What Geriatric Pharmacist Should Know About Antiepileptic Drugs?

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#ASCP50

What Geriatric Pharmacist Should Know About Antiepileptic Drugs?

To enter the Q&A and polling questions for this activity, go to ascp.com/qa and click on the title of this activity, as seen below.
Disclosure

Dr. Marvanova serves as a clinical pharmacy specialist consultant in neurology and psychiatry for Lexicomp, Wolters Kluwer.

Dr. Marvanova will discuss off-label use of brivaracetam, carbamazepine, eslicarbazepine acetate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, perampanel, phenobarbital, phenytoin, pregabalin, primidone, topiramate, valproic acid and its derivatives, and zonisamide.

Learning Objectives

1. Review clinical pharmacology of antiepileptic drugs (AEDs) to ensure safe and effective patient-centered care
2. Discuss indications and efficacy of commonly prescribed AEDs for management of common chronic conditions in older adults
3. Given a case, formulate appropriate AED and monitoring for a complex older adult
4. Discuss the importance of deprescribing AEDs in older adults and describe the strategies to assist with deprescribing AEDs based on indications
Antiepileptic Drugs in Older Adults

- AEDs are used to treat/manage different conditions
- AED are commonly prescribed in older adults
- Use and selection of AED in older adults should be done cautiously

![Diagram of benefit and risk]

Evidence for efficacy
Evidence for ongoing indication(s)
Adverse effects
Interactions
Age-related changes

Antiepileptic Drugs: Mechanism of Action

**Rationale polytherapy** = use of ≥ 2 AEDs with different MOA

<table>
<thead>
<tr>
<th>Drug Target/Mechanism of Action</th>
<th>AED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voltage-gated sodium channels (inhibition)</td>
<td>CMZ; OXC; ESL; LCM; LMT; TPM; VPA; ZNS</td>
</tr>
<tr>
<td>Voltage-gated calcium channels (α2-5 subunit inhibition)</td>
<td>GBP; PGB</td>
</tr>
<tr>
<td>Enhanced GABA transmission</td>
<td>PHB; PRM; VPA</td>
</tr>
<tr>
<td>Decreased glutamate transmission (AMPA receptors)</td>
<td>PER; TPM</td>
</tr>
<tr>
<td>Carbonic anhydrase inhibitors (decreased pH)</td>
<td>TPM; ZNS</td>
</tr>
<tr>
<td>SV2A synaptic unit binding</td>
<td>LEV; BRV</td>
</tr>
</tbody>
</table>

* Risk for metabolic acidosis (hyperchloremic, normal gap)

Antiepileptic Drugs: Kinetics

<table>
<thead>
<tr>
<th>AED</th>
<th>Metabolism</th>
<th>Prot. Binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brivaracetam</td>
<td>90 H (hydrolysis); R&lt;10</td>
<td>&lt;20%</td>
</tr>
<tr>
<td>Carbamazepine (CMZ)</td>
<td>&gt;90 H</td>
<td>73</td>
</tr>
<tr>
<td>Eslicarbazepine (ESI)</td>
<td>70 H (hydrolysis); R&gt;80</td>
<td>40</td>
</tr>
<tr>
<td>Gabapentin (GBP)</td>
<td>&gt;95 R (unchanged)</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Lamotrigine (LMT)</td>
<td>&gt;90 H</td>
<td>55</td>
</tr>
<tr>
<td>Levetiracetam (LEV)</td>
<td>30 H; &lt;45 R (unchanged)</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Oxcarbazepine (OXC)</td>
<td>&gt;55 H; 25 R</td>
<td>40</td>
</tr>
<tr>
<td>Phenytoin (PHN)</td>
<td>25-40 mg/mL</td>
<td></td>
</tr>
</tbody>
</table>

4-12 mcg/mL

10-20 mcg/mL

15-40 mcg/mL

50-100 (125) mcg/mL

* PHT has 0-order kinetics

PHT interaction with omeprazole (increased serum concentration levels, especially when using omeprazole 40 mg daily) via inhibition of CYP2C19.


Live Content Slide
When playing as a slideshow, this slide will display live content

Poll: Based on mechanism of action, which of the following combinations would be a rational polytherapy covering more than one drug target?

To access the polling questions, go to this link: ascp.com/qa and select the "What Geriatric Pharmacist Should Know About Antiepileptic Drugs?" activity, as seen below.

What Geriatric Pharmacist Should Know About Antiepileptic Drugs?
2:45pm – 3:45pm
Marketa Marvanova
Self-Assessment Question #1

Based on mechanism of action, which of the following combinations would be a rational polytherapy covering more than one drug target?

A. Carbamazepine and phenytoin
B. **Lacosamide and levetiracetam**
C. Topiramate and zonisamide
D. Oxcarbazepine and eslicarbazepine

(A) Liver Enzyme Inducers Interactions: CMZ, PHT, PHB, PRM

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Substrate (example)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A4</td>
<td>lurasidone, quetiapine, pimavanserin, donepezil, galantamine, apixaban, methadone, fentanyl, statins, vitamin D, macrolide antibiotics, verapamil, diltiazem, protease inhibitors, cyclosporine, various AEDs.</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>codeine, morphine, tamoxifen, tramadol, haloperidol, b-blockers, TCAs, donepezil, galantamine</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>clozapine, olanzapine, rasagiline, ropinirrole</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>warfarin, PHT, glipizide,</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>PPIs, diazepam, PHT</td>
</tr>
<tr>
<td>UGTs</td>
<td>LMT, VPA</td>
</tr>
</tbody>
</table>
(B) Liver Enzyme Inhibitors Interactions: VPA

<table>
<thead>
<tr>
<th>Hepatic Enzyme</th>
<th>Substrate (Examples)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C9</td>
<td>warfarin, glipizide, PHT</td>
</tr>
<tr>
<td>UGTs</td>
<td>LMT</td>
</tr>
<tr>
<td>Epoxide hydrolase</td>
<td>CMZ 10,11-epoxide</td>
</tr>
</tbody>
</table>

CYP3A4
CMZ ➔ CMZ epoxide ➔ CMZ trans-diol

Level: 4-12 mcg/mL
Level: 0.4-4 mcg/mL

CYP2C19 inhibition by cannabidiol:
concomitant administration with clobazam is associated with a 3-fold increase of desmethyloclobazam

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Poll: In which following clinical situation would you recommend ordering carbamazepine epoxide level for the patient who is treated for the past 2 years with carbamazepine XR 200 mg tablets twice daily with stable carbamazepine levels for the past year (~ 8 mcg/mL)?

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Self-Assessment Question #2

In which following clinical situation would you recommend ordering carbamazepine epoxide level for the patient who is treated for the past 2 years with carbamazepine XR 200 mg tablets twice daily with stable carbamazepine levels for the past year (~ 8 mcg/mL)?

A. Patient is an 82-year-old obese Asian female and resides in a long-term care facility.

B. Patient is a 75-year-old community-dwelling female and was initiated on divalproex sodium 3 weeks ago and reached desired therapeutic dose.

C. Patient is an 80-year-old male and was tapered off lamotrigine to decrease pill burden as he has been seizure free for the past 4 years.

D. Patients is a 78-year-old male with a history of Alzheimer disease dementia who was initiated on donepezil.
Adverse Drug Reactions Associated with AEDs

**DOSE-DEPENDENT**
Associated with a dose increase and high doses/drug serum concentration

- **Neurologic:** dizziness, drowsiness, ataxia, incoordination, blurred vision, nausea, nystagmus
- **Other:**
  - PR-interval prolongation (LCM): ECG monitoring
  - Anticholinergic adverse effects (CMZ)
  - Negative mood effect (LEV, BRV, PHT, TPM, ZNS)
  - Negative cognitive effect (TPM, PHT, PHB, PRM, VPA)
  - Tremor (VPA, LMT)


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Adverse Drug Reactions Associated with AEDs

**IDIOSYNCRATIC**

- Hematologic abnormalities (older generation AEDs: PHT, CMZ, PHB, PRM, VPA)
- Liver abnormalities (older generation AEDs)
- Hyponatremia (CMZ, OXC, ESL)
- Cutaneous reactions (aromatic AEDs: PHT, CMZ, OXC, ESL, LMT, PRM, PHB, ZNS)
- Hyperammonemna and Carnitine deficiency (VPA)

Adverse Drug Reactions Associated with AEDs

**LONG-TERM**

- **Vitamin deficiency** (strong enzyme inducers):
  - vitamin B12
  - folic acid/folate
  - vitamin D

- **Negative bone health** (strong enzyme inducers and and VPA)

- B12 deficiency can be associated with anemia, cognitive impairment and psychiatric symptoms
- Folic deficiency can be associated with anemia, and cognitive impairment


Evidence-Supported Indications of AEDs

**NEUROLOGY**

- Epilepsy and Epilepsy syndromes (early- and late-onset)
- Neuropathic pain (VPA; CMZ; OXC; GBP; PGB)
  - Post-herpetic neuralgia
  - Painful diabetic neuropathy
  - Trigeminal neuralgia
- Fibromyalgia (GBP; PGB)
- Migraine prophylaxis (VPA; TPM)
- Restless leg syndrome (GBP)
- Essential tremor (PRM; GBP; TPM)

**PSYCHIATRY**

- Bipolar disorders (VPA; CMZ; OXC; LMT)
  - Rapid cyclers (VPA)
- Anxiety disorders (GBP; PGB)

Late-Onset Epilepsy in Older Adults: Etiology

1. Stroke/Cerebrovascular Disease
   - focal seizures (predominately complex partial seizures) ± secondary generalization

2. Dementia/Neurodegenerative Brain Processes
   - focal seizures (predominately complex partial seizures) ± secondary generalization, generalized tonic-clonic seizure (GTCS)

Late-Onset Epilepsy in Older Adults: Treatment

FOCAL SEIZURES
- Lamotrigine (LMT)*
- Gabapentin (GBP)*
- Levetiracetam (LEV)*
- Carbamazepine XR (CMZ)
- Oxcarbazepine (OXC)
- Topiramate (TPM)
- Zonisamide (ZNS)
- Lacosamide (LCM)
- Eslicarbazepine (ESL)

FOCAL SEIZURES IN AD
- Levetiracetam (LEV)*
- Lamotrigine (LMT)*
- Topiramate (TPM)
- Phenytoin (PHT)
- Valproic acid/Derivatives (VPA)

GTCS
- Levetiracetam (LEV)*
- Lamotrigine (LMT)*
- Topiramate (TPM)
- Zonisamide (ZNS)
- Phenytoin (PHT)
- Valproic acid/Derivatives (VPA)

* Preferred therapy
Early-Onset Epilepsy in Older Adults

**FOCAL SEIZURES**

- Newer agents (2\textsuperscript{nd} and 3\textsuperscript{rd} generation): LMT\textsuperscript{a,c}, LEV\textsuperscript{a,c}, BRV, OXC\textsuperscript{a,b}, TPM\textsuperscript{a,c}, ZNS\textsuperscript{a}, PGB\textsuperscript{b}, GBP\textsuperscript{b}, LCM, PER, ESL
- Phenytoin (PHT)\textsuperscript{a,b}
- Carbamazepine (CMZ)\textsuperscript{a,b}
- Phenobarbital (PHB)
- Valproic acid and its derivatives (VPA)\textsuperscript{a,c}

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Use of AEDs and Deprescribing

- Medication reconciliation including medication experience
  1. Appropriate indication(s)
  2. Adequate therapeutic response(s)
  3. Tolerance/Toxicity
  4. Length of the therapy
     - Consider AED discontinuation: if seizure freedom for 3-5 years (weight risk vs benefit)
     - Prevention of early vs late seizures in stroke, TBI, IVH, SAH
- Assess for eligibility for deprescribing
- Provide plan for discontinuation and monitoring

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Controversial Use/Unsupported Indications

- Behavioral and psychological symptoms of dementia (BPSD)
- Late seizure prophylaxis in
  - ischemic stroke (IS)
  - intracranial hemorrhage (ICH)
  - subarachnoid hemorrhage (SAH)
  - traumatic brain injury (TBI)
Opportunity for AED Deprescribing:

**BPSD: AGGRESSION, AGITATION, AND HOSTILITY**

VPA, CMZ, OXC, LEV, LMT, TPM, GBP not recommended in general
Low number of quality trials and inconsistent efficacy conclusions

CMZ has the most evidence (agression, hostility) for short 6-7 week periods but carried a high risk for interactions and adverse effects

VPA has low to no efficacy and carries a high risk for adverse effects
Reports of brain atrophy and worsened cognition in in individuals with mild-moderate AD

16-week, preliminary open-label trial: LMT administration in severe AD with BPSD may be effective (agitation) and may make it possible to avoid increasing the dosage of antipsychotics

A single small, prospective, randomized study: Low-dose TPM was found to be equal in efficacy to risperidone

A single randomized, prospective trial: OXC failed to show any benefit

A small case series: GBP reduced aggression among seven patients with vascular dementia or mixed vascular/AD

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**Opportunity for AED Deprescribing:**

**Prevention of EARLY (≤ 7 days of trauma/stroke) versus LATE (>7 days of trauma/stroke) seizures**

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>RECOMMENDATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure prophylaxis in ischemic stroke PHT, LEV</td>
<td>Short course is preferable (3-7 days) if prophylaxis needed Not recommended for prevention of late-seizures</td>
</tr>
<tr>
<td>Seizure prophylaxis in subarachnoid hemorrhage PHT, LEV</td>
<td>Short course is preferable (3-7 days) if prophylaxis needed Not recommended for prevention of late seizures</td>
</tr>
<tr>
<td>Intra-cranial hemorrhage PHT, LEV</td>
<td>Short course is preferable (3-7 days) if prophylaxis needed Not recommended for prevention of late seizures</td>
</tr>
<tr>
<td>Prevention of post traumatic seizures in TBI PHT, LEV</td>
<td>Only a short course, especially in penetration injury (max 7 days) Not recommended for prevention of late PTS</td>
</tr>
</tbody>
</table>
Poll: Which of the following individuals would be the best candidate for AED deprescribing?

To access the polling questions, go to this link: ascp.com/qa and select the “What Geriatric Pharmacist Should Know About Antiepileptic Drugs?” activity, as seen below.

Self-Assessment Question #3

Which of the following individuals would be the best candidate for AED deprescribing?

I. 68-year-old female with history of ischemic stroke who developed 3-years post stroke focal epilepsy. She is currently managed with levetiracetam and is seizure free for the past 1.5 year.

II. 74-year-old male with history of traumatic brain injury who experienced 2 seizures within the first week of injury who is currently managed with phenytoin for the past two years.

III. 83-year-old female with history of moderate-severe AD dementia with history of agitation who was prescribed divalproex sodium.

IV. 70-year-old long-term care facility resident with history of intracranial hemorrhage who developed seizures 1 year post hemorrhage and is currently managed with lamotrigine.

A. I only
B. II, III
C. I, III
D. I, II, IV
AED-Induced Cutaneous Reactions: Types

- Most common with aromatic AEDs
- 1-12 week development
- Types of reactions:
  - **Benign morbilliform rash**
  - **Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS):** 10% mortality
    1) Maculopapular/morbilliform rash starting in face and upper trunk, 2) Exfoliative dermatitis and swollen face may occur, 3) Fever (>38 °C), 4) hepatomegaly, 5) arthralgia; 6) Lymphadenopathy and eosinophilia
  - **Stevens-Johnson Syndrome (SJS):** 9% mortality
  - **Toxic Epidermal Necrolysis (TEN):** up to 50% mortality

Aromatic AEDs: PHT, CMZ/OXC/ESL (also related to tricyclic antidepressants), LMT, PRM, PHB, ZNS (also sulfonamide)

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AED-Induced Cutaneous Reactions: Risk

- **Use of aromatic AEDs**
- **Advanced age**
- **Fast titration** (LMT: slow titration needed) or combination of LMT and VPA
- **Previous skin reaction** after use of an aromatic AED (cross-reactivity): preferably do not use other aromatic AED especially in case of history of life-threatening cutaneous conditions
  - Use: GBP, PGB, TPM, LEV, BRV, LCM, VPA (note: VPA can slow down the elimination of aromatic medication causing cutaneous reaction)
- **Genetics:** 1) **HLA-B*15:02 allele genotyping:**
  - Prior to initiation of CMZ in a patient of Asian descent (negative predictive value also for OXC and most-likely for ESL). May apply for other aromatic AEDs: PHT, PHB, PRM, LMT
  - 2) **HLA-A*31:01 allele:** (Korea, Japan, Northern Europe)- CMZ-induced SJS/TEN
Poll: An 80-year-old with history of Alzheimer disease was treated with oxcarbazepine for his epilepsy (complex focal seizures with or without generalization). He developed a measles-like rash that progressed to Stevens Johnson syndrome (SJS) and was hospitalized. The medical team asks you for a consult to recommend which medication can be used to control seizures while he is hospitalized. Which of the following would you recommend?

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Self-Assessment Question #4

An 80-year-old with history of Alzheimer disease was treated with oxcarbazepine for his epilepsy (complex focal seizures with or without generalization). He developed a measles-like rash that progressed to Stevens Johnson syndrome (SJS) and was hospitalized. The medical team asks you for a consult to recommend which medication can be used to control seizures while he is hospitalized. **Which of the following would you recommend?**

A. Divalproex sodium
B. Carbamazepine
C. **Levetiracetam**
D. Lamotrigine
AEDs and Bone Health

- Use of AED with the highest risk for osteopenia/osteoporosis
- Epilepsy risk factor for fractures
- Assessment/Monitoring:
  1) 25-hydroxyvitamin D level
  2) DEXA scan:
  - every 5 years in all adults except post-menopausal women
  - every 2 years if AED is used in postmenopausal women or elderly men

Prevention/Management

<table>
<thead>
<tr>
<th>25(OH)D Level</th>
<th>INTERVENTION/TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥30 ng/mL</td>
<td>Calcium 1,000-1,500 mg/day</td>
</tr>
<tr>
<td></td>
<td>Vitamin D 800-2,000 IU/day</td>
</tr>
<tr>
<td>20-29 ng/mL</td>
<td>Calcium 1,000-1,500 mg/day</td>
</tr>
<tr>
<td></td>
<td>Vitamin D 2,000-4,000 IU/day</td>
</tr>
<tr>
<td>&lt;20 ng/mL</td>
<td>Calcium 1,000-1,500 mg/day</td>
</tr>
<tr>
<td></td>
<td>Vitamin D 50,000 IU weekly x 8 weeks</td>
</tr>
<tr>
<td></td>
<td>After 8 weeks initiate vitamin D 1,000-2,000 IU if still on AED enzyme inducer</td>
</tr>
<tr>
<td></td>
<td>Repeat 25(OH)D level after 12 wks.</td>
</tr>
</tbody>
</table>

*Endocrin Pract 2016; 22(9):1111-8.*
*J Clin Endocrinol Metab 2011; 96(7):1911-30.*
Poll: A 68-year-old female is being treated with divalproex sodium 400 mg twice daily and atenolol 20 mg daily for her migraine headache and rapid cycling bipolar disorder for the past 3-years with good efficacy and tolerance. She was previously managed long-term with quetiapine and carbamazepine that had to be discontinued due to intolerance and frequent lithium toxicities. Which of the following is the most appropriate recommendation at this time?

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Self-Assessment Question #5

A 68-year-old female is being treated with divalproex sodium 400 mg twice daily and atenolol 20 mg daily for her migraine headache and rapid cycling bipolar disorder for the past 3-years with good efficacy and tolerance. She was previously managed long-term with quetiapine and carbamazepine that had to be discontinued due to intolerance and frequent lithium toxicities. Which of the following is the most appropriate recommendation at this time?

A. Initiate cholecalciferol 800 units daily
B. Order 25-hydroxyvitamin D level
C. Recommend calcium citrate 600 mg daily
D. Order serum valproic acid concentration
Summary: Use of AEDs in Older Adults

1. AEDs are commonly prescribed in older adults
2. Selection of AED in older adults should be made cautiously
3. When combining AEDs, especially in epilepsy, use rational polytherapy
4. Careful review of efficacy and tolerability is critical
5. Assess opportunity for AED deprescribing
6. Provide preventative measures for AED-associated cutaneous reactions and negative bone health

Thank you for your attention!
What questions do you have?
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