Medical Treatments of Dementia

MODULE 8

LIGHT
LAKE ERIE INTEGRATED GERIATRIC HEALTH TEAM

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Outline

- Medications for cognitive symptoms of dementia
- Pharmacologic management of behavioral and psychological symptoms of dementia (BPSD)
- Pharmacologic management of medical comorbidities
- Emerging opinions and clinical trial participation

Learning Objectives

After reviewing this module, the learner will be able to:

- Identify the FDA-approved drugs to treat Alzheimer's disease and related dementias and describe their benefits, side effects and tolerability profiles.
- Describe the medical management of behavioral and psychological symptoms of dementia.
- Describe the medical management of common comorbid conditions.
- Identify when medicinal interventions are recommended.
- Identify dangerous or inappropriate drugs for persons living with dementia.

Key Take-Home Messages

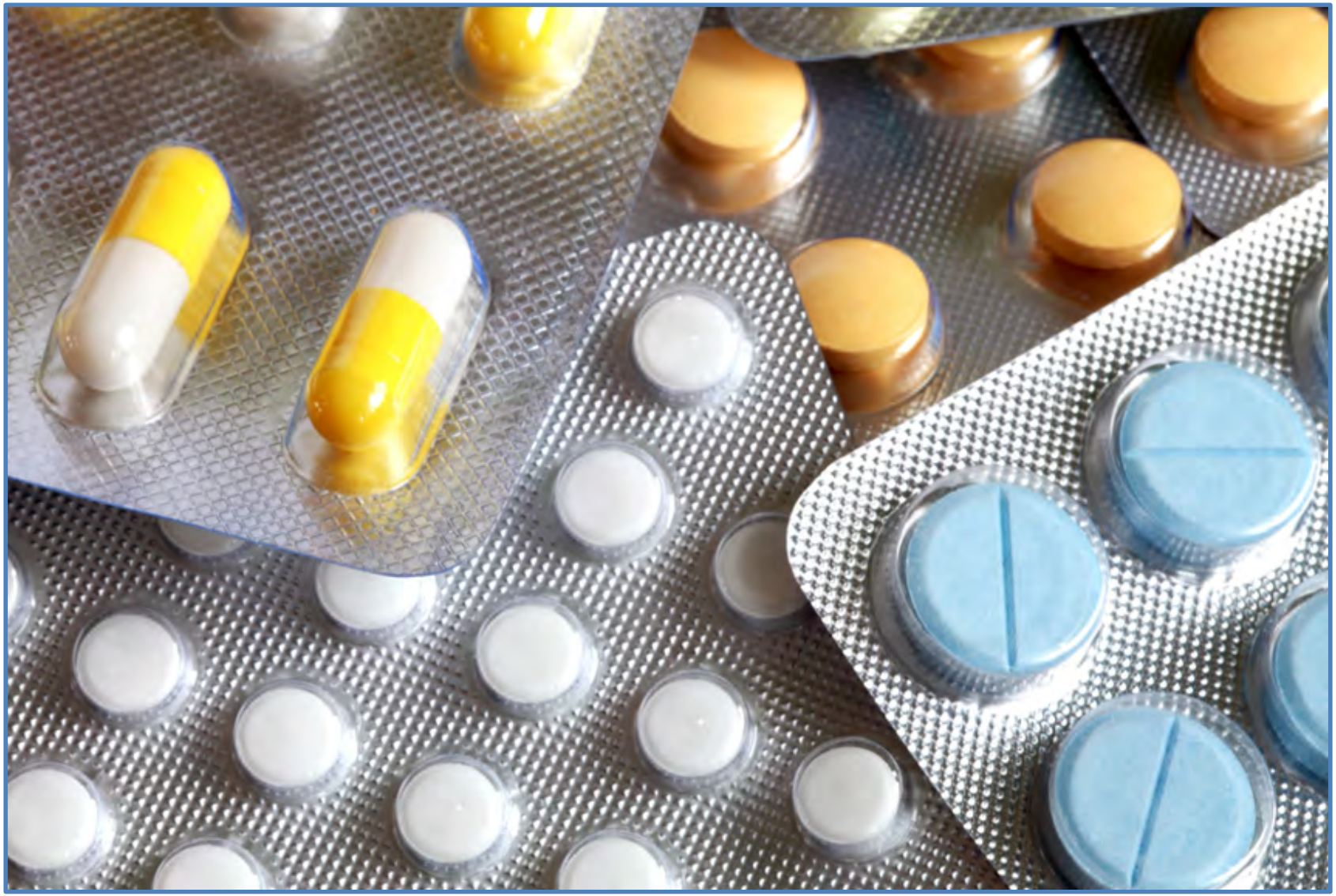
- Currently, there are no curative treatments for the cognitive and functional impairments of dementia.
- The currently approved pharmacological treatments for dementia may slow down the progression of the dementia but cannot reverse cognitive decline.
- Many medications put older persons at risk because they negatively affect cognition or induce delirium in adults ages 65 and older.
- Care must be taken when prescribing drugs for pain and infections in persons living with dementia (PLwD), to ensure that cognition is not further eroded.

Outline

- Medications for cognitive symptoms of dementia
- Pharmacologic management of behavioral and psychological symptoms of dementia (BPSD)
- Pharmacologic management of medical comorbidities
- Emerging opinions and clinical trial participation

Introduction

- There are no curative treatments for cognitive and functional impairments of dementia.
- Nonpharmacologic interventions are considered first-line options, and pharmacotherapies should be considered if these interventions are suboptimal.
- There are 4 agents approved by the FDA for the management of dementia of Alzheimer's disease, and one is also approved for the management of Parkinson's disease dementia.



Pharmacologic Challenges in Treating PLwD

- Prescribing any medication for PLwD must follow a risk-benefit assessment.
- The majority of PLwD are over age 65 and have comorbid conditions (Clodomiro et al., 2013).
- Physiologic changes of aging affect the pharmacokinetics and pharmacodynamics of drugs (Bishara & Harwood, 2014; Pasqualetti et al., 2015).
- PLwD may be taking other medications or products that have no demonstrated benefit for dementia but can interfere with the effectiveness of dementia medications.
- PLwD are at elevated risk of pharmacologic adverse events (AEs) and drug–drug interactions that can limit the use of dementia medications (Clodomiro et al., 2013).
- Practice guidelines are available, but not necessarily current (Rabins et al., 2014; Doody et al., 2001; O'Brien & Burns, 2011).

Medications for the Cognitive Symptoms of Dementia: Overview

- The primary goal of dementia management is to delay the progression of cognitive and functional impairment; secondary goals are to minimize BPSD and preserve quality of life.
- Currently, the only strategies with demonstrated moderate grade of evidence are the 3 approved cholinesterase inhibitors (ChEIs): donepezil, galantamine, and rivastigmine, and the N-methyl-D-aspartate (NMDA) receptor antagonist memantine (Laver et al., 2016).
- These medications do not stop or reverse the course of dementia.
- They should be prescribed with caution due to uncomfortable side effects and cost.


Donepezil
Rivastigmine
Rivastigmine patch


Galantamine
Memantine
Memantine with donepezil

Medications for the Cognitive Symptoms of Dementia: Overview (continued)

- Other approaches have low or very low grades of evidence (Laver et al., 2016; McGuinness et al., 2012).
- Rivastigmine is also approved for management of cognitive impairment associated with Parkinson's disease dementia.
- There are no medications specifically indicated for cognitive impairment in vascular dementia, dementia with Lewy bodies, or frontotemporal degeneration (Li et al., 2015).
- With respect to persons living with dementia and intellectual disability, there is limited data on the usage, benefit and impact upon longevity and quality of life (QoL) of any of the four available medications for dementia, and in particular on those with Down syndrome and early onset Alzheimer's disease (Prasher, 2014). Adverse effects (AEs) may be difficult to determine due to the individuals lower baseline cognitive and language skills. The reliance and adequacy on a treatment effect may be solely dependent on the quality of information obtained from a care provider or aging family member. This may render outcome measures of care inconsistent and potentially unreliable (Livingston et., 2015).

FDA-approved Medications for Dementia

Medication	Indications	Dosing Guidelines	Adverse Effects	Mechanism of Action	Other
Donepezil	Mild to moderate Alzheimer's disease (AD) Moderate to severe AD	5 mg at bedtime, titrate to 10 mg/day at 4-6 weeks Moderate-to-severe: titrate to 23 mg/d at 3 months	Nausea**, vomiting*, diarrhea**, vertigo*, weight loss*, abdominal pain*, constipation*	ChEI	
Galantamine	Mild to moderate AD	4 mg BID, titrate to 8 – 12 mg BID at 4 weeks; ER capsules for QD dosing available	Nausea***, vomiting**, diarrhea*, vertigo**, weight loss*, abdominal pain*, constipation*	ChEI	Adjust dose in renal and hepatic impairment
Rivastigmine	Mild to moderate AD Cognitive Impairment in Parkinson's disease (PD)	1.5 mg BID X 2 weeks; increase by 1.5 mg BID every 2 weeks to max dose of 12 mg/d	Nausea***, vomiting***, diarrhea**, vertigo***, weight loss**, abdominal pain, constipation	ChEI	Caution in low-body weight patients Adjust dose in renal and hepatic impairment

Somewhat*, Moderately**, Very***

FDA-approved Medications for Dementia, continued

Medication	Indications	Dosing Guidelines	Adverse Effects	Mechanism of Action	Other
Rivastigmine Patch	Mild to moderate AD	4.6 mg/24 h topical QD X 4 weeks Titrate to 9.5 mg/24 h topical QD Severe dementia: max of 13.3 mg/ 24 h topical QD after 4 weeks at lower dose		ChEI	Adjust dose in low- and high-body weight patients
Memantine (tablets and solution)	Moderate to severe AD	5 mg/d for 1 week, then 5 mg BID for 1 week, then 10 mg/d am and 5 mg pm then 10 mg BID	Dizziness, headache, confusion, constipation	NMDA	Adjust dose in severe renal and hepatic impairment
Memantine XR capsules	Moderate to severe AD	Memantine XR: 7 mg/d X 1 week, then 14 mg/d X 1 week, then 21 mg/d X 1 week to maximum of 28 mg/d	Dizziness, headache, confusion, constipation	NMDA	Adjust dose in severe renal and hepatic impairment
Memantine XR with Donepezil	Moderate to severe AD	Memantine XR 14 mg/Donepezil 10 mg once daily OR Memantine XR 28 mg/Donepezil 10 mg once daily	Dizziness, headache, confusion, diarrhea, vomiting, anorexia, nausea, ecchymosis	NMDA/ChEI	Adjust dose in severe renal and hepatic impairment

Somewhat*, Moderately**, Very***

Cholinesterase Inhibitors (ChEIs) for Alzheimer's Disease

- It is hypothesized that ChEIs work by inhibiting the enzyme acetylcholinesterase (AChE) which breaks down the neurotransmitter acetylcholine (Li et al., 2015).
- ChEIs are used as symptomatic treatments (Uriri-Glover et al., 2015).
  - They may temporarily delay symptoms from worsening.
  - At best, they afford modest improvements or maintenance of current levels of function for some PLwd (Ströhle et al., 2015.)
- As a class, ChEIs can take up to 6 weeks before improvement is observed (Uriri-Glover et al., 2012).
- As dementia progresses, the effectiveness of ChEIs may be reduced (Caccamo et al.).
- It is not yet known how long PLwD should continue on ChEIs (O'Regan et al., 2015).

Adverse Effects Associated With ChEIs

- There are minimal differences between the ChEIs in effectiveness but some differences in the adverse effects (AE) profiles (Massoud et al., 2011).
- The most common side effects are gastrointestinal (GI) complaints (Borisovskaya et al., 2014; Sheffrin et al., 2015; Uriri-Glover et al., 2012).
  - The increased risk of weight loss should be considered when prescribing for elderly PLwD (Sheffrin et al., 2015).
  - GI complaints are more common than cardiovascular concerns (Howes, 2014; Nordström et al., 2013).
- Risk of AEs increases in PLwD who are over age 85 (Buckley & Saltpeter, 2015).

Adverse Effects Associated with ChEIs (continued)

- Rare but serious AEs include bradycardia, QT prolongations, seizures and syncope (Borisovskaya et al., 2014; Howes, 2014; Uriri-Glover et al., 2012).
- Unique side effect profiles with each of the agents should be considered (Uriri-Glover et al., 2012; Igeta et al., 2014; Lai et al., 2015; Kröger et al., 2015).
- PLwD should discontinue the ChEI if the AEs are intolerable (Borisovskaya et al., 2014).
- Switching to another agent must wait until complete resolution of the AEs (Massoud et al., 2011).

N-methyl D-aspartate (NMDA) Receptor Antagonist Memantine

- Memantine is a potent NMDA receptor antagonist (Dominguez et al., 2011) that is believed to work by regulating glutamate.
- It is indicated for the treatment of moderate to severe dementia associated with Alzheimer's disease (Rive et al., 2013).
  - It can be administered as monotherapy or as an add-on to cholinesterase inhibitors.
  - It is available as tablets, an oral solution, and extended-release capsules (Uriri-Glover et al., 2012; Wilkinson et al., 2014).
- Memantine has been proven to be more effective than other channel blockers (Dominguez et al., 2011).
- Memantine appears to provide benefit in both moderate-to-severe Alzheimer's disease and vascular dementia, but not in mild Alzheimer's disease (Buckley & Saltpeter, 2015). Memantine is associated with improvement by clinical impression in DLB; secondary analyses showed preliminary benefit for cognition and neuropsychiatric features (Aasland et el., 2009; Stubendorff et al., 2014; Wesnes et al., 2014).

NMDA Receptor Antagonist Memantine: Adverse Effects

- It is well-tolerated, has a low abuse potential and confers both cognitive and non-cognitive benefits (Clodomiro et al., 2013; Dominguez et al., 2011; Wilkinson et al., 2014).
- Memantine has a better adverse effect profile than ChEIs (Buckley et al., 2015; Borisovskaya et al., 2014, Clodomiro et al., 2013).

Combination Therapy (ChEI + NMDA Receptor Antagonist)

- Memantine and ChEIs target 2 different aspects of AD pathology (Parsons et al., 2013).
- Donepezil and memantine can be taken separately or in combination (Atri et al., 2013; Howard et al., 2012).
- Adding memantine to either donepezil or galantamine stabilizes cognitive and affective decline for approximately 1 year (Matsuzono et al; Uriri-Glover et al., 2012).
- Not all guidelines recommend combination treatments (Farrimond et al., 2012).

Pharmacological Treatments of Cognitive Impairments in Persons with Lewy Body Dementias (LBD)

- The key treatment targets for LBD include cognitive and functional impairments, Parkinsonism, and BPSD (Ballard et al., 2013).
- There are treatments available for the motor symptoms associated with Parkinson's disease (PD) but few available treatments for cognitive impairment in PD and even fewer in dementia with Lewy bodies (DLB) (Aarsland, 2016).
- Currently, only rivastigmine has been approved for treatment of cognitive impairment in PD.
- There is little-high level evidence related to pharmacotherapy of LBD symptoms (Aarsland et al., 2012; Stinton et al., 2015).

Pharmacological Treatments of Cognitive Impairments in Persons with LBD (continued)

- There is no evidence supporting the use of ChEIs in persons with cognitive impairments in PD that fall short of criteria for dementia (Rolinski et al., 2012).
- There is some evidence of benefit with ChEIs and memantine on cognition, function, and global outcomes in persons with LBD (Aarsland, 2016; Aarsland et al., 2012; Ballard et al., 2013; Manabe et al., 2015; Matsunaga et al., 2015: Mori et al., 2015; Rolinski et al., 2012; Stinton et al., 2015; Wang et al., 2015; Wesnes et al., 2014).
- ChEIs do not appear to have any positive or negative effect on motor function.
- There are associated higher discontinuation rates because of AEs (Matsunaga et al., 2015).

Pharmacological Treatments of Cognitive Impairments in Persons with Parkinson's Disease Dementia

- Persons living with PD dementia (PDD) should be offered ChEIs, but only after performing a careful risk-benefit analysis (Emre et al., 2014).
- Evidence suggests benefits with off-label, high dose donepezil in persons living with PDD (Dubois et al., 2012).
- There are deficits in both dopamine and cholinergic transmission in persons with PDD (Pagano et al., 2015).
- ChEIs could plausibly worsen motor features.
- ChEIs slowed cognitive decline without effect on risk of falls, but there are higher tremor rates and adverse drug reactions with ChEIs.
- The mortality rate is lower in persons with PDD treated with ChEIs.
- Rivastigmine is the only approved treatment for PDD (Pagano et al., 2015).

Pharmacological Treatments of Cognitive Impairment in Persons with Vascular Dementia

- There is no established treatment for cognitive impairment associated with vascular dementia (Birks et al., 2013).
- It is believed that ChEIs have efficacy for the cognitive and neuropsychiatric symptoms associated with vascular dementia (Chen et al., 2016).
  - Research on rivastigmine (Birks et al., 2013) and donepezil (Rockwood et al., 2013) has found small though clinically detectable treatment effects.
  - However, the AE profile of rivastigmine resulted in numerous treatment withdrawals (Birks et al., 2013).

Pharmacological Treatments of Frontotemporal Degeneration (FTD)

- Minimal research has been conducted on ChEIs for FTD (Li et al., 2015).
- The heterogeneity of presentations is particularly challenging (Kaye et al., 2010).
- There is no dedicated treatment for FTD, and no agents have shown efficacy in delaying progression (Alquézar et al 2013; Kaye et al., 2010; Kerchner et al., 2011).
  - ChEIs do not appear to have benefit (Kerchner et al., 2011).
  - There are mixed results regarding benefits of memantine (Boxer et al., 2013; Kerchner et al 2011).

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- Pharmacologic management of medical comorbidities
- Emerging opinions and clinical trial participation

Pharmacologic Management of Behavioral and Psychological Symptoms of Dementia (BPSD): Overview

- BPSD are commonly observed in PLwD – and include depression and anxiety, agitation, apathy, delusions and hallucinations.
- Nonpharmacologic interventions are recommended as first-line treatments of BPSD.
- Some evidence supports the use of dementia medications in PLwD who have BPSD, but the individual agents may not afford comparable benefits (Cummings et al., 2016; Freund-Levi et al., 2014; Wang et al., 2015).
- Currently, there is minimal evidence that any drug improves the quality of life (QoL) in PLwD (Cooper et al., 2013).

Pharmacologic Management of BPSD: Overview (continued)

- Pharmacologic treatments include antidepressants (particularly selective serotonin reuptake inhibitors [SSRIs] and serotonin norepinephrine reuptake inhibitors [SNRIs]), anticonvulsant mood stabilizers, and antipsychotic medications – including both conventional or first generation (FGA), and atypical or second generation (SGA), antipsychotics (Cummings et al., 2016).
- Pharmacologic treatment of BPSD is challenging; the provider must balance the potential benefits of an agent against its potential risks and AEs (Seitz et al., 2013).
- Persons living with dementia and intellectual disability may have had long term behavioral challenges prior to the onset of dementia. They may have been receiving pharmacologic management for many of these behaviors and the impact of this history of behaviors and their treatment may have uncertain consequences upon future treatments including an increased risk of AEs (Moran et al., 2013).

Pharmacologic Management of BPSD: Overview (continued 1)

- Target specific symptoms when selecting an appropriate treatment (Cummings et al., 2016).
- Antipsychotics are limited to management of psychoses and substantially disruptive behaviors (Cummings et al., 2016).
- Antidepressant agents may be used to manage depression, apathy, anxiety, and mild-to-moderate agitation (Leonpacher et al., 2016).
- Mood stabilizing anticonvulsants may be used for aggression or agitation but have considerable AEs (Cummings et al., 2016).
- Of particular concern are the AE profiles of these classes of agents.

Pharmacologic Management of BPSD: Overview (continued 2)

- Of particular concern are the AE profiles of these classes of agents:
  - Antipsychotic agents can adversely affect memory and cognition (Cummings et al., 2016).
    - They should not be used long-term (>12 weeks).
    - There is a black box warning attached to the use of antipsychotics in older persons with dementia.
  - Benzodiazepines should generally be avoided in these populations (Cummings et al., 2016).

Role of Dementia Medications in Management of BPSD

- Evidence supports the use of dementia medications, and particularly ChEIs, in the management of BPSD in PLwD; benefits are generally mild or moderate at best (Berman et al., 2012; Cummings et al., 2016; Freund-Levi et al., 2014; Wang et al., 2015).
- There is less supportive evidence of benefit with memantine in the management of BPSD (Wang et al., 2015).
- Trials have shown some benefit of rivastigmine for neuropsychiatric symptoms in LBD (Ballard et al., 2013; Madson & Brown, 2016).
- However, ChEIs and SGAs have been associated with higher rates of treatment cessations versus memantine (Wang et al., 2015).
- There is little evidence of effectiveness of any agent on treatment of apathy in PLwD; the best results appear to have been associated with ChEIs (Berman et al., 2012).
    - Some evidence supports memantine (Berman et al., 2012).

Pharmacologic Treatments of Psychiatric Symptoms in Persons Living with LBD

- Pharmacologic treatment of psychiatric symptoms in persons living with LBDs can be particularly challenging .
- Persons living with LBD – either DLB or PDD – have symptoms similar to that of AD along with Parkinsonism and visual hallucinations (Ballard et al., 2013).
- Antiparkinsonian treatments have the potential to exacerbate neuropsychiatric symptoms, particularly hallucinations (Ballard et al., 2013).
- Antipsychotic agents should be used with extreme caution in persons with LBDs owing to a risk of severe side effects (Ballard et al., 2013; Gomperts, 2016).
- Not all antidepressants are recommended for persons with LBD (Gomperts, 2016).

Treatment of Visual Hallucinations in LBD

- Treatment of hallucinations or psychosis should include stepwise reduction in medications for the motor symptoms, followed by an antipsychotic (Wood et al., 2010).
- However, there is limited evidence of benefit of antipsychotics except for clozapine (Ballard, Aarsland, Francis, & Corbett, 2013.) As a general rule all traditional antipsychotics like haloperidol should be avoided.
- And, there are serious safety concerns with all antipsychotics in persons living with LBD.
- No systematic clinical trials have convincingly shown that ChEIs can improve visual hallucinations. (Aarsland, 2016).
- There is no systematic evidence for treatment of depression in PDD (Aarsland et al., 2012).

Pharmacologic Treatments of Psychiatric Symptoms in Persons Living with Parkinson's Disease

- Nonmotor symptoms can be more debilitating than motor symptoms (Wood et al., 2010).
- There has been very little research done on the pharmacologic treatment of psychiatric and psychologic issues associated with PD (Connolly & Fox, 2014).
- Pimavanserin was recently approved for the treatment of hallucinations and psychosis in Parkinson's disease.
- Treatment of hallucinations or psychosis:
  - First, eliminate confounding variables (Goldman & Holden, 2014).
  - Next, simplify Parkinsonian medications through a stepwise reduction as tolerated (Goldman & Holden, 2014).

Pharmacologic Treatments of Psychiatric Symptoms in Persons Living with Parkinson's Disease (continued)

- If treatment is still needed, use either quetiapine or clozapine (Emre et al., 2014; Goldman & Holden, 2014).
  - Quetiapine does not require special laboratory monitoring, but strongest evidence of efficacy is with clozapine (Emre et al., 2014; Goldman & Holden, 2014).
  - Antipsychotics should be used with extreme caution (Connolly & Fox, 2014; Hindle, 2013; Wood et al., 2010).
  - FGAs, risperidone, and olanzapine should be avoided (Emre et al., 2014).

Pharmacologic Treatments of Behavioral Symptoms of FTD

- SSRIs and trazodone may have some efficacy for social disinhibition and impulsive behaviors, depressive symptoms, carbohydrate cravings or compulsions (Hughes et al., 2015; Kerchner et al., 2011; Nardell & Tampi, 2014).
- Antipsychotic medications are often used, in low doses, for aggression or delusions (Alquézar et al., 2013).
  - There is minimal evidence supporting their benefit (Kerchner et al., 2011).
  - Persons living with FTD may be more sensitive to the motor side effects of antipsychotic agents, leading to a higher rate of extrapyramidal symptoms (EPS) in this population (Kerchner et al., 2011).

Pharmacologic Management of Depression in PLwD

- Evidence does not support drug treatment of depression as a first choice from a quality of life perspective (Mossello & Ballini, 2012; Herrmann et al., 2013).
- There is insufficient evidence of efficacy for the use of SSRIs for depression in PLwD (Banerjee et al., 2011; Borisovskaya et al., 2014; Herrmann, et al., 2013; Jones et al., 2016; Mossello & Ballini, 2012).
  - SSRIs are generally well tolerated but have no benefit or harm in terms of cognition, mood, agitation, or activities of daily living (ADL) (Jones et al., 2016).
  - There is insufficient evidence to support the efficacy of SSRIs for comorbid depression (Sepehry et al., 2012; Wood et al., 2010).

Pharmacologic Management of Anxiety in PLwD

- There are few systematic studies of medications for anxiety in PLwD.
- SSRIs are often the first choice, followed by mirtazapine, quetiapine and buspirone (Borisovskaya et al., 2014).
- Anxiolytics, including benzodiazepines, can lessen anxiety, restlessness, verbally disruptive behavior, and sleeping problems. However, they generally should be avoided because of AEs (Borisovskaya et al., 2014).

Pharmacologic Management of Agitation in PLwD

- Nonpharmacologic interventions are considered first-line treatment of agitation in dementia.
- Consider medications if:
  - Other possible treatable causes of agitation have been ruled out.
  - The problem behaviors are frequent, aggressive and have the potential for injury (Borisovskaya et al., 2014).
- Care partners should be included in decisions about medications
- Antipsychotic agents are not approved for agitation in dementia but are often used off label (Borisovskaya et al., 2014).

Pharmacologic Management of Agitation in PLwD (continued)

- Studies suggest little benefit of SGAs, and they have AE profiles that offset benefits (Borisovskaya et al 2014).
  - If antipsychotics must be used, SGAs are preferred over FGAs (Borisovskaya et al., 2014).
  - Risperidone has greater effectiveness than galantamine but poorer tolerability (Freund-Levi, Bloniecki, et al., 2014; Freund-Levi, Jedenius, et al., 2014).
- Antidepressants have demonstrated mixed results for agitation in dementia (Borisovskaya et al., 2014).
- Benzodiazepines should be reserved for severe agitation when nothing else works (Borisovskaya et al., 2014).

APA Guidelines for Use of Antipsychotic Medications in PLwD

- The American Psychiatric Association (APA) Practice Guidelines recommend that "*nonemergency antipsychotic medication should only be used for the treatment of agitation or psychosis in patients with dementia when symptoms are severe, are dangerous, and/or cause significant distress to the patient*" (Reus et al., 2016).
- Antipsychotic medications should not be prescribed for any indication without appropriate initial evaluation and appropriate ongoing monitoring (APA, 2015).
- Note that there are instances in which dementia-associated symptoms (e.g., aggressive behavior due to paranoid delusions) pose an acute threat and antipsychotic treatment must be used before formal non-pharmacologic measures can be instituted.

Benefit/Risk Assessment of Antipsychotic Medications in PLwD

- Benefits of antipsychotic medications in PLwD include reduction in severity of symptoms, including hallucinations, delusions, aggression and agitation.
- Risks of antipsychotic medications in PLwD include EPS, hypotension, cognitive decline, and increased risk of stroke.
  - Large-scale studies show increased risk of mortality (up to twice as high as other psychotropic agents), leading to a Food and Drug Administration (FDA) black box warning (Langballe et al., 2014; Maust et al., 2015; Zhai et al., 2016).

Benefit/Risk Assessment of Antipsychotic Medications in PLwD (continued)

- FGA vs SGA:
  - Similar effectiveness, but SGAs generally have better profile on neurological AEs (Atti et al., 2014; Greenblatt & Greenblatt, 2016).
  - Overall increased risk of mortality, especially with FGAs (Greenblatt & Greenblatt, 2016; Pariente et al., 2012; Weintraub et al., 2016)
- Antipsychotics recommended to treat specific symptoms related to a documented diagnosed condition, with close monitoring (CMS, 2013).
- In general, antipsychotics are recommended for shortest duration at lowest dose (Mossello & Ballini, 2012).

Medications for Rapid Eye Movement (REM) Sleep Behavior Disturbance (RBD) in LBD

- Possible treatments for RBD include (high dose) melatonin or (low dose) clonazepam (Aarsland, 2016; Ballard et al., 2013; Emre et al., 2014; Gomperts, 2016; Howell & Schenck, 2015; Zdanys & Steffens, 2015; ; Stevens & Comella, 2013; Trotti & Karroum, 2016).
- There is possible evidence of benefit with memantine (Larsson et al., 2010) and rivastigmine (Brunetti et al., 2014), but very limited evidence for zopiclone, benzodiazepines (other than clonazepam), desipramine, clozapine, carbamazepine, or sodium oxybate (Aurora et al., 2010).

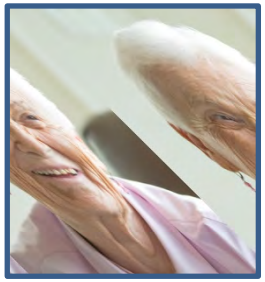
Medications for Other Sleep Disorders

- Sleep problems are common in older people and in persons with dementia; first line treatments are typically nonpharmacologic (McCleery et al., 2014; Zdanys & Steffens, 2015).
- Some evidence suggests improvements with melatonin on sundowning behavior in persons with AD (Zdanys & Steffens, 2015) and insomnia in persons with LBD (Gomperts, 2016).
- Trazodone has shown some benefit for insomnia but has substantial AEs. (Zdanys & Steffens, 2015).

Medications for Other Sleep Disorders (continued)

- The AE profile with benzodiazepines limits their use in older people. If they must be used, they are recommended for short term durations with low doses (Zdanys & Steffens, 2015).
- Nonbenzodiazepine hypnotics may have benefit for management of insomnia, but the elderly may be more sensitive to AEs (Zdanys & Steffens, 2015).
- Sedating antidepressants may be used if the person has insomnia with depression. Mirtazapine may be appropriate if the person has depression with insomnia, but there are no data in nondepressed older people with insomnia (Zdanys & Steffens, 2015).
- No evidence of overall benefit with melatonin, trazodone or ramelteon on increasing total time spent asleep (McCleery et al., 2014).

Outline



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Pharmacologic Management of Medical Comorbidities: Overview

- The American Geriatrics Society (AGS) Beers Criteria identifies medications with high likelihoods of negatively affecting cognition or inducing delirium in adults ages 65 and older. Providers should generally avoid anticholinergics, benzodiazepines, hypnotics, and narcotics, which may worsen amnesia and confusion (AGS, 2015).
- Individuals with dementia who receive primary care often have numerous chronic medical conditions (Reeve et al., 2015).
- Management of these comorbidities is often influenced by or influences management of Alzheimer's disease or other dementias.
- It is important to align pharmacologic treatments with changing goals of care throughout the course of dementia (Reeve et al., 2015).
- Neuroleptic agents may exacerbate motor problems.

Anticholinergic Burden in PLwD: Overview

- Anticholinergic agents are commonly prescribed to older people for treatment of allergies, behavioral problems, depression, urinary incontinence, sleeping problems, gastrointestinal problems, motion sickness, psychotic symptoms, and Parkinson's disease (Kachru et al., 2015).
- AEs of anticholinergics include blurred vision, constipation, dry mouth, impaired sweating, nausea, tachycardia, and urinary retention.
- Anticholinergics can also affect the central nervous system (CNS), causing agitation, confusion, delirium, hallucinations, and memory deficits, as well as leading to further cognitive function impairment in older people with dementia (Kachru et al., 2015).

Anticholinergic Burden in PLwD: Overview (continued 1)

- Anticholinergic toxicity can result from the cumulative burden of multiple medications or metabolites (Lertxundi et al., 2015).
- The combined use of ChEI with an anticholinergic agent may reduce the efficacy of the ChEI (Bishara & Harwood, 2014).
- An estimated 10% to 33% of older PLwD in community settings are taking anticholinergic medications that may be inappropriate (Bishara & Harwood, 2014; Kachru et al., 2015; Reppas-Rindlisbacher et al., 2016).
- There are Anticholinergic Cognitive Burden (ACB) scales that can help determine a person's total anticholinergic burden. A high ACB increases the cumulative risk of cognitive impairment and mortality in older patients (Bishara et al., 2014; Aging Brain Care, 2012).

Anticholinergic Burden in PLwD: Overview (continued 2)

- ChEIs are the most widely prescribed agents for persons with AD, which increases risk of AEs from drug interactions (Pasqualetti et al., 2015).
- Rivastigmine is the only dementia medication that does not undergo hepatic metabolism so is less likely to have pharmacokinetic interactions with other drugs (Pasqualetti et al., 2015).
- Memantine should not be administered alongside compounds acting upon the NMDA receptor system due to the risk of pharmacotoxic psychosis (Pasqualetti et al., 2015).
- Studies show a high proportion of persons with PD are prescribed anticholinergic drugs (Lertxundi et al., 2015).
- Prescribing medications with anticholinergic properties to persons with PD could aggravate some conditions (Lertxundi et al., 2015).
- Using anticholinergic drugs was associated with reduced physical functioning in health-related QoL in older PLwD (Sura et al., 2014).

Use of Antibiotics in PLwD

- The use of antibiotics in PLwD is often related to the stage of dementia. Antibiotics are appropriate for persons living with early and middle stages of dementia but may not be as appropriate for persons living with end-stage disease.
- For persons living with end-stage dementia, antibiotic use is common and may prolong life, but often not for a substantial time, and instead may prolong the dying process (Pengo et al., 2016; Van der Maaden et al., 2015; Van der Steen et al., 2012).
- Persons living with middle or late-stage dementia are often treated with antimicrobials for suspected urinary tract infections in the absence of minimum criteria to support such treatment (D'Agata et al., 2013).

Treating Lower Urinary Tract Symptoms (LUTS) in PLwD

- LUTS are common in older PLwD (Averbeck et al., 2015; Hee et al., 2015).
- Some data indicate different types of LUTS occur at different stages with various dementias (Averbeck et al., 2015).
- ChEIs can lead to urinary incontinence (UI), and UI can occur with dementia (Bishara & Harwood, 2014).

Treating Lower Urinary Tract Symptoms (LUTS) in PLwD (continued)

- Common treatments of LUTS (including UI) include antimuscarinic and anticholinergic agents, such as oxybutynin, tolterodine, solifenacin, trospium or darifenacin.
- Oxybutynin is associated with cognitive worsening and may not be appropriate for use in older PLwD (Bishara & Harwood, 2014; Kachru et al., 2015).
- Tolterodine appears not to have adverse CNS effects, but has been linked anecdotally with amnesia, hallucinations and delirium (Bishara & Harwood, 2014).
- Darifenacin, fesoterodine and trospium appear to have minimal or no effect on cognition (Bishara & Harwood, 2014).
- For persons with urinary retention, alpha-blockers such as tamsulosin, alfuzosin and prazosin have no reported effects on cognition (Bishara & Harwood, 2014).

Pain Management for PLwD

- Pain is common in community-dwelling older PLwD (Hunt et al., 2015; Husebo et al., 2016; Trenkwalder et al., 2015).
- It can be difficult to recognize, diagnose, and assess severity of pain in PLwD.
- Pain may be the underlying cause of agitation (Husebo et al., 2014).
- Many PLwD rarely or never take any pain medications (Hunt et al., 2015).
- Evidence indicates pain remains prevalent despite use of analgesics, likely from suboptimal doses (Husebo et al., 2016).

Outline

- Medications for cognitive symptoms of dementia
- Pharmacologic management of behavioral and psychological symptoms of dementia (BPSD)
- Pharmacologic management of medical comorbidities
- Emerging opinions and clinical trial participation

Emerging Options

- Providers may be asked by care partners and PLwD about over-the-counter alternative and complementary compounds and their effect on cognitive performance. Many pharmacologic agents, vitamins, and herbal products, among others, have been and/or are currently being investigated for the management of impaired cognition in dementia.
- Ginkgo biloba may provide some added benefits to persons with Alzheimer's disease already receiving cholinesterase inhibitors, although the clinical meaningfulness of these benefits is unclear (Canevelli et al., 2014).
- There is inconsistent evidence for the effects on cognition of vitamin E, vitamin B12, vitamin B6, folic acid, omega 3 in fish oil, ibuprofen (Uriri-Glover et al., 2012).
- Various members of the interdisciplinary team may know of new alternatives to medication

Emerging Options (continued)

- No apparent benefit is reported on cognition in women living with AD treated with the selective estrogen receptor modulator (SERM) raloxifene (Henderson et al., 2015).
- There is no evidence of benefit of melissa oil (Burns et al., 2011).
- Cannabinoids have antioxidative and anti-inflammatory properties and reduce the formation of amyloid plaques and neurofibrillary tangles, which are the hallmarks of Alzheimer's disease (Ahmed et al., 2015).

Supporting Participation in Clinical Trials

- Providers can inform persons living with dementia and their care partners about ongoing clinical trials.
  - Discuss potential medical and psychological benefits to participating
  - Be realistic about potential benefits or placebo effects.
- Clinical trials in dementia frequently exclude persons with more than mild symptoms or with significant comorbidities.
- Clinical trials in dementia have previously excluded persons with intellectual disability (and in particular Down syndrome); however, guidelines are now noting that trials should include those adults with Down syndrome (Heller et al., 2018).
- Providers should explain the clinical trial and assess the person's capacity for consent to participate.

Evaluation

1. **Which of the following drugs has FDA approval to manage cognitive impairment in Parkinson's disease?**
   a. Donepezil
   b. Galantamine
   c. Memantine
   d. Rivastigmine

Evaluation (continued 1)

2. **If nonpharmacologic interventions are not successful in managing mild to moderate agitation, which of the following might be the most appropriate initial choice?**
   a. Antidepressant agents
   b. Anticonvulsant agents
   c. Mood stabilizing antipsychotic agents
   d. Benzodiazepines

Evaluation (continued 2)

3. When treating a person for a comorbid medical condition who has Alzheimer's disease, what is the primary concern?

a. Helping to prolong quantity of life

b. Minimizing the anticholinergic burden

c. Avoiding medications that exacerbate motor problems

d. Avoid medications that exacerbate sleep disorders

Evaluation (continued 3)

4. **When might antibiotics not be appropriate?**
    a. For persons with early- or middle-stage vascular dementia
    b. For persons with confirmed urinary tract infections in middle stage dementia
    c. For persons with pneumonia in end-stage dementia
    d. Antibiotics are always appropriate for management of a confirmed bacterial infection

5. **Which of the following types of medications should be avoided specifically for persons with Lewy body dementia?**
    a. Narcotics
    b. Hypnotics
    c. Neuroleptics
    d. Antihistamines

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