td>
<td>≤ 60 mins</td>
<td>PO: 20 mg</td>
<td>Every 4-6 hrs</td>
<td>Do not use if recent MI or QTc prolong</td>
</tr>
</tbody>
</table>

PO olanzapine and ziprasidone not ideal. *If use olanzapine suggest the ODT = orally disintegrating form

Lexi-Drugs, 2017


Case Vignette – Back to NH

78 yr female discharged back to nursing home after hip replacement surgery complicated by delirium. She returns to nursing home with the following new medications:

- Enoxaparin 30 mg every 12 hours
- Oxycodone 5/325 0.5 tablet every 4 hours PRN
- Oxycodone 5/325 1 tablet every 6 hours PRN
- Quetiapine 25 mg at bedtime
- Docusate 100 mg at bedtime

Open discussion

Case Vignette

85+ year old AAF with a PMH of A.Flutter, TIA, hyperlipidemia, HTN and DM presents with altered mental status over the past month, escalating in the past few days. Recent behaviors include episodes of hollering, trying to throw self out of bed/wheelchair, and general disorientation.

HPI: 1 week ago was diagnosed and treated for UTI with ciprofloxacin 500 mg BID; U/A was sensitive to fluoroquinolones.

1 month ago started on diltiazem and rivaroxaban for A.Flutter
**Case Vignette - Labs**

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Urea Nitrogen (BUN)</td>
<td>142 mmol/L</td>
</tr>
<tr>
<td>Creatinine</td>
<td>108 mmol/L</td>
</tr>
<tr>
<td>Sodium</td>
<td>142 mmol/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.0 mmol/L</td>
</tr>
<tr>
<td>Glucose</td>
<td>28 mmol/L</td>
</tr>
<tr>
<td>Calcium</td>
<td>1.8 mg/dL</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>13.4 mmol/L</td>
</tr>
<tr>
<td>AST</td>
<td>242 mg/dL</td>
</tr>
<tr>
<td>ALT</td>
<td>25 mg/dL</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>280 mg/dL</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>159.16 mg/dL</td>
</tr>
</tbody>
</table>

AST 100 units/L; ALT 119 units/L; total Bili 0.3 mg/dL

Repeat glucose 310 mg/dL

CBC

- WBC = 4.5 x 10^3/mm^3 [10,9 L]
- Hgb = 8.7 g/dl [87g/L]
- HCT = 25.6% [0.256]
- PLT = 253 x 10^3/mm^3 [10^9/L]

U/A no infection noted; protein (+); glucose 150 mg/dL [8.3 mmol/L]

CXR: Within Normal Limits (WNL)

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**Case Vignette – Medication List**

What additional information would you like?

- acetaminophen 650 mg – 1 tab PO every 4 hours PRN pain
- acetaminophen-OXYcodeine 325 mg-5 mg - 1 tab, PO, every 6 hours, PRN severe pain
- amlopidine 5 mg PO daily
- aspirin EC 81 PO daily
- bisacodyl 10 mg per rectum daily, PRN constipation
- calcium carbonate 500 mg 2 tabs every 4 hours, PRN indigestion
- cholecalciferol 400 i.u. PO daily
- diltiazem 180 mg PO, daily
- insulin glargine 10 Units SQ daily
- metoprolol tartrate 50 mg PO BID
- phenytoin 100 mg – 3 capsules PO daily
- pravastatin 10 mg PO bedtime
- rivaroxaban 15 mg PO before dinner
- senna 1 tab PO bedtime, PRN constipation

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**Case Vignette**

What additional information would you like?

Head CT Impression:

No CT evidence of acute intracranial abnormality.

Phenytoin level 29.7 mg/L [118.8 umol/L]

Delirium secondary to phenytoin toxicity

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**Antiepileptics**

Identify the key monitoring parameters for antiepileptic drugs.

Evaluate a given antiepileptic regimen in an older adult for efficacy and toxicity.

---

**Epilepsy in the Elderly**

- Risk factors/Causes
  - Stroke
  - Up to 50% of new diagnoses
  - Dementia (late stage)
  - Approximately 20% of late-onset epilepsy
  - Head trauma
  - Intracranial hemorrhage
  - Brain tumors
  - Meningitis or viral encephalitis
  - Alcohol withdrawal

- Primarily associated with Focal Epilepsy

---

**Epilepsy in the Elderly**

- Epilepsy incidence is bimodal peak during childhood; second peak later in life
- 30% of new epilepsies present in older adults
- In > 70 yo prevalence is twice that of children
- Rate increases every decade after 60
  - Rate of > 100-159/100,000

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- Primarily associated with Focal Epilepsy
2016 Expert Opinion - Elderly

- Focal seizures
  - Medically stable elderly
  - Preferred lamotrigine and levetiracetam
  - Second-line or equivocal: lacosamide
- Genetically mediated (idiopathic generalized)
  - Preferred lamotrigine and levetiracetam
  - Second-line: valproic acid, zonisamide, and topiramate
- Changes since 2001 Expert Opinion
  - In the elderly
  - Increase in preference for lamotrigine and levetiracetam
  - Decline in preference of phenytoin, oxcarbazepine, gabapentin and carbamazepine


Epilepsy in Alzheimer’s

- Seizures occur more frequently in Alzheimer’s than regular elderly population
  - Beta amyloid plaques and tau proteins may promote cortical excitability
- Medications that affect seizure threshold
  - Antipsychotics reduce seizure threshold
  - Controversy regarding cholinesterase inhibitors and memantine
- Cognitive adverse effects of Antiepileptics
  - Phenobarbital – significant cognitive worsening as compared to levetiracetam (mild improvement) and lamotrigine (mild impairment)
- Preference for lamotrigine or levetiracetam
  - Note valproic acid has been found to be inferior to carbamazepine in focal epilepsy


Epilepsy – Treat or Not to Treat?

- Indicated when risk of recurrent seizures is unacceptably high
- After 2 unprovoked seizures occurring over 24 hours apart risk increases significantly
- In the elderly recurrent seizure risk is increased with a structural etiology and neuroimaging abnormalities
- If a definitive etiology is identified (e.g. post-stroke) consider initiating treatment after the 1st seizure


Status Epilepticus (SE)

- Estimated annual incidence is 86/100,000 in elderly, twice that of adult population


Initial Management of Status Epilepticus in Elderly

- First-line: Benzodiazepines
  - IM midazolam may be equivalent or superior to lorazepam, however was primarily patients <60 yo
  - IV lorazepam
  - Lorazepam is preferred over diazepam duration of action is 12-24 hrs vs 15-30 mins respectively
  - Intranasal or buccal midazolam, parenteral or rectal diazepam, or clonazepam
- Second-line:
  - Phenytoin/fosphenytoin or VPA in theory the agents of choice based on evidence
  - Levetiracetam or lacosamide potential alternatives
  - Phenobarbital generally not favorable in elderly

Non-Epilepsy Uses of Antiepileptics

- Bipolar disorder
- Migraine prophylaxis
- Seizure prevention following neurosurgery
- Restless legs syndrome
- Neuropathic pain
  - Post herpetic neuralgia
  - Trigeminal neuralgia
  - Diabetic peripheral neuropathy
  - Phantom limb syndrome

Antiepileptics

- Carbamazepine (CBZ)
- Phenobarbital (PB)
- Primidone (PRM)
- Phenytoin (PHT)
- Valproic Acid (VPA)
- Ethosuximide (ESX)
- Felbamate (FLB)
- Gabapentin (GBP)
- Lamotrigine (LMT)
- Levetiracetam (LEVE)
- Oxcarbazepine (OXC)
- Pregabalin (PRG)
- Topiramate (TOP)
- Zonisamide (ZON)

Newer Approvals

- 2016 Brivaracetam (BRV)
- 2016 Carbamazepine IV
- 2013 Eslicarbazepine (ESLC)
- 2012 Perampanel (PRPL)
- 2011 Clobazam (CLOB)
- 2011 Ezogabine (EZO)
- 2009 Vigabatrin (VIG)
- 2008 Rufinamide (RUF)
- 2008 Lacosamide (LAC)

Reduction in Oral Clearance in Elderly

<table>
<thead>
<tr>
<th>Medication</th>
<th>Reduction in CL/F (mL/h/kg) in elderly vs. young</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brivaracetam</td>
<td>8%</td>
<td>Initial dose 25 mg BID, max 75 mg BID ~ 50-59% ↑ in exposure hepatic impair</td>
</tr>
<tr>
<td>Eslicarbazepine</td>
<td>No change</td>
<td>Mean age just under 70 years in one study</td>
</tr>
<tr>
<td>Felbamate</td>
<td>20-30%</td>
<td>PK variability affected by enzyme inducers</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>30-50%</td>
<td>CL/F shows strong correlation with CrCl</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>15-25%</td>
<td>N/A</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>20-35%</td>
<td>PK variability affected by drug interactions</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>20-60%</td>
<td>PK variability affected by enzyme inducers</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>25-35%</td>
<td>PK variability affected by enzyme inducers</td>
</tr>
<tr>
<td>Perampanel</td>
<td>Insufficient data</td>
<td>Study did include patients up to 74 years</td>
</tr>
</tbody>
</table>

Reduction in Oral Clearance in Elderly

<table>
<thead>
<tr>
<th>Medication</th>
<th>Reduction in CL/F (mL/h/kg) in elderly vs. young</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregabalin</td>
<td>30-50%</td>
<td>CL/F shows strong correlation with CrCl</td>
</tr>
<tr>
<td>Retigabine</td>
<td>30%</td>
<td>N/A</td>
</tr>
<tr>
<td>Rufinamide</td>
<td>No Change</td>
<td>Single dose study including patients 66-77 years</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>30%</td>
<td>PK affected by enzyme inducers</td>
</tr>
<tr>
<td>Topiramate</td>
<td>20%</td>
<td>PK affected by enzyme inducers</td>
</tr>
<tr>
<td>5-Vigabatrin</td>
<td>50-90%</td>
<td>Based on a single-dose study that included elderly patients with renal impairment</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>No change</td>
<td>Study inclusion mean age just under 70 Years PK variability affected by enzyme inducers</td>
</tr>
</tbody>
</table>

It is important to calculate creatinine clearance with the following AEDs:

- Eslicarbazine
- Gabapentin
- Lacosamide
- Levetiracetam
- Pregabalin
- Topiramate
- Zonisamide

https://www.centerwatch.com/drug-information/fda-approved-drugs/therapeutic-area/10/neurology
Dosage Adjustment in Renal Impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>50 or 60-80 mL/min</th>
<th>Moderate 30-50 or 35-59 mL/min</th>
<th>Severe &lt; 30 mL/min</th>
<th>Dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Use with caution</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eslicarbazine</td>
<td>↓ dose by 50%</td>
<td></td>
<td>Same as 50</td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>500-700 mg/48 hrs</td>
<td>200-700 mg/24 hrs</td>
<td>&lt; 150-150 mg/day</td>
<td></td>
</tr>
<tr>
<td>Lacosamide</td>
<td>↓ dose Max 300 mg/day</td>
<td>Supplement up to 50% of dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>500-1000 mg every 12 hrs</td>
<td>250-750 mg every 12 hrs</td>
<td>250-500 mg every 24 hrs</td>
<td>500-1000 mg every 24 hrs</td>
</tr>
<tr>
<td>Perampanel</td>
<td>Not recommended</td>
<td></td>
<td></td>
<td>Not rec'd</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>&lt; 10 mL/min every 12-16 hrs</td>
<td>&lt; 40 mL/min every 12-16 hrs</td>
<td>50% dose reduction</td>
<td></td>
</tr>
</tbody>
</table>

Pregabalin
- 50% of dose 2-3x/day max 300 mg
- 15-30: 25% of dose 1-2x/day max 150 mg
- 5-12: 25-75 mg/day
- 25-75mg/day Post-dialysis supplementation

Primidone
- 10-50 mL/min every 12-24 hrs
- 10-30: every 12-24 hrs
- < 10: every 24 hrs

Rufinamide
- Adjust dose for loss during dialysis

Topiramate
- If < 70% 50% of the dose
- 50% of the dose
- Supplemental dose may be needed

Zonisamide
- < 50 mL/min use not recommended


High Protein Binding

- Phenytoin 90%
- Perampanel 95%
- Tiagabine 96%
- Valproic Acid ~ 90%

VERSUS
- Carbamazepine 70-80%
- Lamotrigine 50%
- Levetiracetam negligible

AED Drug Interactions

- Major enzyme inducers
  - Phenytoin – CYP 1A2, 2C19, 3A4, UGT, P-gp
  - Phenobarbital – CYP 1A2, 3A4, UGT, P-gp
  - Carbamazepine – CYP 1A2, 2C9/19, 3A4, UGT
  - Oxcarbazepine – CYP 3A4
  - Valproic Acid – CYP 2C19

- Minor enzyme inducers
  - Lamotrigine – UGT (low)
  - Minor enzyme inhibitors
  - Valproic Acid – UGT (low)

Therapeutic Drug Monitoring

<table>
<thead>
<tr>
<th>Drug</th>
<th>PHT</th>
<th>PB</th>
<th>VPA</th>
<th>CBZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapeutic</td>
<td>10-20 mg/L</td>
<td>15-40 mg/L</td>
<td>50-100 mg/L</td>
<td>4-12 mg/L</td>
</tr>
<tr>
<td>Range USA</td>
<td>*Free: 1-2 mg/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range Canada</td>
<td>40-80 umol/L</td>
<td>60-160 umol/L</td>
<td>350 – 700 umol/L</td>
<td>20-50 umol/L</td>
</tr>
<tr>
<td>Order a phenobarbital level to monitor primidone (range 5-12 mg/L; 20-48 umol/L) as roughly 15-25% metabolized to PB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Order a phenobarbital level to monitor primidone (range 5-12 mg/L; 20-48 umol/L) as roughly 15-25% metabolized to PB |

AED Black Box Warnings

<table>
<thead>
<tr>
<th>Medication</th>
<th>Black Box Warning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Serious rash and HLA B*1502 allele</td>
</tr>
<tr>
<td></td>
<td>Aplastic anemia and agranulocytosis</td>
</tr>
<tr>
<td>Valproic Acid</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Serious rash</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>Vision loss</td>
</tr>
<tr>
<td>Perampanel</td>
<td>Psychiatric and Behavioral Disturbances</td>
</tr>
</tbody>
</table>


HLA-B*1502

- Boxed warning on CBZ since 2008
- HLAB*1502 was associated with CBZ induced SJS/TEN 92.3% (24/26) vs 11.9% of controls OR 89.95 CI 19.25-413.83
  - 46.7 % (7/15) phenytoin
  - 33% of VPA (1/3) and of LMT (2/6)
  - 0% of PB, gabapentin or levetiracetam induced
- More recent study in Han Chinese found also associated with SJS/TEN:
  - oxcarbazepine (OR= 80.7, 95%CI 3.8-1714, p=<0.005)
  - phenytoin (OR= 5.1, 95% CI 1.8-15.1, p=<0.005)
  - lamotrigine (OR= 5.1, 95% CI 0.8-33.8, p=0.127)


AED Black Box Warnings

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<td>Aplastic anemia and agranulocytosis</td>
</tr>
<tr>
<td>VPA</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td>LMT</td>
<td>Serious rash</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>Vision loss – can cause permanent bilateral concentric constriction of the visual field in ≥30% of patients; tunnel vision can occur, can damage central retina, reduce visual acuity.</td>
</tr>
</tbody>
</table>

Perampanel Psychiatric and Behavioral Disturbances


AEDs and Fractures

- Long recognized increased risk of fractures with antiepileptic medications
- Reduced bone-mineral density (BMD)
- Enzyme Inducers: phenytoin, carbamazepine, phenobarbital, oxcarbazepine
- ? Valproic Acid
- Preliminary studies did not find an association with lamotrigine or levetiracetam on BMD
- Low Vitamin D levels
- Increased falls
- Management
  - Screening: DXA scan hip, femur, lumbar; vitamin D levels
  - Calcium and Vitamin D supplementation
  - Bisphosphonates


AED Monitoring Parameters

<table>
<thead>
<tr>
<th>Medication</th>
<th>Weight</th>
<th>Rash</th>
<th>CBC w/diff</th>
<th>BMP</th>
<th>LFTs</th>
<th>EKG</th>
</tr>
</thead>
<tbody>
<tr>
<td>PB</td>
<td>Decr</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>PM</td>
<td>Incr</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>VPA</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>CBZ</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>OXC</td>
<td>Incr</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>TPR</td>
<td>Incr</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>FLB</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
</tbody>
</table>

Monitor labs at baseline and periodically every 6-12 months.
CBC Concerns with AEDs

<table>
<thead>
<tr>
<th>WBC</th>
<th>H/H</th>
<th>PLT</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHT</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>PB and PM</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>CBZ</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>VPA</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OMC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FLB</td>
<td>↓ or ↑</td>
<td>↓</td>
<td>Aplastic anemia</td>
</tr>
<tr>
<td>ZON</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>ESX</td>
<td>↓</td>
<td></td>
<td>↓</td>
</tr>
<tr>
<td>RJF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLOB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESLC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRV</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CBC = Complete Blood Count; WBC = white blood cells; H/H = hemoglobin/hematocrit; PLT = Platelets

Efficacy Monitoring

- Seizure free
- Reduced frequency

Antiepileptic Withdrawal

- If symptomatic etiology (e.g. stroke, tumor) – lifelong therapy is recommended
- Can be considered in carefully selected patients
  - Benefit – reduced pill burden, avoid side effects
  - Risk – reemergence of seizures
    - Overall risk 20 – 50%
    - Carefully selected patients < 15%
- Bryson et al. recommends a minimum of 2 years of seizure-free
- Taper slowly over months

AED Case Vignettes

Evaluate a given antiepileptic regimen in an older adult for efficacy and toxicity.

Case Vignette

85+ year old AAF with a PMH of A.Flutter, TIA, hyperlipidemia, HTN and DM presents with altered mental status over the past month, escalating in the past few days. Recent behaviors include episodes of hollering, trying to throw self out of bed/wheelchair, and general disorientation.

HPI: 1 week ago was diagnosed and treated for UTI with ciprofloxacin 500 mg BID; U/A was sensitive to fluoroquinolones.
1 month ago started on diltiazem and rivaroxaban for A.Flutter

Case Vignette - Labs

<table>
<thead>
<tr>
<th>Labs:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>142 mmol/L</td>
<td>108 mmol/L</td>
</tr>
<tr>
<td>4.0 mmol/L</td>
<td>28 mmol/L</td>
</tr>
<tr>
<td>159.16 µmol/L</td>
<td>242 mg/dL</td>
</tr>
<tr>
<td>AST 100 units/L; ALT 119 units/L; total Bili 0.3 mg/dL.</td>
<td></td>
</tr>
<tr>
<td>Repeat glucose 306 mg/dL [17 mmol/L]</td>
<td></td>
</tr>
</tbody>
</table>

CBC:
WBC = 4.5 x 10⁹/mm³ [10⁹/L], Hgb = 8.7 g/dL [87g/L], HCT = 25.6 % [0.256] PLT = 253 x 10⁹/mm³ [10⁹/L]
U/A no infection noted; protein (+); glucose 150 mg/dL [8.3 mmol/L]
CXR: within normal limits
Case Vignette – Medication List

• acetaminophen 650 mg – 1 tab PO every 4 hours PRN pain
• acetaminophen-OXycodone 325 mg:5 mg - 1 tab, PO, every 6 hours, PRN severe pain
• amlodipine 5 mg PO daily
• Aspirin EC 81 PO daily
• bisacodyl 10 mg per rectum daily, PRN constipation
• calcium carbonate 500 mg 2 tabs every 4 hours, PRN indigestion
• cholecalciferol 400 i.u. PO daily
• diltiazem 180 mg PO, daily
• insulin glargine 10 Units SQ daily
• metoprolol tartrate 50 mg PO BID
• phenytoin 100 mg – 3 capsules PO daily
• pravastatin 10 mg PO bedtime
• senna 1 tab PO bedtime, PRN constipation
• rivaroxaban 15 mg PO before dinner
• metoprolol 50 mg PO daily
• pravastatin 10 mg PO bedtime
• rivaroxaban 15 mg PO before dinner
• senna 1 tab PO bedtime, PRN constipation

Case Vignette

What additional information would you like?

Head CT Impression:
• No CT evidence of acute intracranial abnormality.

Phenytoin level
• Admission 29.7 mg/L [118.8 umol/L] at 12:46 pm
• Day 3 at 6:00 am 20.1 mg/L [80.4 umol/L]
• Day 7 11.6 mg/L [46.4 umol/L]

Free Phenytoin
• Day 3 at 12 pm 3.9 mg/L [15.6 umol/L]
• Day 7 1.5 mg/L [6 umol/L]

Phenytoin vs. Free Phenytoin

Role of Free PHT Monitoring

• Phenytoin is 90% bound to albumin
• Free phenytoin crosses the BBB and can cause toxicity
• Symptomatic phenytoin toxicity can be experienced even at “normal” PHT levels in the presence of hypoalbuminemia and hyperbilirubinemia
• If free PHT levels not available, check albumin levels and calculate a corrected PHT level


Corrected Total Phenytoin Level

• Original Winter-Tozer Equation

\[
\text{Corrected phenytoin} = \frac{\text{Measured phenytoin}}{0.3 \times \text{albumin} + 0.1}
\]

• Controversies
  • Revised Winter-Tozer equation suggests a coefficient of 0.25 for elderly patients as more accurate

Symptoms of Phenytoin Toxicity

• CNS Depression
  • 5-15 mg/L [20 – 60 umol/L] mild
  • Mild sedation, inability to concentrate, confusion, coma
  • Nystagmus
  • 15 – 20 mg/L [60 – 80 umol/L] far lateral; mild
  • 20 – 30 mg/L [80 – 120 umol/L] nystagmus
  • > 50 mg/L (> 200 umol/L) straight ahead
  • Mild nystagmus is not generally thought to be a toxic symptom
  • > 20 mg/L [> 80 umol/L] ataxia, impairment in motor function, falls, slurred speech
  • > 40 mg/L [> 160 umol/L] lethargy and confusion

Phenytoin Drug Interactions

MAJOR Substrate of CYP2C19, CYP2C9 and minor CYP3A4
Inducer of 2B6, 2C19, 2C9, 3A4, P-glycoprotein, UGT1A1

Increase PHT Concentrations
- Amiodarone
- Cimetidine
- Disulfiram
- Folic Acid
- Fluconazole
- Fluoxetine
- Isoniazid
- Sulfonamides (CYP and protein binding)
- Ticlopidine
- Trimethoprim
- Phenobarbital

Decrease PHT Concentrations
- Ciprofloxacin
- Rifampin
- Phenobarbital

Protein Binding
- Salicylates
- Valproic acid
- Decreased absorption
- Antacids

Murphy JI, Clinical Pharmacokinetics 3rd ed. ASHP

Phenytoin Drug Interactions

MAJOR Substrate of CYP2C19, CYP2C9 and minor CYP3A4
Inducer of 2B6, 2C19, 2C9, 3A4, P-glycoprotein, UGT1A1

Increase PHT Concentrations
- Amiodarone
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- Disulfiram
- Folic Acid
- Fluconazole
- Fluoxetine
- Isoniazid
- Sulfonamides (CYP and protein binding)
- Ticlopidine
- Trimethoprim
- Phenobarbital

Calcium Channel Blockers
- Diltiazem weakly inhibits CYP2C9 and CYP2D6; moderately inhibits CYP3A4

Ciprofloxacin potent CYP1A2; weak CYP3A4

Decrease PHT Concentrations
- Ciprofloxacin
- Rifampin
- Phenobarbital

Protein Binding
- Salicylates
- Valproic acid
- Decreased absorption
- Antacids

Phenytoin & Phenobarbital: Interactions with Anticoagulants

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Metabolism</th>
<th>Combine with Phenobarbital?</th>
<th>Combine with Warfarin?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>MAJOR CYP2C9, minor CYP3A4</td>
<td>↓ INR</td>
<td>↑ INR, ↑ PHT levels &amp; toxicity*</td>
</tr>
<tr>
<td>NOACs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Primarily Pgp</td>
<td>Noval</td>
<td>Noval</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>MAJOR CYP3A4</td>
<td>Noval</td>
<td>Noval</td>
</tr>
<tr>
<td>Apixaban</td>
<td>MAJOR CYP3A4</td>
<td>Noval</td>
<td>Noval</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Primarily Pgp</td>
<td>Monitor</td>
<td>Monitor</td>
</tr>
</tbody>
</table>

PHT: CYP2C9 inducer, CYP3A4 inducer; Pgp inducer
PB: CYP2C9 inducer, CYP3A4 inducer
* Reports of doubling of PHT levels

LexiDrugs 2017

Case Vignette

- 84 year old F with a PMH seizures, hyperlipidemia, diabetes, HTN, and arthritis is develops a pulmonary embolism during hospitalization for an upper respiratory infection
- Current medications:
  - Phenobarbital 34. BID
  - Phenytoin 300 mg daily alternating with 400 mg daily
  - Pravastatin 40 mg at bedtime
  - Lisinopril 10 mg daily
  - Pioglitazone 15 mg daily
  - Acetaminophen 650 mg TID
- What oral anticoagulant do you recommend?

Long Term Effects of Phenytoin

- Hypertrichosis – excessive hair growth
- Coarsening of facial features
- Folate deficiency
- Glucose intolerance
- Gingival hyperplasia
- Vitamin D deficiency
- Osteomalacia

Phenobarbital Toxicity

- Lethargy
- Coma
- Reduced pupillary light reflex
- Nystagmus
- Strabismus
- Vertigo
- Slurred speech
- Ataxia
- Reduced deep tendon reflexes
- Impaired cognition
- Respiratory depression
- HR changes
- Hypotension
- Skin “barbiturate blisters”

Emedicine.Medscape.com/article/813155 Barbiturate Toxicity
Lamotrigine

A 67 year old with a history of epilepsy has been treated with lamotrigine 100 mg BID for “years”. Recently has been having breakthrough seizures. Divalproex Na has been added to his regimen. What do you recommend?
A. Continue lamotrigine 100 mg BID
B. Increase lamotrigine to 200 mg BID
C. Decrease lamotrigine to 50 mg BID
D. Discontinue lamotrigine

Case Vignette

66 year old female with a PMH of seizures and bipolar disorder. Weight 66 kg
1. Divalproex Na ER 500 mg Take 2 tab PO bedtime
2. Famotidine 20 mg Take 1 tab PO every 12 hours
3. Metoprolol tartrate 25 mg 1 tab PO every 12 hours

VPA level on admission undetectable

VPA vs Free VPA

VPA Weight-based Dosing

• NOT ideal for the elderly!
• For this patient: 66 kg x 15 mg/kg = 990 mg
• Elderly should start
  • 125 mg TID or 250 mg BID

VPA Adverse Effects

• GI symptoms – diarrhea
  • Less with the enteric-coated (over immediate release) and even less with ER (extended-release) formulation
• Hyponatremia
• Thrombocytopenia
• Tremor
• Peripheral edema (in combination with antipsychotics most reports with concurrent risperidone)
• If experience altered mental status check an ammonia level → hyperammonemia encephalopathy
  • VPA is contraindicated in persons with Urea Cycle Disorders and significant hepatic dysfunction

VPA-induced Hyponatremia
VPA-induced Thrombocytopenia

Levetiracetam

A 75 + year old admitted to psychiatry for new onset manic symptoms. Started on new meds VPA and Olanzapine, but was refusing most doses. On day 14 of admission developed new-onset partial-complex seizures.

Labs: Na = 137; glucose = 120 mg/dL [6.7 mmol/L]; BUN 6 mg/dL [2.14 mmol/L]; Scr = 0.53 mg/dL [46.9 umol/L]; CrCl = 40 mL/min; Weight = 47 kg

Plan:
- Transfer to NSICU under neurology service
- Obtain prolonged video EEG
- Start levetiracetam 1500mg bid
- Check CXR, TSH, LFT’s

Do you agree with this plan?

Case Vignette

A 64 year old patient admitted for elective knee replacement surgery. Home divalproex Na 250 mg TID. Has been seizure free for over 9 months (Level on admission 68 mg/L [476 umol/L]).

During hospitalization develops hospital-acquired pneumonia and is started on an antibiotic.

3 days later she has a seizure. Repeat VPA level 22 mg/L [154 umol/L]. Which antibiotic were they started on?

A. Vancomycin
B. Meropenem
C. Levofloxacin
D. Piperacillin/tazobactam

VPA + Carbapenem Interaction

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>VPA level Pre-CBPM</th>
<th>VPA level during CBPM</th>
<th>% decrease</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ertapenem (n=9)</td>
<td>66.5 ± 24.5 &lt;465</td>
<td>20.1 ± 15.7 &lt;140</td>
<td>72 ± 17</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Imipenem/clastatin (n=17)</td>
<td>62.9 ± 16.3 &lt;440</td>
<td>36.1 ± 16.2 &lt;252</td>
<td>42 ± 22</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Meropenem (n=26)</td>
<td>53.1 ± 18.1 &lt;371</td>
<td>16.9 ± 11.8 &lt;118</td>
<td>67 ± 19</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Total (n=52)</td>
<td>58.6 ± 19.2 &lt;410</td>
<td>25.7 ± 16.3 &lt;166</td>
<td>60 ± 23</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

CBPM = carbapenem


Case Vignette

A 64 year old patient admitted for elective knee replacement surgery.

Home medications included: lisinopril 10 mg daily, calcium 500 mg TID, diclofenac 75 mg BID, divalproex Na 250 mg TID.

Has been seizure free for over 9 months (Level on admission 68 mg/L [476 umol/L]).

During hospitalization develops hospital-acquired pneumonia and is started on an antibiotic.

3 days later she has a seizure. Repeat VPA level 22 mg/L [154 umol/L]. Which antibiotic were they started on?

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VPA Thrombocytopenia

Case Vignette

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Levetiracetam Neuropsychiatric Adverse Effects

• Anyone have any experience to share?

Levetiracetam

• Psychiatric ADEs
  • Rage
  • Irritability
  • Aggression
  • Depression/Suicidality

Psychiatric ADEs
• Mania
• Psychosis
• OCD
• Rage
• Irritability
• Aggression
• Depression/Suicidality

Elderly Case Reports

• A 73 yo AAM with stage 4 kidney disease was prescribed levetiracetam 500 mg BID for partial-complex seizures. New onset depression within 5 months; resolved within 4 weeks of discontinuation

• A 92 year old CF with CKD and new onset partial seizure was started on levetiracetam 500mg once daily. Depression symptoms noted within 5 weeks; improvement in mood and cognition within 8 days of discontinuation

Brivaracetam vs Levetiracetam

• Like levetiracetam, brivaracetam also includes a warning regarding psychiatric adverse reactions including psychotic symptoms, irritability, depression, aggression, and anxiety

• Unlike levetiracetam, brivaracetam is hepatically cleared and has CYP drug interactions

Case Vignette

90 + year old with a history of seizures is currently treated with

• Levetiracetam 500 mg BID
• Lacosamide 50 mg BID

• Labs: SCr 1.5 mg/dL [132.6 umol/L]; Est Cr Cl = 26 mL/min

• Do you recommend any adjustments?

Lacosamide

• Cardiac monitoring
  • PR interval prolongation which may result in irregular heart beat, syncope

• Caution in patients with a cardiac conduction abnormality (2nd degree AV block), are taking drugs that prolong PR interval, or in myocardial infarction or heart failure

• If at risk check a baseline ECG and when steady state is achieved.
A 68 year old with a history of epilepsy that has been controlled on carbamazepine but has begun to experience leukopenia. Team wants to switch her off CBZ and transition to levetiracetam.

Current medication list includes:
- Amlodipine 10 mg daily
- Diazepam 5 mg at bedtime
- Lamotrigine 200 mg BID
- Simvastatin 40 mg at bedtime
- Oxycodone SR 20 mg every 12 hours

What concern(s) do you have?

Carbamazepine is an inducer of:
- CYP1A2
- CYP2B6
- CYP2C9
- CYP2C19
- CYP3A4
- UGT
- P-gp

Questions??

Neurology Update

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