GERIATRIC PHARMACIST

BOOT CAMP

Neurologic Disorders in the Older Adult

Marketa Marvanova, PharmD, PhD, BCGP, BCPP, FASCP

Dean and Professor

Pacific University School of Pharmacy, Hillsboro, Oregon

Supported in part by an educational grant from the ASCP Foundation.

1

Meet the Speaker

Dr. Marvanova serves as the Professor and Dean of the Pacific University School of Pharmacy in Hillsboro, Oregon. She is a Board-Certified Psychiatric and Geriatric Pharmacist, as well as a Fellow of the American Society of Consultant Pharmacists (ASCP). She holds an M.S. (Pharm), Pharm.D., and a Ph.D. in Pathological Neurobiochemistry from Charles University in the Czech Republic, along with a Ph.D. in Neuropharmacology from the University of Eastern Finland. She also completed a medical research fellowship in neuropharmacology at Vanderbilt University School of Medicine and a Parkinson's disease traineeship at Northwestern University.

Her clinical expertise lies in geriatrics and neuropsychiatry, and she has extensive experience practicing in both inpatient and outpatient team-based clinical settings. Since 2013, she has served on the editorial board of *Continuum: Lifelong Learning in Neurology* (published by the American Academy of Neurology) and acts as a clinical pharmacy specialist consultant in neurology and psychiatry for Lexicomp, Wolters Kluwer. As a clinician, educator, and scholar, Dr. Marvanova is deeply committed to advancing training in geriatrics and neuropsychiatry while working to improve health outcomes for older adults.

2

Disclosure

Marketa Marvanova does not have relevant financial relationships with ineligible companies.

None of the planners for this activity have relevant financial relationships to disclose with ineligible companies.

This presentation will include discussion of off-label, experimental, and/or investigational use of drugs or devices.

3

Learning Objectives

- Determine therapeutic options for Alzheimer's disease, Parkinson's disease, epilepsy, and pain in the older adults.
- Interpret neurologic clinical findings and incorporate functional status into therapeutic decision-making.
- Resolve and/or prevent neurologic medication-related problems.
- Apply neurologic therapy recommendations and person-specific goals to senior patient cases.

4

GERIATRIC PHARMACIST
BOOT CAMP

ALZHEIMER'S DISEASE (AD)

Supported in part by an educational grant from the ASCP Foundation.

5

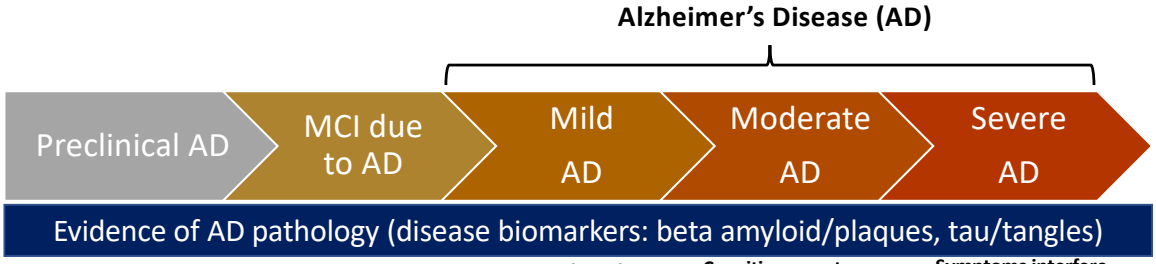
Alzheimer's Disease (AD)

- Chronic IRREVERSIBLE neurodegenerative disorder with progressive clinical course
  - AD tends to develop slowly and gradually worsens over several years
  - Eventually, AD pathology affects most brain areas
- AD affects at least 6.9 million Americans aged 65 years and older
  - Every 65 seconds, a new person develops AD in the U.S.
- Prevalence of sporadic AD increases with advanced age
- Incurable disease (survival rate: average 8-12 years)

2024 Alzheimer's Disease Facts and Figures. Available at https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf. Accessed on May 9, 2024.

6

AD Continuum and Clinical Course



No noticeable symptoms.

Function preserved.

Very mild cognitive symptoms that do not interfere with everyday activities and function preserved (ability to compensate).

Functions relatively independently but may feel as if he or she is having memory lapses.

Problems with memory and thinking begins to impact IADL.

Cognitive symptoms are more pronounced impacting ADL and will require assistance.

Significant personality changes and psychiatric and behavioral symptoms of dementia.

Symptoms interfere with most everyday activities and need for 24/7 care.

Inability to interact with the environment.
Movement and communication become difficult.

MCI=mild cognitive impairment
IADL=instrumental activities of daily living
ADL=activities of daily living

GERIATRIC PHARMACIST BOOT CAMP

2024 Alzheimer's Disease Facts and Figures. Available at https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf. Accessed December 29, 2024.

7

7

Symptoms of Alzheimer's Disease

Cognitive Symptoms

Memory loss | Impaired Visuospatial orientation | Language disturbance | Executive dysfunction

- MiniCog
- Mini Mental State Exam (MMSE)
- Montreal Cognitive Assessment (MoCA)

Neuropsychiatric=Behavioral and Psychiatric Symptoms of Dementia (BPSD)

Mood disturbances | Agitation | Aggression | Sleep disturbance | Wandering | Psychosis

Functional Decline

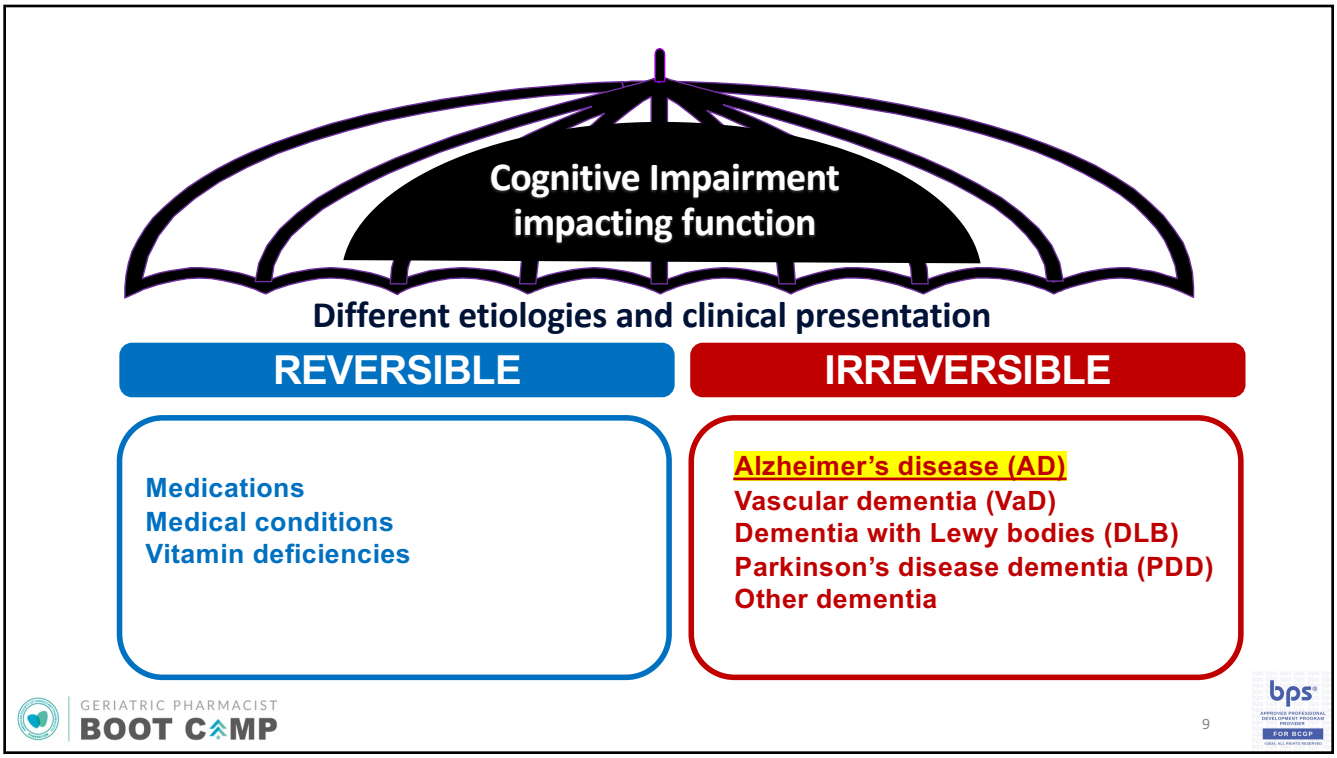
Reduced ability to carry out activities of daily living

GERIATRIC PHARMACIST BOOT CAMP

2024 Alzheimer's Disease Facts and Figures. Available at https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf. Accessed on May 9, 2024;
Arvanitakis Z, Shah RC, Bennett DA. Diagnosis and Management of Dementia: Review. *JAMA*. 2019;322(16):1589-1599.

8

8



9

Common Reversible Causes of Cognitive Impairment

(A) MEDICATIONS

- **Anticholinergic medications**
  - *TCAs (e.g., amitriptyline)*
  - *Overactive bladder medications (e.g., oxybutynin)*
  - *Antihistamines (e.g., diphenhydramine)*
- **Opioids**
- **Benzodiazepines**
- **Sedatives and hypnotics**

(B) MEDICAL CONDITIONS

- **Depression** (*pseudodementia)*
- **Anemia**
- **Hypothyroidism**
- **Hyperammonemia** (*ammonia-induced encephalopathy*)
- **Hypoglycemia**
- **Low blood pressure and HR**

(C) VITAMIN DEFICIENCIES

(Vitamin B1, B12 and folic acid/folate)

- Nutritional and medication-induced deficiencies
  - *Metformin (B12)*
  - *Phenytoin (B12, folate)*
  - *Methotrexate (folate)*
  - *Alcoholics (B1)*
  - *Bariatric surgery (B1, B12, folate)*

2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2023;71(7):2052-2081; Zanni GR, Wick JY. *The Consultant Pharmacist.* 2007;22(1):14-28.

GERIATRIC PHARMACIST BOOT CAMP 10

10

Assessment: "Dementia Workup"

- To **rule out reversible causes**, the following items should be reviewed:
  1. Medication reconciliation/review
  2. Medical history
     - Vital signs: BP; HR; RR
     - Labs: CBC; CMP; TSH; B_{12} & folate levels
     - Presence of depression
       - ✓Patient Health Questionnaire-9 (PHQ-9): ≥5 points: depression
     - Imaging: CT/MRI ONLY if needed
  3. Social history (substance use)

Complete blood count=CBC; comprehensive metabolic panel=CMP; blood pressure=BP; heart rate=HR; respiratory rate=RR

Arvanitakis Z, Shah RC, Bennett DA. Diagnosis and Management of Dementia: Review. *JAMA*. 2019;322(16):1589-1599.

Self-Assessment Question #1:

In addition to CMP, CBC, B12, which laboratory data (blood test) should be assessed as a part of a routine dementia workup?

A. Ammonia level
B. Thyroid stimulating hormone
C. Magnesium level
D. Vitamin D level

AD Pharmacotherapy and Goals

(1) DISEASE MODIFYING THERAPY

- **Purpose/Impact**: Slows down the disease progression by AD biology modification
  - **Beta-amyloid plaque clearance**
- **Indication: mild cognitive impairment (MCI) and mild AD**
- **Classes:**
  1. **Amyloid beta-directed antibody (immunotherapy/monoclonal antibodies)**

(2) SYMPTOMATIC THERAPY

- **Purpose/Impact**: Cognitive symptoms improvement/stabilization without AD biology modification and select beneficial effects on various BPSDs
- **Indication: mild, moderate and severe AD**
- **Classes:**
  1. **Acetylcholinesterase inhibitors (AChEIs)**
  2. **NMDA receptor antagonist**
  3. **Other symptomatic therapy to manage other than cognitive symptoms in AD (e.g., antidepressants)**

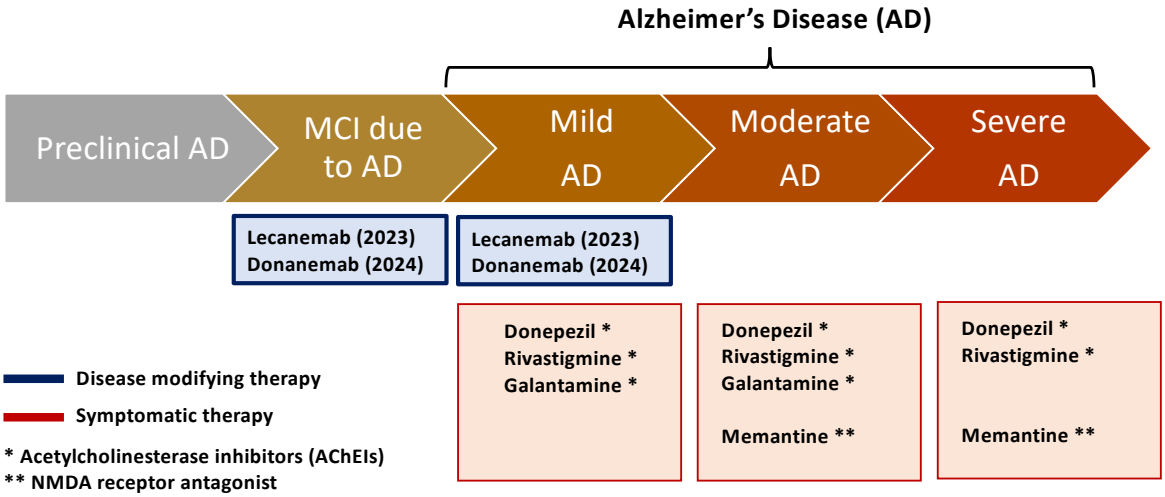
To maintain patient's **cognition**, **function** and **quality of life** at the highest levels for the longest period of time

GERIATRIC PHARMACIST BOOT CAMP

13

13

AD Pharmacotherapy



GERIATRIC PHARMACIST BOOT CAMP

Lexicomp Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2019; Prescribing information. Available at: www.dailymed.nlm.nih.gov. Accessed on January 16, 2024.
2024 Alzheimer's Disease Facts and Figures. Available at https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf. Accessed December 29, 2024.

14

14

FDA Approved Monoclonal Antibodies for AD

Feature	Lecanemab (Leqembi) MMSE score of 22-30 (Clarity)	Donanemab (Kisunla) MMSE score of 20 to 28 (TRAILBLAZER-ALZ-2)
Primary Drug Target	Protofibrils and oligomers (soluble) and amyloid beta plaque (insoluble)	N-truncated pyroglutamate amyloid beta plaque (insoluble)
Administration	Intravenous (IV) infusion every 2 week	Intravenous (IV) infusion every 4 week
Dose	10 mg/kg	700 mg for the first three doses and 1400 mg thereafter.
Length of Treatment	Usually taken long-term/indefinite	Based on removal of amyloid plaques to minimal levels (~50% of patients in 12 months, 69% in 18 months)
Cost /year	$26,500	~$32,000
Efficacy	Lowered brain beta amyloid Statistical delay in in the cognitive and functional decline by about 27%.	Lowered brain beta amyloid Statistical ~35% reduction in cognitive and functional decline 39% lower risk of progressing to the next stage of the disease

GERIATRIC PHARMACIST BOOT CAMP

KISUNLA (donanemab-azbt) [prescribing information]. Eli Lilly and Company. Indianapolis, IN. July 2024.
LEQEMBI (lecanemab-irmb) [prescribing information]. Eisai Inc. Nutley, NJ. 2023.

15

15

Significant AEs with Monoclonal Antibodies in AD (> 10% Incidence)

1. Amyloid Related Imaging Abnormalities (ARIA)

- ARIA-E (Edema: brain swelling)
- ARIA-H (Hemorrhage: small microbleeds and superficial hemosiderosis)
- Symptoms: onset of headache, dizziness, confusion and nausea
- Often asymptomatic and self-resolving
- **Who is at increased risk?**
  - Higher incidence in Apo ε4 allele carriers especially homozygotes
  - Increased risk in those on anticoagulants and history of bleeding disorders

2. Infusion-Related Reactions

- Flu-like symptoms (e.g., fever, chills, body ache, joint pain)
- Feeling flushed
- Rash
- Dizziness and lightheadedness
- Changes in blood pressure
- Consider pre-medication with antihistamines, acetaminophen, and/or corticosteroids.

GERIATRIC PHARMACIST BOOT CAMP

KISUNLA (donanemab-azbt) [prescribing information]. Eli Lilly and Company. Indianapolis, IN. July 2024.
LEQEMBI (lecanemab-irmb) [prescribing information]. Eisai Inc. Nutley, NJ. 2023.

16

16

Treatment with Monoclonal Antibodies in AD

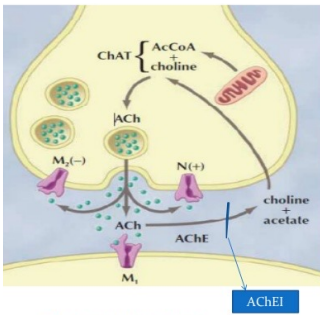
STEP 1	STEP 2	STEP 3
Identify Eligibility and Diagnosis	**Administration**	**Monitoring Between Administration**
1. Confirm MCI or mild AD 2. Confirm presence of beta amyloid • Brain PET scan or CSF analysis 4. Baseline brain MRI 5. APOE ε4 genotyping • APO ε4 homozygotes: high risk for complications (commonly excluded) 4. Exclusion criteria • Anticoagulants and bleeding disorder • Stroke/TIA • Epilepsy/Seizure • Other	• Hospital outpatient infusion centers • 30 (donanemab) to 60 min (lecanemab) infusion • Mandatory monitoring immediately after infusion ○ 1st infusion: 3 hours ○ 2nd infusion: 2 hours ○ 3rd and forward: 30 minutes	• Monitoring for amyloid related imaging abnormalities (ARIA): edema and bleeding • Using scheduled MRIs for each treatments • Increased vigilance for ARIA is recommended for lecanemab during the first 14 weeks and for donanemab during the first 24 weeks • Monitor symptoms such as onset of headache, dizziness, confusion and nausea

GERIATRIC PHARMACIST BOOT CAMP

KISUNLA (donanemab-azbt) [prescribing information]. Eli Lilly and Company. Indianapolis, IN. July 2024.
LEQEMBI (lecanemab-irmb) [prescribing information]. Eisai Inc. Nutley, NJ. 2023.
Cummings J, Apostolova L, Rabinovici GD, et al. Lecanemab: Appropriate Use Recommendations. *J Prev Alzheimers Dis*. 2023;10(3):362-377

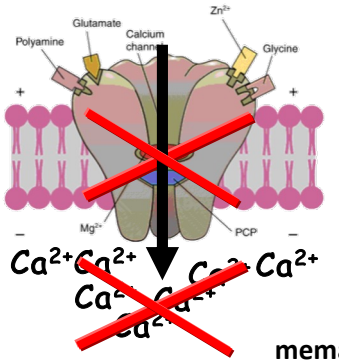
Available Symptomatic Pharmacotherapy for Cognitive Symptoms

(1) Acetylcholinesterase Inhibitors (AChEIs)



donepezil, rivastigmine, galantamine

(2) NMDA Receptor Antagonist



memantine

NOTE: huperzine A = herbal supplement with MOA similar to AChEIs

GERIATRIC PHARMACIST BOOT CAMP

DArvanitakis Z, Shah RC, Bennett DA. Diagnosis and Management of Dementia: Review. *JAMA*. 2019;322(16):1589-1599.
iannopoulou KG, Papageorgiou SG. Current and Future Treatments in Alzheimer Disease: An Update. *J Cent Nerv Syst Dis*. 2020;12:1179573520907397.

Symptomatic Treatment

Generic (Brand)	Dosing	Information
Donepezil tablet (Aricept®) Donepezil ODT (Aricept ODT®) Donepezil **patch** (Adlarity® patch) Donepezil/memantine capsule (Namzaric®)	Daily Daily **Weekly** Daily	• Initiate with slow titration to decrease risk for GI adverse effects • Patch needs to be stored in the refrigerator • Namzaric capsule can be opened
Galantamine tablet (Razadyne®) Galantamine solution Galantamine XR (Razadyne XR®)	BID BID Daily	• Initiate with slow titration to decrease risk for GI adverse effects
Rivastigmine tablet (Exelon®) Rivastigmine solution Rivastigmine **patch** (Exelon patch®)	BID BID **Daily**	• Initiate with slow titration to decrease risk for GI adverse effects • Patch is stored at room temperature
Memantine tablet (Namenda®) Memantine XR capsule (Namenda XR®) Donepezil/memantine capsule (Namzaric®)	BID Daily Daily	• AEs: headache, constipation, dizziness • Monotherapy or can be combined with AChEIs • Namenda XR and Namzaric capsule can be opened

Lexicomp Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2019; Prescribing information. Available at: www.dailymed.nlm.nih.gov. Accessed on January 16, 2024; Yiannopoulou KG, Papageorgiou SG. Current and Future Treatments in Alzheimer Disease: An Update. *J Cent Nerv Syst Dis.* 2020;12; Szilcz M, Wastesson JW, Calderón-Larrañaga A, at al. Cholinesterase inhibitors and non-steroidal anti-inflammatory drugs and the risk of peptic ulcers: A self-controlled study. *J Am Geriatr Soc.* 2023. doi: 10.1111/jgs.18647. Epub ahead of print.
ADLARITY® (donepezil transdermal system) [prescribing information]. Corium, Inc., MI. March 2022.
EXELON PATCH (rivastigmine transdermal system) [prescribing information]. Novartis Pharmaceuticals Corporation, NJ. June 2020.

Efficacy of AChEIs and Memantine

- **MODEST IMPROVEMENT of**:
  1. Cognitive function (cognitive stabilization)
  2. Stabilization or improvement of select BPSD
  3. Daily and global function
- Assess efficacy after 12 weeks of therapy initiation
- Further assessment on a 6-month basis to determine ongoing efficacy and response with the predetermined treatment goals
- Can be combined with monoclonal antibodies (e.g., lecanemab)

Reasonable to try another AChEI when first one is not tolerated or ineffective

Yiannopoulou KG, Papageorgiou SG. Current and Future Treatments in Alzheimer Disease: An Update. *J Cent Nerv Syst Dis.* 2020;12; Hampel H, Mesulam MM, Cuello AC, et al. *Brain.* 2018;141(7):1917–1933; Giacobini E, Cuello AC, Fisher A. *Brain.* 2022;145(7):2250–2275.

AChEIs Adverse Effects (AEs)

	Donepezil	Galantamine	Rivastigmine po	Rivastigmine patch
Nausea	19%	24%	47%	7%
Vomiting	8%	13%	31%	6%
Diarrhea	15%	12%	19%	6%

AChEIs = Cholinergic AEs

- GI (N/V/D, anorexia, weight loss)
  - Careful use in gastric ulcer disease, history of GI bleeding
  - Increased risk with coadministration with NSAIDs
- Cardiac (bradycardia, syncope, heart block) AGS Beers Criteria
  - *Especially in those with pre-existing cardiac condition or as a result of drug-drug interactions*
  - *Careful use in bradycardia*
- Increased pulmonary & gastric secretion
  - Careful use in uncontrolled asthma and COPD
- Dizziness / Headache / Insomnia
- Vivid dreams (donepezil)

GERIATRIC PHARMACIST BOOT CAMP

2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2023;71(7):2052-2081;
Lexicomp Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2019
Prescribing information. Available at: www.dailymed.nlm.nih.gov. Accessed on December 5, 2022.

Important AChEI Interactions

(A) Pharmacodynamic Interactions

- **Anticholinergic agents** = decreased efficacy
- **PR interval prolongation agents** (e.g., verapamil, diltiazem, lacosamide, beta-blockers) = increased risk for bradycardia and heart block
- **NSAIDs** = increases risk for dyspepsia, peptic ulcer disease, and gastric bleeding

(B) Pharmacokinetic Interactions

- Donepezil and galantamine are metabolized by **CYP2D6** and **CYP3A4** enzymes (NOT rivastigmine)
- Inhibitors (e.g., fluoxetine, ketoconazole, bupropion, paroxetine, duloxetine)=can increase donepezil or galantamine serum concentrations (drug adverse effects)
- Inducers (e.g., rifampin, phenytoin, carbamazepine, phenobarbital) = can decrease efficacy (decrease drug levels)

Lexicomp Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2019; Prescribing information. Available at: www.dailymed.nlm.nih.gov. Accessed on December 27, 2025; Yiannopoulou KG, Papageorgiou SG. Current and Future Treatments in Alzheimer Disease: An Update. *J Cent Nerv Syst Dis.* 2020;12; Szilcz M, Wastesson JW, Calderón-Larrañaga A, at al. Cholinesterase inhibitors and non-steroidal anti-inflammatory drugs and the risk of peptic ulcers: A self-controlled study. *J Am Geriatr Soc.* 2024;72(2):456-466..

GERIATRIC PHARMACIST BOOT CAMP

How long to Continue Symptomatic Therapy?

- No consensus on how long to continue AChEIs in patients who are tolerating therapy, and even patients who respond initially will ultimately progress
- When to discontinue?

Non-adherence	Continued deterioration	Terminal illness	Serious comorbidity	Patient/ caregiver choice

Avoid	• Avoid abrupt discontinuation UNLESS severe adverse drug reactions to minimize withdrawal symptoms
Taper	• Taper using 50% dose reduction or stepwise reduction via available dose formulations every 4 weeks to lowest dose prior to discontinuation
Reinitiate	• Reinitiate if worsening of conditions after withdrawal

GERIATRIC PHARMACIST BOOT CAMP

O'Brient JT et al. *J Psychopharmacol.* 2017;31:147-168; Winslow BT, et al. *Am Fam Physic.* 2011;83(12):1403-1412; Howard R et al, *NEJM.* 2012;366(10):893-903.

23

bps APPROVED PROFESSIONAL DEVELOPMENT PROGRAM PROVIDER FOR BCGP

23

Table 5: Recommended tapering schedule for ChEIs and memantine

Drug	Dose-reduction schedule *(start at individual's current dose)*	Time until next dose reduction	Five half-lives of the medication [1] *(duration of inhibition of acetylcholinesterase)* [181–184,253]
Donepezil (available in 5 and 10 mg tablets)	10 mg once daily → 5 mg once daily → cease	Four weeks	15 days (reversible inhibitor)
Galantamine (available in 8, 16 and 24 mg extended release capsule)	24 mg once daily → 16 mg once daily → 8 mg once daily → cease	Four weeks	Two days [2,3] (reversible inhibitor)
Rivastigmine capsule (available in 1.5, 3, 4.5 and 6 mg capsules)	6 mg twice daily → 4.5 mg twice daily → 3 mg twice daily → 1.5 mg twice daily → 1.5 mg once daily → cease	Four weeks	One day [2,3] (six to nine hours)
Rivastigmine patch (available in 4.6, 9.5, 13.3 mg/24 hours)	13.3 mg/24 hours → 9.5 mg/24 hours → 4.6 mg/24 hours → cease	Four weeks	17 days [2,3] (six to nine hours)
Memantine (available in 10 and 20 mg tablets)	20 mg once daily (or 10 mg twice daily) → 10 mg once daily → cease	Four weeks	21 days [2]

Evidence-based Clinical Practice Guideline for Deprescribing Cholinesterase Inhibitors and Memantine. Available at https://cdpc.sydney.edu.au/wp-content/uploads/2019/06/deprescribing-guideline.pdf. Accessed on December 27, 2024.

GERIATRIC PHARMACIST BOOT CAMP

24

bps APPROVED PROFESSIONAL DEVELOPMENT PROGRAM PROVIDER FOR BCGP

24

AGS Beers Criteria

Potentially Inappropriate Medications in AD

- **Anticholinergic medications**: cognitive worsening and risk for delirium, and pharmacodynamic interaction with AChEIs
- **Nonbenzodiazepine receptor agonists ("Z-drugs")**
- **Benzodizepines:** cognitive worsening, paradoxical disinhibition, risk for delirium
- **Antipsychotics:** Box-warning: "Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death". Primary causes of mortality:
  - ➢ Cardiovascular: stroke, heart failure, sudden death
  - ➢ Infectious: pneumonia (aspiration)

GERIATRIC PHARMACIST BOOT CAMP

2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2023;71(7):2052-2081; Rochon PA, Vozoris N, Gill SS. *CMAJ.* 2017;189(14) E517-E518.

25

bps APPROVED PROFESSIONAL DEVELOPMENT PROGRAM PROVIDER FOR BCGP

25

Antipsychotics Use in Dementia

- **None approved** for management of dementia-related psychosis
  - Use in AD is OFF-LABEL USE
- Brexpiprazole (Rexulti™) was approved for treatment of agitation associated with AD (AAD) in May 2023.
- If prescribed:
  1. Assess ongoing need
  2. Periodic deprescribing attempts should be considered
  3. Lowest effective dose
  4. Document indication

GERIATRIC PHARMACIST BOOT CAMP

2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2023;71(7):2052-2081.
REXULTI (brexpiprazole) [prescribing information] Otsuka Pharmaceutical Co., Ltd., Tokyo, May 2024.

26

bps APPROVED PROFESSIONAL DEVELOPMENT PROGRAM PROVIDER FOR BCGP

26

When Is an Antipsychotic Justified in AD?

1. Option only after failure of non-pharmacological intervention/s
2. Individual is dangerous to him/herself or others
3. Appropriate BPSD targets
   - **Aggressive behavior (physical)**
   - **Distressing hallucinations**
   - **Distressing delusions**
4. Not due to other reversible cause

	Dementia Overall	Dementia Psychosis	Dementia Agitation
Aripiprazole	++	+	+
Olanzapine	+	+/-	++
Quetiapine	+	+/-	+/-
Risperidone	++	++	++

++ moderate-high level of efficacy
+ (low or very low level of efficacy)
+/- (mixed results)
Aripiprazole risperidone, olanzapine and quetiapine: off-label

Seitz DP, et al. *Cochrane Database Syst Rev.* 2011;(2):CD008191

Brexpiprazole (Rexulti): FDA-approved for agitation in AD dementia

Lee D, Slomkowski M, Hefting N, et al. *JAMA Neurol.* 2023;80(12):1307–1316.

GERIATRIC PHARMACIST BOOT CAMP

27

bps APPROVED PROFESSIONAL DEVELOPMENT PROGRAM PROVIDER FOR BCGP

27

GERIATRIC PHARMACIST

BOOT CAMP

PARKINSON'S DISEASE (PD)

bps APPROVED PROFESSIONAL DEVELOPMENT PROGRAM PROVIDER FOR BCGP

Supported in part by an educational grant from the ASCP Foundation.

28

28

Parkinson's Disease (PD)

- Slowly progressive neurodegenerative disorder
- Incurable disorder
- Average onset of sporadic PD is 60 years
- Biggest risk for sporadic PD is <u>advanced age</u>
  - 1% population over age 60
  - 5% population over age 85
- 1.5-2:0 more common in men vs women
- Lifespan: 10-15 years on average

Yang. *NPJ Parkinsons Dis* 2020;6:15.; Willis AW, et al. *NPJ Parkinsons Dis* 2022;8:170; Lee TK, Yankee EL. *Neuroimmunol Neuroinflammation* 2021;8:222-244; Yang W, et al. *NPJ Parkinsons Dis* 2020;6:15; Reeve A, et al. *Ageing Res Rev*. 2014;14(100):19-30.

PD: Motor and Non-Motor Symptoms

(A) MOTOR (Parkinsonian) Symptoms

- Degeneration of substantia nigra *pars compacta*
- Loss of **dopamine** (when symptoms emerge= reduction of 80% of brain dopamine)
- Hypoactive nigrostriatal pathway

T: TREMOR (REST TREMOR)

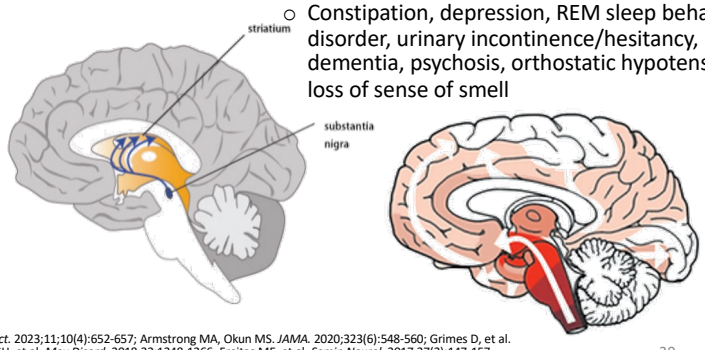
R: RIGIDITY

A: AKINESIA/BRADYKINESIA

P: POSTURAL INSTABILITY

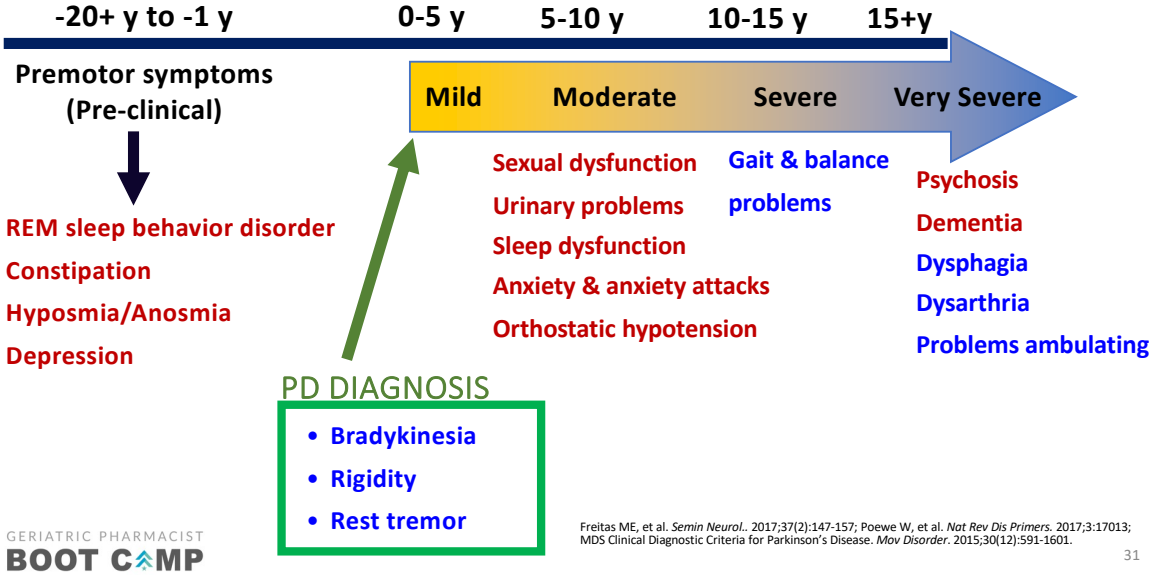
(B) NON-MOTOR Symptoms

- Degeneration of other parts of brain causing loss of other neurotransmitter systems (**cholinergic, serotonergic, adrenergic**):
  - Constipation, depression, REM sleep behavior disorder, urinary incontinence/hesitancy, dementia, psychosis, orthostatic hypotension, loss of sense of smell



Isaacson SH, et al. *Mov Disord Clin Pract*. 2023;11;10(4):652-657; Armstrong MA, Okun MS. *JAMA*. 2020;323(6):548-560; Grimes D, et al. *CMAJ*. 2019;191(36):E989-E1004; Fox SH, et al. *Mov Disord*. 2018;33:1248-1266; Freitas ME, et al. *Semin Neurol*. 2017;37(2):147-157,

PD is a Neurodegenerative Progressive Disorder



GERIATRIC PHARMACIST BOOT CAMP

Freitas ME, et al. *Semin Neurol.*. 2017;37(2):147-157; Poewe W, et al. *Nat Rev Dis Primers.* 2017;3:17013; MDS Clinical Diagnostic Criteria for Parkinson's Disease. *Mov Disorder.* 2015;30(12):591-1601.

31

31

Potentially Inappropriate Medications in PD

- Avoid administration of medications that act as central dopamine receptor antagonists =worsening motor symptoms (AGS Beers Criteria)

Antipsychotics
- ✓ Haloperidol
- ✓ Fluphenazine
- ✓ Risperidone
- ✓ Other antipsychotics EXCEPT for:
  - **Clozapine, quetiapine and pimavanserin**

Antiemetics*
- ✓ Prochlorperazine
- ✓ Metoclopramide
- ✓ Promethazine

* If need to administer antiemetic in PD: 5HT3 antagonists (e.g., ondansetron)

GERIATRIC PHARMACIST BOOT CAMP

2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2023;71(7):2052-2081.

32

32

Available Pharmacotherapy for PD

- No cure and no proven disease-modifying pharmacotherapy
- **Symptomatic pharmacotherapy** is gold standard
- For select patients, symptomatic surgical therapy (e.g., pallidotomy, deep brain stimulation [DBS]) is available

(A) Symptomatic-PHARMACOTHERAPY

- TREATMENT OF MOTOR SYMPTOMS
  - (1) Chronic maintenance therapy
  - (2) Intermittent therapy

(B) Symptomatic-PHARMACOTHERAPY

- TREATMENT OF NON-MOTOR SYMPTOMS

INCREASE FUNCTION AND QUALITY OF LIFE

GERIATRIC PHARMACIST BOOT CAMP

Tsukita K, et al. *Neurology.* 2022;98(8):e859-e871; Freitas ME, et al. *Semin Neurol.* 2017;37(2):147-157; Grimes D, et al. *CMAJ.* 2019;191(36):E989-1004.

33

bps APPROVED PROFESSIONAL DEVELOPMENT PROGRAM PROVIDER FOR BCGP

33

Pharmacologic Therapy for Motor Symptoms: "Antiparkinson" Medications

Medication Class	Medication
Dopamine precursors	Carbidopa/Levodopa (CD/LD); Levodopa (LD); Foscarbidopa/Foslevodopa
Dopamine D2 receptor agonists (D2RAs)	Pramipexole; Ropinirole; Rotigotine; Apomorphine
Catechol-O-methyltransferase (COMT) inhibitors	Entacapone; Tolcapone; Opicapone
Monoamine oxidase type B (MAO-B) inhibitors	Rasagiline; Selegiline; Safinamide
Miscellaneous (NMDA-receptor antagonist and indirect dopaminergic effect)	Amantadine
Adenosine A_{2A} receptor antagonists	Istradefylline
Anticholinergic agents AGS Beers Criteria	Benztropine; Trihexyphenidyl

Dopaminergic therapy (helps to increase dopaminergic activity in brain in nigrostriatal pathway)
Non-dopaminergic therapy

GERIATRIC PHARMACIST BOOT CAMP

Isaacson SH, et al. *Mov Disord Clin Pract.* 2023;11;10(4):652-657; Armstrong MA, Okun MS. *JAMA.* 2020;323(6):548-560; Grimes D, et al. *CMAJ.* 2019;191(36):E989-E1004; Fox SH, et al. *Mov Disord.* 2018;33:1248-1266; Freitas ME, et al. *Semin Neurol.* 2017;37(2):147-157,

34

bps APPROVED PROFESSIONAL DEVELOPMENT PROGRAM PROVIDER FOR BCGP

34

Antiparkinson Medications Adverse Effects (AEs)

Dopaminergic AEs*

- Nausea/vomiting
- Orthostatic hypotension
- Vivid dreams
- Dyskinesia
- Psychotic symptoms
- Impulse control disorder

Anticholinergic AEs

- Constipation
- Urinary retention
- Xerostomia
- Xeropthalmia
- Cognitive impairment (subacute/chronic use)

* Including istradefylline (except for orthostasis)

2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2023;71(7):2052-2081; Stocchi F. *Expert Opin Pharmacother.* 2006;7:1399-1407; Rascol O, et al. *Lancet.* 2002;359:1589-98; Olanow Cwet al. *Neurology.* 2001;56(11 suppl 5):S1-88; Lexicomp Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2019; Prescribing information. Available at www.dailymed.nlm.nih.gov. Accessed on December 27, 2024.

Antiparkinson Symptomatic Pharmacotherapy

(A) Maintenance Therapy (MT)

- Daily scheduled regimen

a) Different monotherapy in early PD stages based on symptoms severity

b) Rational polytherapy in mid-late stages (advanced disease) using carbidopa/levodopa (CD/LD) plus adjunctive therapies to manage OFF periods and dyskinesia

(B) Rescue/On-demand Therapy

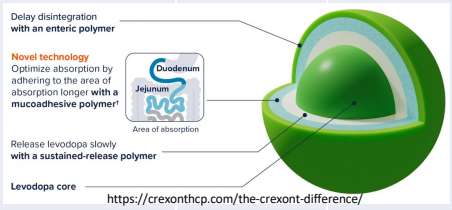
- Intermittent use for OFF periods
- Non-oral delivery
- Max use 5 times daily
- Fast onset of action: 15-20 minutes
- Short duration: ≈60 minutes

Subcutaneous (SubQ)	Apomorphine SubQ pen
Inhaled	LD inhalation powder

Isaacson SH, et al. *Mov Disord Clin Pract.* 2023;11;10(4):652-657; Armstrong MA, Okun MS. *JAMA.* 2020;323(6):548-560; Grimes D, et al. *CMAJ.* 2019;191(36):E989-E1004; Fox SH, et al. *Mov Disord*..2018;33:1248-1266; Freitas ME, et al. *Semin Neurol.* 2017;37(2):147-157,

Highlights of Oral CD/LD Formulations

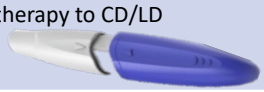
Generic	Brand	Place in Therapy	Comments
CD/LD immediate release (IR)	Sinemet DHIVY	Maintenance therapy (MT)	Can be crushed or chewed (IR tablets) Most commonly used formulation (initial TID dosing) DHIVY: IR 25/100 mg CD/LD fractional tablet with increments CD/LD 6.25 mg/25 mg increments.
CD/LD ER capsule	Rytary Crexont	MT	In general, both ER capsules provides for better with better pharmacokinetic profiles. They are not interchange among themselves and dosing is not same. Rytary: capsule filled with immediate and extended release beads. 3-4 times daily administration. Crexont also known as IPX203: capsules filled with IR and XR beads with adhesive layer of a mucoadhesive polymer and sustained-release polymer, up to 4 times daily administration. CREXONT LD plasma levels lasted longer than other oral CD/LD formulations (IR and ER capsule formulations) in patients with PD.



https://crexonthcp.com/the-crexont-difference/

CREXONT (carbidopa and levodopa). [prescribing information] Amneal Pharmaceuticals LLC. Bridgewater, NJ. August 2024.
RYTARY (carbidopa and levodopa). [prescribing information] Amneal Pharmaceuticals LLC. Bridgewater, NJ. December 2019.
DHIVY (carbidopa and levodopa). [prescribing information]. Riverside Pharmaceuticals Corporation. Washington, DC November 2021
SINEMET (carbidopa and levodopa). [prescribing information]. Organon Global Inc, Jersey City, NJ. June 2021.

Highlights of Non-Oral Oral CD/LD Formulations

Generic	Brand	Place in Therapy	Comments
CD/LD enteral suspension	Duopa	MT in advanced stages and significant motor fluctuations (without ability to control it by other medications)	Surgery (insertion of PEG-J tube); 16-hour infusion bypassing stomach with more continuous dopaminergic stimulation; need to access to caregiver support.
Foscarbidopa/foslevodopa continuous infusion	Vyalev	Maintenance therapy (MT) for advanced PD and significant motor fluctuations 	Subcutaneous 24-hour/day infusion for the treatment administered via small, lightweight (10 oz) nonsurgical wearable pump. Replaces all levodopa-containing medications. https://www.rxabbvie.com/pdf/vyalev_pat_vyafuserpump.pdf. A solution of carbidopa and levodopa prodrugs. Most common AEs: Infusion/catheter site reactions and infections, hallucinations, and dyskinesia.
Levodopa inhalation powder	Inbrija	Rescue therapy only as add on therapy to CD/LD 	Full dose=2 inhaled freshly loaded capsules (2 separate inhalations); need to have dexterity to load the capsule or access to caregiver; contraindications: COPD, asthma.

VYALEV (foscarbidopa and foslevodopa) [prescribing information]. AbbVie Inc. North Chicago, IL. October 2024.
INBRIJA (levodopa inhalation powder). [prescribing information]. Acorda Therapeutics, Inc. Pearl River, NY. December 2022.
DUOPA (carbidopa and levodopa). [prescribing information]. Smiths Medical ASD, Inc. St. Paul, MN. January 2015.

Highlights of Other Antiparkinson Medications

Medication Class	Brand	Place in Therapy and Comment
Dopamine D2 agonists *Pramipexole tablet* *Ropinirole tablet* *Rotigotine transdermal patch* *Apomorphine (SubQ injection)*	 Mirapex Requip Neupro Apokyn	Highest risk for impulse control disorder (pathologic gambling, shopping, hypersexuality, eating) from all dopaminergic drugs! Daily patch Rescue therapy ONLY (SubQ pen)
MAO inhibitors (MAOI) *Rasagiline tablet* *Selegiline tablet (IR; ODT)* *Safinamide tablet*	 Azilect Eldepryl; Zelapar Xadago	Rasagiline once daily dosing Selegiline IR is metabolized to amphetamine and methamphetamine metabolites; Dosed twice daily (the last dose needs to be administered before 3 pm) Selegiline ODT=once daily dosing and absorption in oral cavity (bypassing first-pass metabolism)
COMT inhibitors (COMTI) *Entacapone tablet* *Tolcapone tablet* *Opicapone capsule*	 ComTan Tasmar Ongentys	Only adjunctive therapy to CD/LD (extender of LD bioavailability) Opicapone: once-daily dosing; no delayed diarrhea and brown-orange urine discoloration as other COMTI

GERIATRIC PHARMACIST BOOT CAMP

Lexicomp Online, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2019; Prescribing information. Available at www.dailymed.nlm.nih.gov. Accessed on December 27, 2024; APOKYN (apomorphine hydrochloride injection) [prescribing information]. Supernus Pharmaceuticals, Rockville, MD. June 2022.

39

39

Highlights of Other Antiparkinson Medications

Medication Class	Brand	Place in Therapy and Comment
Adenosine A2 antagonist *Istradefylline tablet*	Nourianz	Only adjunctive to CD/LD (advanced stages, improvement of OFF periods) Dosing needs to be adjusted for smoking status (≥20 cigarettes/day requires dose of 40 mg/day) Patients on strong CYP3A4 inhibitors: 20 mg/day Patient on strong CYP3A4 inducers: avoid use Similar AEs as dopaminergic drugs without orthostasis
Anticholinergics *Benztropine tablet* *Trihexyphenidyl tablet*	 Cogentin Artane	Monotherapy in tremor predominant PD in young patients Not commonly used due to poor efficacy and anticholinergic adverse effects (AGS Beers Criteria)
Miscellaneous *Amantadine IR tablet* *Amantadine XR tablet* *Amantadine XR capsule*	Not available Osmolex Gocovri	IR formulation as monotherapy in early stages IR and XR formulations as adjunctive therapy for dyskinesia AEs: dopaminergic and anticholinergic AEs, livedo reticularis

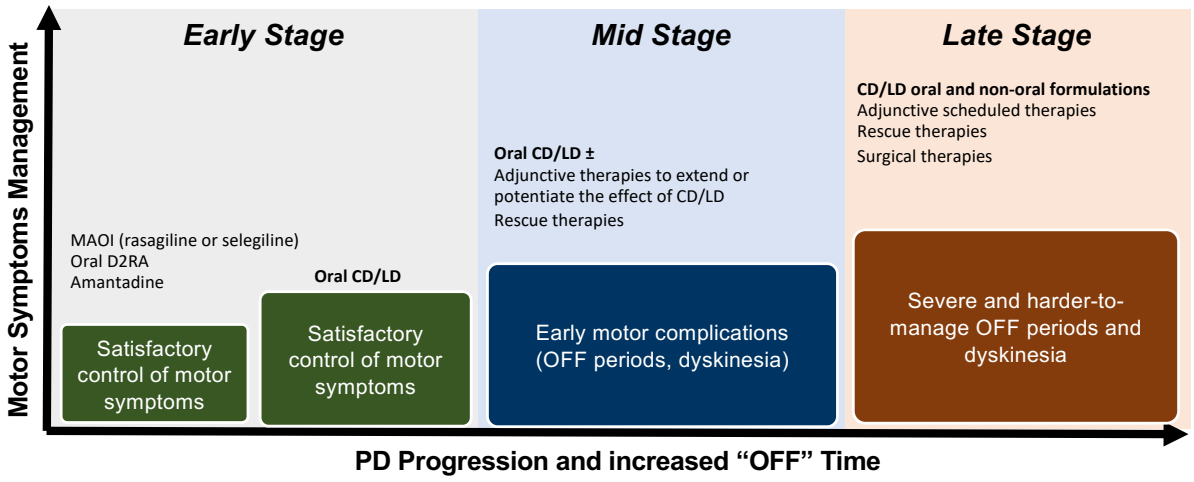
GERIATRIC PHARMACIST BOOT CAMP

NOURIANZ (istradefylline) [prescribing information] Kyowa Kirin, Inc., Princeton, NJ. March 2023.
OSMOLEX ERTM (amantadine) [prescribing information] Vertical Pharmaceuticals, LLC; Bridgewater, NJ . February 2018.
GOCOVRI ® (amantadine) [prescribing information] Adamas Pharma, LLC, Emeryville, CA. January 2021.

40

40

Continuum of Motor Symptom Management



CD/LD=carbidopa/levodopa; MAOI=monoamine oxidase inhibitor; D2RA= dopamine D2 receptor agonist (non-ergot)

GERIATRIC PHARMACIST BOOT CAMP

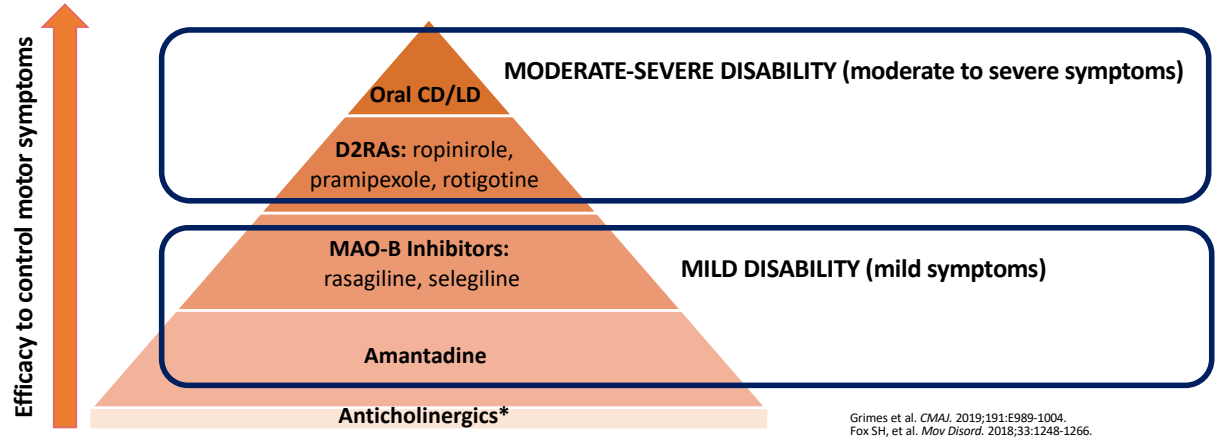
41

41

Initial Monotherapy in *De Novo PD*

Not all antiparkinson medications have the same efficacy

NOTE: catechol-o-methyltransferase inhibitors (COMTIs) or istradefylline are never used as monotherapy



*Weak medications only good for younger patients with predominant rest tremor

Grimes et al. *CMAJ.* 2019;191:E989-1004.
Fox SH, et al. *Mov Disord.* 2018;33:1248-1266.
Oertel W, Schulz JB. *J Neurochem.* 2016;139 Suppl 1:325-337.

GERIATRIC PHARMACIST BOOT CAMP

42

42

Common Motor Complications in PD

Motor Fluctuation	Clinical Presentation/Description
Wearing OFF periods	**Predictable return** of PD symptoms ("OFF" period) before the next scheduled dose of LD **Hypokinetic state due to decreased dopaminergic stimulation**
Random OFF periods	**Unpredictable and random return** of PD symptoms without a clear relationship to LD dosing schedule **Hypokinetic state due to decreased dopaminergic stimulation**
Dyskinesia	**Uncontrolled, involuntary**, choreiform movement primarily of limbs and torso. **Hyperkinetic state due to Increased dopaminergic neurotransmission** Most common type: **peak-dose dyskinesia (30-45 min after LD dose)**

Chaudhuri KR, et al. Mov Disord. 2018;33:909-919; Chou KL, et al. *Parkinsonism Relat Disord.*. 2018;51:9-16;Freitas ME, et al. *Semin Neurology.* 2017;37:147-157.

GERIATRIC PHARMACIST BOOT CAMP

43

43

Management of Common Motor Complications

"Wearing OFF" Hypokinetic state

- Take carbidopa/levodopa on empty stomach
- Increase frequency or dosing of CD/LD
- Switch to ER CD/LD
- Add a COMT or MAO-B
- Add istradefylline or dopamine agonist

Freitas ME, et al. *Semin Neurology.* 2017;37:147-157.
Atoninini A, et al. *Nat Rev Neurol.* 2018;14:693-694.
Fox SH, et al. *Mov Disord.* 2018;33:1248-12667

Random "OFF" Hypokinetic state

- Add rescue medication: inhalation levodopa or subcutaneous apomorphine PLUS
- Take CD/LD on empty stomach
- Increase frequency or dosing of CD/LD
- Switch to ER CD/LD
- Rationale polytherapy (add other antiparkinson adjunctive agents)
- CD/LD intestinal gel of subcutaneous infusion of foscarbidopa/foslevodopa

Peak dose dyskinesia Hyperkinetic state

- Modification of current therapy: REDUCTION OF dopaminergic treatment
- Switch to ER CD/LD
- Add amantadine
- Later: CD/LD intestinal gel or subcutaneous infusion of foscarbidopa/foslevodopa

GERIATRIC PHARMACIST BOOT CAMP

44

44

Self-Assessment Question #2:

A 78-year-old patient with a 3-year history of Parkinson's disease takes carbidopa/levodopa 25/100 orally four times daily. He reports the return of tremors and stiffness approximately 20 minutes before each dose. Which of the following is the best approach to managing this complication?

A. Add benztropine
B. Add morning dose of inhalation levodopa
C. Decrease carbidopa/levodopa dose
D. Initiate tolcapone

45

Management of Orthostatic Hypotension (OH)

- First steps: **non-pharmacologic modalities**

1. Medication reconciliation
   - If on antihypertensives: adjust antihypertensive medication(s)
   - If on other medication(s) worsening OH, evaluate an alternative
2. Increase fluid and salt intake (if not contraindicated)
3. Waist-high compression stockings

- If above steps ineffective: **Pharmacologic management**
  - Midodrine
  - Fludrocortisone
  - Droxidopa

Fanciulli A, Leys F, Falup-Pecurariu C, et al. *J Parkinsons Dis*. 2020;10(s1):S57-S64.

46

Parkinson's Disease Psychosis (PDP)

- Hallucinations: visual > voices
- Higher prevalence in presence of cognitive impairment or dementia

STEPWISE APPROACH
1. Rule out and/or address secondary causes of mental status change
2. If dementia, initiate AChEI (i.e., rivastigmine, donepezil, galantamine)
3. Reduce/Simplify PD regimen in a step-wise approach
4. If symptoms persist, consider atypical antipsychotics (**last step**)

Anticholinergics
⇓
Amantadine
⇓
MAO-B inhibitors
⇓
Dopamine agonists
⇓
COMT inhibitors
⇓
Carbidopa/levodopa

2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2023;71(7):2052-2081.
Seppi K, Chaudhuri RK, Coelho M, et al. *Movement Disorders*. 2019;34:180-198.
Ferreira et al. *Eur J Neurol.* 2013;20:5-15.
Brandt NJ, Chen JJ, Menza M. *Consultant Pharmacist.* 2016; 31:1-16.

Antipsychotics Recommendations for PDP

Drug	Efficacy	Safety	Practice Implications
Clozapine*	Efficacious	Acceptable risk with specialized monitoring	Clinically useful
Quetiapine*	Insufficient evidence	Acceptable risk without specialized monitoring	Possibly useful
Pimavanserin**	Efficacious	Acceptable risk without specialized monitoring	Clinically useful

* off-label use ** FDA-approved use: hallucinations and delusions associated with PDP with or without dementia

2023 Meta-analysis of 19 unique studies assessing antipsychotics in patients with PDP showed that pimavanserin and clozapine showed the most significant ability to improve symptoms without worsening motor function. There was similar probability of improving psychosis for pimavanserin and clozapine.

Use of antipsychotics by patients with PD is associated with a risk of death that was more than twice that of patients who did not use

Yunusa I, Rashid N, Rajagopalan K, et al. *J Geriatr Psychiatry Neurol.* 2023;36(5):417-432.
Seppi K, Chaudhuri RK, Coelho M, et al. *Movement Disorders.* 2019;34:180-198.

Atypical Antipsychotics More Appropriate in PD

- **Clozapine** (5-HT_{2A} > dopamine D2 receptors)
  - 6.25–50 mg once daily (qhs); May increase 25 mg weekly if needed
  - Agranulocytosis risk (frequent CBC monitoring), increased salivation, orthostasis, somnolence
- **Quetiapine** (5-HT_{2A} > dopamine D2 receptors)
  - 12.5–25 mg once daily (qhs); may increase 25 mg weekly if needed
  - Risk for orthostasis and somnolence
- **Pimavanserin** (Inverse 5-HT_{2A} agonist)
  - Delayed onset of action: takes up to 6 weeks to full response
  - 34 mg once daily (qhs)
  - Main substrate for CYP3A4 (dose adjustments)
  - confusional state, peripheral edema, headache, QT interval prolongation risk

GERIATRIC PHARMACIST BOOT CAMP

Seppi K, Ray Chaudhuri K, Coelho M, et al. *Mov Disord*. 2019;34(2):180-198
NUPLAZID (pimavanserin) [prescribing information]. Acadia Pharmaceuticals Inc. San Diego, CA. September 2023.

bps APPROVED PROFESSIONAL DEVELOPMENT PROGRAM PROVIDER FOR BCGP

GERIATRIC PHARMACIST

BOOT CAMP

SEIZURES AND EPILEPSY

bps APPROVED PROFESSIONAL DEVELOPMENT PROGRAM PROVIDER FOR BCGP

Supported in part by an educational grant from the ASCP Foundation.

Seizures in Older Adults

Provoked Seizures (Acute Symptomatic Seizures)

- **TEMPORARY changes in cortical function triggered by reversible causes-leading to <u>provoked</u> seizures**
  - ✓ Medications
  - ✓ Metabolic abnormalities
  - ✓ CNS infection
  - ✓ Acute head trauma
  - ✓ Acute Stroke

Medications Decreasing Seizure Threshold

- Diphenhydramine
- Tramadol
- Bupropion
- Meperidine
- Clozapine
- Haloperidol

GERIATRIC PHARMACIST BOOT CAMP

Neurology. 2018;81:74-81; *Expert Opin Pharmacother.* 2018;19(11):1201-1209; *Expert Rev Neurother.* 2017;17(3):309-318; Lancet Neurol 2017;16(4):311-322; Misra UK, Kalita J. *Ann Indian Acad Neurol.* 2011;14(1):2-8.

51

51

Seizures in Older Adults

Epilepsy (Disorder)

- **PERMANENT changes: leading to <u>unprovoked</u> seizures**

  (A) Pre-existing epilepsy

  (B) Late-onset epilepsy (after age of 65)
  - ✓ Stroke/cerebrovascular disease
  - ✓ AD/Dementia and other neurodegenerative diseases

GERIATRIC PHARMACIST BOOT CAMP

Neurology. 2018;81:74-81; *Expert Opin Pharmacother.* 2018;19(11):1201-1209; *Expert Rev Neurother.* 2017;17(3):309-318; Lancet Neurol 2017;16(4):311-322; Pharmacological Research 2016;106:21-26; Epilepsia 2015;56(3);450-459; NICE Guideline: Epilepsies: Diagnosis and Management. Available at https://www.nice.org.uk/guidance/cg137/resources/epilepsies-diagnosis-and-management-35109515407813. Accesses on January 16, 2024.

52

52

Principles for Treatment Epilepsy

1. Goals of treatment is seizure freedom with minimal/no AEs
   - Better response in seizure freedom in post-stroke epilepsy (80-90%)
2. Educate on seizure triggers and epilepsy/eliminate/control seizure triggers (medications, alcohol, lack of sleep/sleep deprivation , stress, excessive use of stimulants and caffeine)
3. Start with ASM monotherapy at a low dose and slow upward titration
   - Maximal seizure control with minimal or no side effects
   - Usually lower dose might be needed than in younger counterparts
4. ASM selection is driven by 1) seizure type efficacy and 2) other patient's and medication's factors
5. Close monitoring for safety and efficacy
6. If needed use rationale polytherapy (ASM with different MOAs)

53

Antiseizure Medications (ASMs): Older ASMs

Older ASMs

- Carbamazepine (CMZ)
- Valproic acid/divalproex sodium(VPA)
- Phenytoin (PHT)
- Phenobarbital (PHB)
- Primidone (PRM)

AGS Beers Criteria

High rate of physical dependence, tolerance to sleep benefits, greater risk of overdose at low dosages

Why to avoid or less preferable?

1. Liver metabolism (phase II)
2. Many AEs and complications
3. Induction and inhibition of liver enzymes (interactions)
4. Phenytoin has a zero-order kinetics
5. Phenytoin and valproic acid have clinically significant albumin-protein binding=impact on free fraction
   - Hypoalbuminemia
   - Displacement from albumin binding sites (e.g., drug interaction, uremia)

2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2023;71(7):2052-2081.

54

Liver Enzyme Inducers Interactions: CMZ, PHT, PHB, PRM

Enzyme	Substrate Examples
CYP3A4	lurasidone, quetiapine, pimavanserin, donepezil, galantamine, apixaban, methadone, fentanyl, statins, vitamin D, vitamin B12, folic acid, estrogen/birth control
CYP2D6	codeine, tamoxifen, tramadol, β-blockers, TCAs, donepezil, galantamine
CYP1A2	clozapine, olanzapine, rasagiline, ropinirole
CYP2C9	warfarin, phenytoin, glipizide,
CYP2C19	PPIs, diazepam, phenytoin
UGTs	Lamotrigine

Marvanova M. *Ment Health Clin* 2016; 6(1):8-20.
Pharmacotherapy: A Pathophysiologic Approach. 10th ed. New York: McGraw-Hill; 2016.
Curr Neuropharmacol 2010; 8(3):254-67.

55

Liver Enzyme Inhibitors Interactions: VPA

Hepatic Enzyme	Substrate Examples
CYP2C9	warfarin
CYP2C19	cannabidiol, clobazam
UGTs	**lamotrigine***

* When valproic acid/divalproex sodium is added to the already established lamotrigine monotherapy with sustained levels, the dose of lamotrigine needs to be decreased, usually by 50% and patient should be monitored for safety and efficacy.

Marvanova M. *Ment Health Clin 2016*; 6(1):8-20.
Pharmacotherapy: A Pathophysiologic Approach. 10th ed. New York: McGraw-Hill; 2016.
Curr Neuropharmacol 2010; 8(3):254-67.

56

Antiseizure Medications (ASMs): Newer ASMs

Newer ASMs

- **Lamotrigine (LMT)**
- **Levetiracetam (LEV)**
- **Lacosamide (LCM)**
- **Gabapentin (GBP)**
- Topiramate (TPM)
- Zonisamide (ZNS)
- Brivaracetam (BRV)
- Oxcarbazepine (OXC)
- Pregabalin (PGB)

Why more favorable?

1. Linear kinetics
2. More favorable safety profile
3. Less pharmacokinetic interactions
   - Minimal to no liver enzyme induction or inhibition
     - **Topiramate (≥ 200mg/day):** reduce plasma levels of select CYP3A4 substrates such as estrogen and vitamin D
     - **Oxcarbazepine (≥ 1,200mg/day):** significant impact on substrate drug levels, requiring dose adjustments including vitamin D metabolism

GERIATRIC PHARMACIST BOOT CAMP

Marvanova M. *Ment Health Clin* 2016; 6(1):8-20.
Pharmacotherapy: A Pathophysiologic Approach. 10th ed. New York: McGraw-Hill; 2016.

57

57

Preferred ASMs in Older Adults

	Lamotrigine	Levetiracetam	Lacosamide
Clinical Benefit(s)	Broad and potent ASM Mood stabilizing	Broad and potent ASM IV and PO	Broad and potent ASM IV and PO
Effect on Weight	-	-	-
Impact on Bone Health	-	-	-
Induction/Inhibition	-	-	-
Serum Level Monitoring	4-18 mcg/mL	Available, not as useful	Not available
Titration Speed	Slow (SJS/TEN risk)	Rapid	Rapid
Monitoring Need	CBC, CMP	CBC, CMP	CBC, CMP, ECG
Metabolism	Glucuronidation	CYP450 metabolism	Liver/Renal
Adverse Effects (AEs)	Activation	Irritability, depression, behavior changes	PR prolongation, arrhythmia
Interactions	Valproic acid/divalproex, estrogen	N/A	PR prolonging drugs (e.g., β-blockers, verapamil, diltiazem)

GERIATRIC PHARMACIST BOOT CAMP

Prescribing information. Available at www.dailymed.nlm.nih.gov. Accessed on January 16, 2024; French JA, et al. *Neurology.* 2004;62:1252-1260; Abou-Khalil B. Antiepileptic Drugs Review. *Continuum.* (Minneap Minn) 2016;22(1):132-156. [Am.Academy of Neurology]

58

58

Other Commonly Used ASMs In Older Adults

	Advantages	Disadvantages
Topiramate (Topamax™)	• **Broad and potent ASM** • Limited dose-dependent enzyme induction • Minimal to no interactions • Neutral bone effect	• Monitoring: CBC, CMP and weight • AEs: renal calculi, secondary angle closure glaucoma, metabolic acidosis, psychomotor and mental slowing. • Weight loss
Zonisamide (Zonegran™)	• **Broad and potent ASM** • No enzyme induction • Minimal drug interactions • Once daily dosing (long $T_{1/2}$)	• Monitoring: same as topiramate • AEs: same as topiramate • Weight loss
Gabapentin (Neurontin™)	• No enzyme induction or inhibition • Minimal to no drug interactions • Neutral bone effect	• **Weak antiseizure medication (limited efficacy for select focal seizures)** • Monitor CBC, CMP, weight • AEs: swelling, dizziness, drowsiness, • Weight gain • Renal clearance • Multiple daily dosing (three times daily)

GERIATRIC PHARMACIST BOOT CAMP

Prescribing information. Available at www.dailymed.nlm.nih.gov. Accessed on January 16, 2024; French JA, et al. *Neurology*. 2004;62:1252-1260; Abou-Khalil B. Antiepileptic Drugs Review. *Continuum.* (Minneap Minn) 2016;22(1):132-156. [Am.Academy of Neurology]

59

59

Other Commonly Used ASMs In Older Adults

	Advantages	Disadvantages
Oxcarbazepine (Trileptal™)	• Better pharmacokinetics and adverse effect profile than carbamazepine and no autoinduction • Mild-moderate CYP3A4 induction at doses ≥ 1,200mg/day • Not many drug interactions	• Monitoring: CBC, CMP, vit D, and BMD • Negative bone effect at doses ≥ 1200mg/day • AEs: hyponatremia, blood dyscrasia

2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2023;71(7):2052-2081.
Prescribing information. Available at www.dailymed.nlm.nih.gov. Accessed on January 16, 2024;.
TRILEPTAL (oxcarbazepine) [prescribing information].Novartis Pharmaceuticals Corporation, NJ, March 2017.
Abou-Khalil B. Antiepileptic Drugs Review. *Continuum.* (Minneap Minn) 2016;22(1):132-156.

AGS Beers Criteria

TCAs, SNRIs, carbamazepine: May exacerbate or cause SIADH or hyponatremia
The risk remains applicable to oxcarbazepine despite its absence from the 2023 AGS criteria.

GERIATRIC PHARMACIST BOOT CAMP

60

60

Treatment of Epilepsy in Older Adults

FOCAL SEIZURES

- **Lamotrigine (LMT)***
- **Levetiracetam (LEV)***
- **Lacosamide (LCM)***
- **Gabapentin (GBP)***
- Zonisamide (ZNS)
- Topiramate (TPM)
- Oxcarbazepine (OXC)
- Other ASMs for focal seizures

GENERALIZED TONIC CLONIC SEIZURES

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

ABSENCE SEIZURES

- **Ethosuximide (1st line therapy)**
- Lamotrigine
- Levetiracetam

* Preferred therapy in older adults

Kanner AM, et al. *Neurology*. 2018;91:74-81; *Expert Opin Pharmacother*. 2018;19(11):1201-1209; *Expert Rev Neurother*. 2017;17(3):309-318; *Lancet Neurol*. 2017;16(4):311-322; Pharmacological Research 2016;106:21-26; *Epilepsia*. 2015; 56(3);450-9; NICE Guideline: Epilepsies: Diagnosis and Management. Available at https://www.nice.org.uk/guidance/cg137/resources/epilepsies-diagnosis-and-management-35109515407813. Accessed on December 29, 2024.

Bone Health In Epilepsy

25(OH)D Level	Interpretation[1]
≥ 30 ng/mL	Target/Sufficient level
20-29 ng/mL	Suboptimal level
< 20 ng/mL	Deficient level

- If a patient is on high-risk medication or will start high-risk medication as a maintenance therapy:
  - Carbamazepine, phenytoin, primidone, phenobarbital, valproic acid/divalproex sodium > doses of oxcarbazepine ≥ 1,200mg/day (less but still)

1. Monitor 25(OH) vitamin D (maintain levels ≥ 30 ng/mL)
2. Recommend daily vitamin D 1,000-2,000 IU to prevent deficiency
3. DEXA scan in 2 years (if postmenopausal women or men ≥ 65 years)

[1] American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis. Camacho M, et al. *Endocrin Pract.* 2016;22(9):1111-1118.; *Epilepsy Research.* 2015;116:59-66.; *Epilepsia.* 2013;54(11):1997-2004.; *J Clin Endocrinol Metab.* 2011; 96(7):1911-1930.; *Ann Epidemiol,* 2009;19(2);73-78.; *Epilepsia.* 2007; 48(suppl):39-41.

Treatment of Vitamin D Deficiency with ASM

25(OH)D Level	TREATMENT
<20 ng/mL	**Step 1:** Initiate vitamin D 50,000 IU weekly x 8 wks **Step 2:** Initiate vitamin D 1,000-2,000 IU/day and continue until on ASM with negative bone health **Step 3**: Repeat 25(OH)D level after 12 wks

American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis. Camacho M, et al. *Endocrin Pract.* 2016; 22(9):1111-1118; *Epilepsia.* 2013;54(11):1997-2004; *Nat Rev Endocrinol.* 2011; 7(2):73–75.; *Neurology.* 2006;67(11):2005–2014.; *Rev Endocrinol.* 2011;7(2):73-75.

63

Self-Assessment Question #3:

A 67-year-old with a history of ischemic stroke, depression, osteoporosis, obesity, and hypertension develops focused seizures 6 months after stroke. He is diagnosed with epilepsy. **Which of the following would be an appropriate pharmacotherapy recommendation to control his epilepsy?**

A. Oxcarbazepine
B. Levetiracetam
C. Lamotrigine
D. Phenytoin

64

AEs Associated with ASMs

DOSE-DEPENDENT

Associated with a dose increase and high doses/drug serum concentration

- **Neurologic (ALL)**: dizziness, drowsiness, nausea, ataxia, incoordination, blurred vision, double vision, nystagmus
- **Other (medication specific):**
  - **PR-interval prolongation** (lacosamide)*
  - **Depression and irritability** (levetiracetam)
  - **Cognitive slowing** (topiramate ≥200 mg/day)

* ECG monitoring and interaction (risk for heart block) with medication prolonging PR interval such as beta blockers and dihydropyridine calcium channel antagonists (verapamil and diltiazem)

65

Mood Stabilizing Effect of Select ASMs

- On the other hand, several ASMs possess a **mood stabilizing effect** and can improve some psychiatric symptoms
  - **Valproic acid**
  - **Lamotrigine**
  - **Carbamazepine**
  - **Oxcarbazepine**
  - **Eslicarbazepine**
- Use in bipolar disorder
- Can improve irritability and depression in individuals with epilepsy

66

AEs Associated with ASMs

IDIOSYNCRATIC

- **Hematologic abnormalities** (older ASMs)
- **Liver abnormalities** (older ASMs)
- **Hyponatremia*** (CMZ, OXC, ESL)
- **Rash** (aromatic ASMs: PHT, CMZ, OXC, ESL, LMT, PRM, PHB)
- **Alopecia** (valproic acid/divalproex)

AGS Beers Criteria

*May exacerbate or cause SIADH or hyponatremia; monitor sodium level closely when starting or changing dosages in older adults.

AEs Associated with ASMs

LONG-TERM

- **Vitamin B12 and folate deficiency** (older ASMs but not valproic acid/divalproex)
- **Osteoporosis, osteopenia due to vitamin D deficiency** (older ASMs)
- **Kidney stones** (topiramate, zonisamide)
- **Hirsutism, gingival hyperplasia** (phenytoin)
- **Weight gain** (valproic acid/divalproex, gabapentin, pregabalin)
- **Weight loss** (topiramate, zonisamide, ethosuximide)
- **Hyperchloremic, metabolic acidosis*** (zonisamide, topiramate)

* decreased serum bicarbonate below the normal reference range caused by renal bicarbonate loss due to carbonic anhydrase inhibition

GERIATRIC PHARMACIST
BOOT CAMP

PAIN

Supported in part by an educational grant from the ASCP Foundation.

69

Pain Management in Older Adults

Type/Subtype	Examples of Chronic Non-Cancer Pain
Nociceptive-Somatic	Osteoarthritis; Back pain; Pressure ulcers; Tendonitis; Bursitis
Nociceptive-Visceral	Chronic cystitis; End-stage renal disease
Neuropathic	Painful diabetic neuropathy (PDN); Fibromyalgia; Postherpetic neuralgia

- Realistic treatment (SMART) goals
  - **A. Acute somatic pain**: Pain relief = control and reduction of pain to acceptable level (not necessarily 0 level pain)
  - **B. Chronic/neuropathic pain**: Pain reduction to acceptable level = pain reduction of 30-50% as remission might not be attainable.
    - ✓ Concentrate on function and daily activities preservation and restoration

CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022. Available at https://www.cdc.gov/mmwr/volumes/71/rr/rr7103a1.htm?s_cid=rr7103a1_w. accessed on January 16, 2024; Pop-Busui R, et al. *Diabetes Care.* 2017; 40:136-54; Reid MC, et al. *BMJ.* 2015; 350:h532; Bruckenthal P. Pain in the Older Adult. In: Fillit HM, et al., Eds. Brocklehurst's Textbookof Geriatric Medicine and Gerontology. Philadelphia, PA: Elsevier, 2017.

70

Pharmacologic Management of Pain

SOMATIC Pain

- NSAIDs
- Acetaminophen (APAP)
- Opioid analgesics
- Muscle relaxants

NEUROPATHIC Pain

- Antidepressants
  - TCAs
  - SNRIs
- ASMs
  - Gabapentinoids
  - Sodium channel blockers (e.g., carbamazepine, lamotrigine, lacosamide)
- Topical lidocaine
- Topical capsaicin
- α-lipoic acid (nutraceutical for DPN)

Price, R., Smith, D., Franklin, G., Gronseth, G., et al. *Neurology. 2022;98*(1),31–43; CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022. Available at https://www.cdc.gov/mmwr/volumes/71/rr/rr7103a1.htm?s_cid=rr7103a1_w. accessed on January 16, 2024; Pop-Busui R, et al. *Diabetes Care.* 2017;40:136-54; Bruckenthal P. Pain in the Older Adult. In: Fillit HM, et al., Eds. Brocklehurst's Textbookof Geriatric Medicine and Gerontology. Philadelphia, PA: Elsevier, 2017; Dworkin, R. H., O'Connor, A. B., Backonja, M., et al. *Mayo Clinic Proceedings 2007; 82*(4), 527–545.

Mild-Moderate Somatic Pain Considerations in Older Adults

Acetaminophen (APAP)

- **Lack of antiinflammatory effect**
- Favorable safety profile related to risk of bleeding, cardiovascular (CV), gastric and renal negative impacts
- Do not use in severe hepatic insufficiency/liver diseases (cirrhosis, hepatitis)
- Reasonable prescribing in older adults:
  - ≤ 4 gram/24 hours
  - 2 grams/24 hours in more vulnerable patients (frail, very advanced age)

NSAIDs (Rx and OTC)

- **Antiinflammatory effect**
- Gastric and renal toxicity, increased risk for bleeding, cardiovascular AEs and drug/disease interactions (e.g., HTN, MI/ACS, stroke, HF, HTN)

AGS Beers Criteria — Avoid chronic use unless other alternatives are not effective and gastroprotective agent (proton-pump inhibitor or misoprostol) is taken.

- Lower AEs for topical formulations of diclofenac vs oral formulation
  - 1-2 weeks until in full effect

2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2023;71(7):2052-2081; AGS Pharmacological Management of Persistent Pain in Older Adults. Available at http://mysccg.com/generalDocuments/AGS%20Pain%20Guidelines.pdf accessed on January 16, 2024.; Schofield P. The Assessment of Pain in Older People: UK National Guidelines. Age and Ageing 2018; 47:suppl._1.

High-Risk Medications to Avoid

AGS Beers Criteria

- **NSAIDs**: Risk of GI bleeding, renal, and cardiovascular issues. Avoid chronic use unless other alternatives are not effective and gastroprotective agent (proton-pump inhibitor or misoprostol) is taken.
- **Gabapentinoids:** Avoid combination with opioids or benzodiazepines (sedation, overdose, respiratory depression). Adjust for renal clearance (GFR <60 mL/min)
- **TCAs, SNRIs, carbamazepine:** May exacerbate or cause SIADH or hyponatremia
- **Tertiary TCAs:** avoid in syncope due to bradycardia
- **TCAs:** worsening delirium and cognitive function due to anticholinergic AEs.
- **Opioids**: Use cautiously; monitor for dependency and sedation. May cause or worsen delirium
- Meperidine: may have higher risk of neurotoxicity, including delirium, than other opioids;
- **Skeletal muscle relaxants:** are poorly tolerated by older adults due to anticholinergic AEs, sedation, increased risk of fractures; effectiveness at dosages tolerated by older adults is questionable.
  - Avoid: carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol, orphenadrine
  - This criterion does not apply to skeletal muscle relaxants typically used for management of spasticity (i.e., baclofen and tizanidine)

2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2023;71(7):2052-2081.

Pain Management Considerations

- **Non-opioids for nociceptive pain:**
  - Acetaminophen (1st line)
  - Topical diclofenac preferred over oral NSAID (if applicable)
  - NSAID as an alternative if it is needed or it is safe for shorter period using PPI
  - Topicals can be used alone or as add-ons
- **Non-opioids for neuropathic pain:**
  - SNRIs are preferred over TCA
  - If TCA is needed use low dose (secondary > tertiary)
  - ASMs (e.g., gabapentinoids)
  - Select one first line oral agent (**12 weeks** to test efficacy)

a) **Response**: continue
b) **Partial response**: augment with second oral agent or topical
c) **No response**: try other first line therapy

- **Opioids (generally avoid, or use short-term if possible)**:
  - Reserve for those with moderate to severe nociceptive pain or with substantial impairments in physical functioning unresponsive on other therapy

Management of Pain in Severe CKD (stage 4 and 5)

Recommended	AVOID
Acetaminophen	Morphine
Hydromorphone	Codeine
Fentanyl	Systemic NSAIDs
Alfentanil	Meperidine
Buprenorphine	
Methadone	
Gabapentin	
Pregabalin	

GERIATRIC PHARMACIST BOOT CAMP

Roy PJ, Weltman M, Dember LM, et al. *Curr Opin Nephrol Hypertens*. 2020;29(6):671-680.

75

75

Self-Assessment Question #4

Which of the following medications used to treat pain is best **AVOIDED** in older persons with end-stage renal disease?

A. Acetaminophen
B. Gabapentin
C. Hydromorphone
D. Meperidine

GERIATRIC PHARMACIST BOOT CAMP

76

76