

FACULTY GUIDE

Core Module 8:

Medical Treatments of

Dementia

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Slide 1:

- This module—Module 8—identifies and discusses medications used to help lessen symptoms of cognitive and functional impairment in persons living with neurodegenerative dementing diseases. In addition, this module examines the use of medications to treat behavioral and psychiatric symptoms of dementia (BPSD); medical comorbidities and conditions associated with dementia; and participation in clinical trials.

Slide 3:

- In this Module (8) we will discuss the pharmacologic management of dementia, as well as the pharmacologic management of common psychological, psychiatric, and medical comorbidities.
- We specifically focus on the issue of anticholinergic burden in persons living with dementia.
- We conclude by addressing participation in clinical drug trials.

Slide 4:

- Our goal, by the time we finish with this module, is for you to learn about the following topics:
- The FDA-approved drugs used to treat Alzheimer's disease and related dementias and their benefits, side effects, and tolerability profiles.
- The medical management of behavioral and psychological symptoms of dementia.
- The medical management of common comorbid conditions—specifically, pain, lower urinary tract symptoms, and infections.
- Dangerous or inappropriate drugs for persons living with dementia.

Slide 5:

- There are no curative treatments for the progressive cognitive and functional impairments associated with dementia.
- The currently approved pharmacological treatments for dementia may slow down the progression of 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, to ensure that cognition is not further eroded.

Slide 6:

- We begin this module with a discussion of the medications used in the management of cognitive impairment associated with dementia.

Slide 7:

- There are no curative treatments for the progressive cognitive and functional impairments associated with dementia.
- As we discussed in Modules 5 and 6, nonpharmacologic interventions are recommended as first-line treatments for the noncognitive as well as the behavioral and psychological symptoms of dementia.

- We will discuss the four medications for the cognitive symptoms of dementia that are approved by the Food and Drug Administration (FDA) for the management of Alzheimer’s disease; three are cholinesterase inhibitors (ChEIs), and one is an N-methyl D-aspartate (NMDA) receptor antagonist. One of these agents is also approved for the management of dementia associated with Parkinson’s disease.

Slide 9:

- Before prescribing any medications for management of dementia or related conditions, providers must perform a risk–benefit evaluation, taking into consideration all of the factors that might influence effectiveness, safety, and tolerability.
- The majority of persons living with dementia are over age 65, and many have comorbid conditions for which they are already taking medications. They may also be frail. (See Module 5 for information on frailty.)
- The physiologic changes of aging affect the pharmacokinetics and pharmacodynamics of many drugs, causing older people to be more sensitive to the effects of medications.
- Persons living with dementia may also be taking medications, vitamins, herbs, and/or over-the-counter products for other conditions or for illness prevention. These compounds may have no demonstrated efficacy for the prevention or management of dementia but can influence the safety and efficacy of other medications they are taking.
- Together, these factors increase the risk of pharmacologic adverse events and drug–drug interactions and may limit the use of dementia medications.
- There are numerous practice guidelines on the treatment of dementia; some are current, some are out of date. Providers should be careful when consulting out-of-date materials. It is important to keep current with information about treatments, including emerging and alternative options. All are listed in the Resources segment at the end of this guide.

Slide 10:

- The primary goal of dementia management is to delay the progression of cognitive and functional impairment associated with dementia; secondary goals include minimizing other symptoms, particularly the behavioral and psychological symptoms of dementia (BPSD). The underlying focus is preservation of quality of life.
- Although many agents have been investigated to prevent or delay functional decline, the only effective strategies that have a moderate grade quality of evidence supporting their ability to lessen symptoms, including memory loss and confusion, are the three approved cholinesterase inhibitors and the N-methyl-D-aspartate (NMDA) receptor antagonist, memantine.
- The four currently approved medications approved by the Food and Drug Administration (FDA) for management of dementia associated with Alzheimer’s disease: donepezil, galantamine, rivastigmine, and the NMDA memantine. Rivastigmine is also approved for management of cognitive impairments associated with Parkinson’s disease dementia.
- These medications do not stop or reverse the course of dementia. They do not appear to prolong life, and they may have unpleasant side effects. For persons living with Alzheimer’s disease (and possibly other forms of dementia), these medications may lessen some symptoms of the disease, but it is unknown for how long as each case is different.

Slide 13:

- Other approaches, which have included exercise, selegiline, huperzine, *Ginkgo biloba*, and statins, had low or very low grades of evidence.
- 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 or frontotemporal degeneration.

Slide 14-15:

- Currently, there are four approved medications for treatment of dementia associated with Alzheimer's disease. The three cholinesterase inhibitors are donepezil, galantamine, and rivastigmine, which are available in both oral and transdermal formulations.
- Tacrine was the original cholinesterase inhibitor, but it was associated with dosing challenges and significant adverse effects, including hepatotoxicity (Birks, Chong, Grimley Evans, & Tsolaki, 2015; Uriri-Glover, McCarthy, & Cesarotti, 2012), which led to it being discontinued in the U.S. in 2013.
- Memantine is an N-methyl D-aspartate (NMDA) receptor antagonist approved for management of moderate to severe Alzheimer's disease.
- None of these agents is recommended or approved for persons with mild cognitive impairment, as they have demonstrated minimal effectiveness in this population and have the potential for substantial side effects (Russ, 2014).
- It is not known how long the benefits of cholinesterase inhibitors persist. Some studies have found safety and some benefit with longer-term use (up to 18 or 24 months) (Arai et al., 2015; Hager et al., 2014). Studies suggest greatest benefits are observed when treatment is initiated early in the course of the disease (Borisovskaya, Pascualy, & Borson, 2014). There is no evidence of benefit with cholinesterase inhibitors in persons with advanced dementia or those who are older than 85 years (Buckley & Salpeter, 2015).
- The benefits of memantine are more apparent in individuals with moderate to severe disease. Another option for this population is high-dose donepezil (23 mg), which has been approved for moderate-to-severe Alzheimer's disease.
- Currently, rivastigmine is the only FDA-approved medication for dementia in Parkinson's disease.

Slide 16:

- There is substantial scientific evidence that cholinesterase inhibitors work by inhibiting the enzyme acetylcholinesterase (AChE), which breaks down the neurotransmitter acetylcholine.
- These agents are used as symptomatic treatments—they do not modify the course of the disease. They may temporarily help to lessen symptoms or prevent them from worsening, and may help control some of the behavioral symptoms. However, they are not effective for all patients and afford only modest improvements or maintenance of current levels of function.
- As a class, cholinesterase inhibitors can take up to 6 weeks before any improvement over baseline memory or behavior is observed, and it can be months before there is evidence of stabilization in the degenerative course of the disease.

- As the dementia progresses, the brain produces less acetylcholine, which reduces the effectiveness of cholinesterase inhibitors. In addition, ChEIs are not disease-modifying agents, suggesting they would likely lose their efficacy over time .
- The clinical challenge remains: For how long do you keep a person with advanced dementia on a cholinesterase inhibitor medication? Most guidelines and clinical recommendations suggest persons living with dementia should continue on cholinesterase inhibitors until the therapeutic benefit is no longer evident, but provide no clear guidance as to when to discontinue. In addition, evidence notes significant worsening of cognition and neuropsychiatric symptoms after persons discontinue with cholinesterase inhibitors. Currently, there is no clear answer.

Slide 17:

- Although there are minimal differences between the three cholinesterase inhibitors in terms of effectiveness, there may be some minor differences in their adverse effects profiles.
- As a class, cholinesterase inhibitors are generally safe; the most common side effects are cholinergically mediated gastrointestinal complaints, including nausea, diarrhea, vomiting, decreased appetite, and weight loss. In fact, the higher risk of weight loss should be considered when considering these agents for an elderly person living with dementia (Sheffrin, Miao, Boscardin, & Steinman, 2015).
- Cardiovascular effects are less frequent than gastrointestinal effects, and there is some evidence suggesting a possible beneficial effect of cholinesterase inhibitors on cardiovascular outcomes, including reduced myocardial infarctions and cardiovascular mortality.
- Risk of adverse effects substantially increases in persons living with dementia who are over age 85.

Slide 18:

- Rare but serious adverse events include bradycardia, QT prolongations, seizures, and syncope.
- Evidence suggests a higher rate of sleep disturbances associated with donepezil compared with the other two agents (Uriri-Glover et al., 2012). In addition, donepezil should be administered with care in patients with atrioventricular block, or in patients taking other drugs that can prolong the PR interval. There is no apparent effect of donepezil on QT intervals (Igeta, Suzuki, Tajiri, & Someya, 2014).
- Rivastigmine has been associated with a lower risk of pneumonia than donepezil or galantamine (Lai, Wong, Iwata, Zhang, Hsieh, Yang, & Setoguchi, 2015), but a greater likelihood of causing gastrointestinal distress (Uriri-Glover et al., 2012).
- Galantamine has fewer worldwide reports of adverse events than either rivastigmine or donepezil, and the most frequently reported adverse effects were neuropsychiatric, gastrointestinal, general and cardiovascular in nature (Kröger, Moulis, Wilchesky, Berkers, Carmichael, van Marum, ... & Laroche, 2015).
- Persons should be advised to discontinue the cholinesterase inhibitor if the adverse effects are intolerable. However, the second agent should not be initiated until complete resolution of the side effects following discontinuation of the first agent. In comparison, switching to a second agent can occur overnight in cases of lack of efficacy. Switching is not recommended if person living with dementia show a loss of benefit several years after treatment initiation, at which point any ChEI should be discontinued.

Slide 19:

- Memantine is a potent N-methyl D-aspartate (NMDA) receptor antagonist, even at low concentrations that is believed to work by regulating glutamate.
- It is indicated for the treatment of moderate to severe dementia associated with Alzheimer's disease and appears to slow the decline in learning and memory, delay progression of some symptoms, and allow patients to maintain function somewhat longer. It can be administered as monotherapy or as an add-on to cholinesterase inhibitors, and it is available as tablets, an oral solution, and extended-release capsules.
- Memantine has been proven to be more effective than other channel blockers.
- Memantine appears to provide benefit in both moderate-to-severe Alzheimer's disease and vascular dementia but demonstrates no significant benefit in mild Alzheimer's disease or in Lewy body dementias.

Slide 20:

- Memantine is well-tolerated, has a low abuse potential, and confers both cognitive and non-cognitive benefits.
- Memantine has a better adverse effect profile than cholinesterase inhibitors. It does not cause the gastrointestinal effects seen with cholinesterase inhibitors (Borisovskaya, Pascualy, & Borson, 2014) and has better safety in persons with pulmonary, cardiovascular, and central nervous system comorbidities. Drug interactions with memantine are not as likely to involve drugs commonly used in elderly populations (Clodomiro et al., 2013).

Slide 21:

- Memantine and cholinesterase inhibitors target two different aspects of Alzheimer's disease pathology. Specifically, memantine addresses dysfunction in glutamatergic transmission, and cholinesterase inhibitors increase the reduced levels of acetylcholine.
- Donepezil and memantine can be taken separately or in combination. Some studies suggest combination therapy has greater benefits on cognition, function, and global status in persons with moderate to severe Alzheimer's disease than monotherapy with donepezil (Atri, Molinuevo, Lemming, Wirth, Pulte, & Wilkinson, 2013; Farrimond, Roberts, & McShane, 2012), although other studies report no significant benefits of the combination in comparison to monotherapy with either agent (Howard, McShane, Lindesay, Ritchie, Baldwin, Barber, ... & Phillips, 2012).
- Adding memantine to either donepezil or galantamine can stabilize cognitive and affective decline for approximately one year. There may be a greater benefit on apathy with the combination of donepezil and memantine, and a greater benefit for cognitive function with galantamine plus memantine. Combining memantine with a cholinesterase inhibitor is more effective and has fewer side effects than combining two cholinesterase inhibitors. Remember that all benefits are modest.
- It should be noted that not all guidelines recommend combination treatments.

Slide 22:

- Lewy body dementias encompass both dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD). These are considered different diseases with different diagnostic criteria. We have discussed this in greater detail in the prior modules.
- The key treatment targets for Lewy body dementias include cognitive and functional impairments, Parkinsonism, and behavioral and psychological symptoms of dementia (BPSD)—including intense and persistent visual hallucinations, and sleep disturbances.
- Although there are treatments available for the motor symptoms associated with Parkinson's disease, such as carbidopa-levodopa, there are few available treatments for cognitive impairment in Parkinson's disease and no agents are approved for cognitive impairment dementia with Lewy bodies.
- Currently, only rivastigmine has been approved for treatment of cognitive impairment in Parkinson's disease.
- There is little high-level evidence related to pharmacotherapy of LBD symptoms.

Slide 23:

- There is no evidence supporting the use of cholinesterase inhibitors in persons with cognitive impairments in Parkinson's disease that fall short of criteria for dementia.
- There is evidence of benefit with rivastigmine, galantamine, and donepezil, and some evidence of benefit with memantine, on cognition, function, and global outcomes in persons with LBD.
- ChEIs do not appear to have any positive or negative effect on motor function, but there is evidence they are associated with higher discontinuation rates because of adverse effects (AEs), leading to need of careful monitoring of adverse effects throughout treatment.

Slide 24:

- Persons living with Parkinson's disease dementia should be offered cholinesterase inhibitors, but only after performing a careful risk-benefit analysis.
- Some evidence suggests benefits with off-label, high dose donepezil on cognition, executive function, and global status in persons living with Parkinson's disease dementia.
- Dopamine depletion is the key neurochemical impairment in persons with Parkinson's disease, but there are also significant deficits in cholinergic transmission.
- Cholinesterase inhibitors are often used to improve cognitive function and reduce risk of falls, but could plausibly worsen motor features. A systematic review of randomized controlled trials found cholinesterase inhibitors slowed cognitive decline without effect on risk of falls but were associated with higher tremor rates and adverse drug reactions.
- Currently, rivastigmine is the only FDA-approved medication for cognitive symptoms in persons with Parkinson's disease.

Slide 25:

- There is no established treatment for cognitive impairment associated with vascular dementia.
- It is believed that cholinesterase inhibitors have efficacy for the cognitive and neuropsychiatric symptoms associated with vascular dementia.

- Research on rivastigmine and donepezil have found possible effectiveness; findings showed overall small but clinically detectable treatment effects.
- Side effect profile of rivastigmine resulted in numerous treatment withdrawals.

Slide 26:

- There are no FDA-approved drug treatments for frontotemporal degeneration (FTD), which is also known as frontotemporal dementia, frontotemporal disorder, and frontotemporal lobar degeneration.
- A 2015 Cochrane Report noted only one trial on cholinesterase inhibitors for FTD, and the trial was open label with no data of primary outcomes reported (Li, Hai, Zhou, & Dong, 2015).
- The heterogeneity of presentations is particularly challenging.
- There is no dedicated treatment for FTD, and no agents have shown efficacy in lessening symptoms or delaying progression.
- Cholinesterase inhibitors do not appear to have benefit. This is likely related to the relative preservation of cholinergic neurons in persons with FTD.
- There are mixed results regarding benefits of memantine.

Slide 27:

- We now focus on the pharmacologic management of BPSD.

Slide 28:

- As we discussed in Modules 5 and 6, behavioral and psychological symptoms (BPSD) are commonly observed in persons living with Alzheimer’s disease and related dementias—including depression and anxiety, agitation, apathy, delusions, and hallucinations.
- Nonpharmacologic interventions are recommended as first-line treatments of BPSD, but are not always sufficiently effective, necessitating pharmacologic approaches.
- There is some evidence supporting the use of dementia medications in persons living with dementia who have BPSD, but the individual agents may not afford comparable benefits.
- Currently, there is minimal evidence that any drug improves the quality of life in persons living with dementia.

Slide 29:

- In addition to dementia medications, pharmacologic treatments include antidepressants (particularly selective serotonin reuptake inhibitors [SSRIs], serotonin and norepinephrine reuptake inhibitors [SNRIs], among others), anticonvulsant mood stabilizers (such as carbamazepine and valproate), and antipsychotic medications—including both conventional, or first generation, and atypical, or second generation, antipsychotics.
- Pharmacologic treatment of BPSD is challenging; the provider must balance the potential benefits of an agent against its potential risks and adverse effects. In addition, there can be different risks depending upon the type of dementia a person has, particularly with regard to antipsychotic agents.

Slide 30:

- It is important to target the specific symptom when selecting an appropriate treatment.
- Antipsychotics—aripiprazole, haloperidol, risperidone, quetiapine, and olanzapine—are generally limited to management of psychoses and substantially disruptive behaviors, such as agitation and aggression.
- Antidepressant agents may be used to manage depression, apathy, anxiety, and moderate agitation.
 - Commonly used antidepressants include fluoxetine, citalopram, paroxetine, sertraline, trazodone, and mirtazapine.
 - Dosage constraints may be necessary to minimize possible adverse events.
- Mood stabilizing anticonvulsants, such as carbamazepine and valproate, may be used for aggression or agitation, but they have considerable adverse effects.

Slide 31:

- Of particular concern are the adverse event profiles of the following classes of agents:
 - Antipsychotic agents can adversely affect memory and cognition.
 - They should not be used long-term (longer than 12 weeks).
 - They may be associated with a small increased risk of death versus placebo.
 - Risperidone and olanzapine have been associated with increased cerebrovascular events versus placebo.
 - There is a black box warning attached to the use of antipsychotics in older people with dementia, specifically noting that both conventional and atypical antipsychotics are associated with an increased risk of mortality in elderly patients treated for dementia-related psychosis.
- Benzodiazepines should generally be avoided in these populations, but single low doses of lorazepam or zopiclone may be useful to prevent or reduce agitation in very stressful situations.

Slide 32:

- Most evidence supports the use of dementia medications, and particularly cholinesterase inhibitors, in the management of BPSD in persons with different types of dementia, although benefits are generally mild or moderate at best for apathy, agitation, and psychosis.
- There appears to be less evidence supporting the benefit of memantine in the management of BPSD.
- Trials have shown some benefit of rivastigmine for managing neuropsychiatric symptoms in LBD.
- However, cholinesterase inhibitors (as well as second generation antipsychotics) have been associated with higher rates of treatment cessations versus memantine.
- There is little evidence of the effectiveness of any agent on treatment of apathy in persons living with dementia, although the best results appear to have been associated with cholinesterase inhibitors.
 - There is some evidence supporting the use of memantine, but little to no evidence supporting use of stimulants, calcium antagonists, antipsychotics, antidepressants, or anticonvulsants.

Slide 33:

- Pharmacologic treatment of psychiatric symptoms in persons living with Lewy body dementias (LBDs) can be particularly challenging.
- As we have previously noted in many of the modules, persons living with LBD—either dementia with Lewy bodies (DLB) or Parkinson’s disease dementia (PDD)—have symptoms similar to that of Alzheimer’s disease but also have Parkinsonism and a high frequency of neuropsychiatric symptoms, including visual hallucinations.
- Antiparkinsonian treatments have the potential to exacerbate neuropsychiatric symptoms, particularly hallucinations.
- Neuroleptic and antipsychotic agents should be used with extreme caution in persons living with LBDs, owing to a risk of severe side effects—such as increased confusion, worsened Parkinsonism, and orthostatic hypotension, as well as the potential of neuroleptic malignant syndrome (NMS).
 - Approximately 30 percent to 50 percent of persons living with DLB may experience severe drug sensitivity reactions to neuroleptic medications, which can also trigger or exacerbate potentially irreversible Parkinsonism.
 - NMS is a life-threatening neurological disorder.
 - Symptoms of NMS include muscle rigidity, fever, delirium, and autonomic instability.
 - Persons taking antipsychotic agents for psychosis or agitation in LBD should be carefully monitored (Gomperts, 2016).
 - The best evidence for psychotic symptoms is with clozapine in persons living with Parkinson’s disease (Aarsland, 2016).
- Not all antidepressants are recommended for persons living with LBD. Tricyclic antidepressants should be avoided because of their anticholinergic activity, but most selective serotonin reuptake inhibitors (SSRIs) have a low risk for worsening tremor.

Slide 34:

- Treatment of hallucinations or psychosis should include stepwise reduction in medications for the motor symptoms, followed by an antipsychotic—either quetiapine or clozapine.
- However, there is limited evidence of benefit of antipsychotics except for clozapine.
- There are serious safety concerns with all antipsychotics in persons with LBD.
- No systematic clinical trials have convincingly shown that cholinesterase inhibitors can improve visual hallucinations.
- There is no systematic evidence for treatment of depression in PDD.

Slide 35:

- The nonmotor symptoms of Parkinson’s disease can be more debilitating than motor symptoms.
- There has been very little research done on the pharmacologic treatment of psychiatric and psychological issues associated with Parkinson’s disease.
- Pimavanserin was recently approved for the treatment of hallucinations and psychosis in Parkinson’s disease. However, the label notes “it is not approved for the treatment of dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson’s disease psychosis.”

- Treatment of hallucinations or psychosis includes:
 - First eliminate confounding variables—such as delirium, infection, or toxic-metabolic imbalances.
 - Next, simplify Parkinsonian medications through a stepwise reduction as tolerated.

Slide 36:

- If treatment is still needed, use either quetiapine or clozapine.
 - Quetiapine is an atypical antipsychotic that does not require special monitoring. However, the strongest evidence of efficacy is with clozapine.
 - Antipsychotics should be used with extreme caution in Parkinson’s disease, as they can have severe side effects and have the potential of inducing neuroleptic malignant syndrome.
 - Classical neuroleptics (or first generation antipsychotics [FGAs]), risperidone, and olanzapine should be avoided.

Slide 37:

- Serotonin reuptake inhibitors (SSRIs), such as citalopram, fluoxetine, paroxetine, or sertraline, may have some efficacy for social disinhibition and impulsive behaviors, depressive symptoms, carbohydrate cravings or compulsions.
 - Paroxetine may minimize ritualistic behaviors, although studies are contradictory.
 - Trazodone has also been used to minimize BPSD (Kerchner et al., 2011).
- Antipsychotic medications are often used, in low doses, for aggression or delusions.
 - There is minimal evidence supporting their benefit.
 - 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.

Slide 38:

- Evidence does not support drug treatment of depression as a first choice from a quality of life perspective (Mossello & Ballini, 2012).
 - In fact, the 2012 Canadian Consensus Conference moved antidepressants from being a firm recommendation to being an option for management of affective (mood) disturbances in dementia and also noted there is insufficient evidence to recommend for or against SSRIs or trazodone for the treatment of agitation or aggression (Herrmann, Lanctôt, & Hogan, 2013).
- There is insufficient evidence of efficacy for the use of SSRIs for depression in persons living with dementia.
 - In general, SSRIs are well tolerated, but they have no benefit or harm in terms of cognition, mood, agitation, or activities of daily living.
 - The studies on SSRIs and *serotonin–norepinephrine reuptake inhibitors (SNRIs)* in persons living with Alzheimer’s disease with comorbid depression use different diagnostic criteria, different outcome measures, and different compounds being tested. As a result, there is no true evidence to support efficacy of SSRIs for comorbid depression.

Slide 40:

- There are few systematic studies of medications for anxiety in persons living with dementia. This was first discussed in modules 5 and 6.
- Typically, SSRI antidepressants are the first choice, followed by mirtazapine, quetiapine, and buspirone.
- Anxiolytics, including benzodiazepines, can lessen anxiety, restlessness, verbally disruptive behavior, and sleeping problems. However, they generally should be avoided because of the potential to cause delirium and increase the risk of falls; there are also concerns with drowsiness and dizziness. In addition, they should not be taken for long durations because of the risk for tolerance and dependence.

Slide 41:

- As mentioned in modules 5 and 6, nonpharmacologic interventions are considered first-line treatment of agitation in dementia.
- Medications can be considered:
 - After other possible treatable causes of agitation have been ruled out
 - The problem behaviors are frequent, aggressive, and have the potential for injury.
- Care partners may be overwhelmed by agitation in the person living with dementia and may request that the person be medicated before attempting nonpharmacologic interventions. It is important for providers to limit medications to those situations where they are truly indicated.
- Antipsychotic agents are not approved for agitation in dementia, but are often used off label.

Slide 42:

- Results from the Clinical Antipsychotic Trials of Intervention Effectiveness- Alzheimer's Disease (CATIE-AD) found little benefit of second generation antipsychotics and greater adverse event profiles that offset any benefits.
 - Antipsychotics have an increased risk of mortality, with a black box warning.
 - They are associated with extrapyramidal symptoms, sedation, and metabolic syndrome.
 - If antipsychotics must be used, second generation agents are preferred over first-generation agents.
 - Studies have shown risperidone to have greater effectiveness than galantamine on symptoms of irritation and agitation in dementia but poorer tolerability.
- Studies on the use of antidepressants for agitation in dementia have demonstrated mixed results. There can be a worsening of cognition with SSRIs, and the adverse event profile, including nausea, diarrhea, and anorexia, can be particularly problematic for older people with dementia.
- Benzodiazepines can cause a worsening of cognitive function and an increased risk of falls; they should be reserved for severe agitation when nothing else works.

Slide 43:

- 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.”

- Providers should direct care partners to first try nonpharmacologic interventions.
- Providers must discuss potential risks versus benefits with people living with dementia or their care partners.
- If antipsychotics are chosen, they should be initiated at a low dose and titrated up to the minimum effective dose tolerated.
- If clinically significant adverse effects appear, review and taper or discontinue use as necessary.
 - If, after a 1-month trial at an adequate dose, there is no clinically significant response of an antipsychotic drug for a person living with dementia with agitation or psychosis, consider switching or discontinuing.
 - If an adequate response is observed after 4 months—discuss the possibility of tapering and continue to monitor closely while tapering and for at least 4 months thereafter (Reus, Fochtmann, Eyler, Hilty, Horvitz-Lennon, Jibson, ... & Yager, 2016).
- Antipsychotic medications should not be prescribed for any indication without appropriate initial evaluation and appropriate ongoing monitoring (APA, 2015).
- It is noted 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 nonpharmacologic measures can be instituted.

Slide 44:

- Benefits of antipsychotic medications in persons living with dementia include reduction in the severity of symptoms, including hallucinations, delusions, aggression, and agitation.
- Risks of antipsychotic medications in persons living with dementia 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.

Slide 45:

- First-generation versus second-generation antipsychotic agents:
 - Have similar effectiveness, but second generation antipsychotics (SGAs) generally have better profiles on neurological adverse effects.
 - Second generation antipsychotics are associated with more severe metabolic adverse effects, including weight gain, hyperglycemia, diabetes risk, and hyperlipidemia, compared with typical antipsychotics (Atti et al., 2014). This can be even more problematic because older people with dementia have physiologic changes causing reduced liver and kidney function.
 - Evidence points to a higher relative risk of mortality with first versus second generation antipsychotic agents.

- The highest risk of mortality among use of second generation agents is associated with olanzapine, risperidone, quetiapine, and fumarate (Weintraub et al., 2016).
 - Antipsychotic use is associated with a modest, time-limited increase in risk of myocardial infarction among community-dwelling older patients being treated with cholinesterase inhibitors (Pariante, Fourrier-Réglat, Ducruet, Farrington, Béland, Dartigues, ... & Moride, 2012).
- Other guidelines recommend use of antipsychotics when they are used to treat specific symptoms related to a documented diagnosed condition, the person is closely monitored, and they are used sparingly.
- In general, antipsychotics are recommended for the shortest duration at the lowest dose. The provider also has a responsibility to educate the care partner in all risks and adverse side effects, and to encourage first-line options of nonpharmacological interventions.

Slide 46:

- Possible treatments for rapid eye movement (REM) sleep behavior disorders frequently associated with LBD include (high-dose) melatonin or (low-dose) clonazepam.
 - Clonazepam has been shown effective in up to 90 percent of patients with RBD (Stevens & Comella, 2013).
 - Studies of melatonin have not shown strong effects—reporting no apparent benefit on sleep quantity in Alzheimer’s disease, no benefits on cognition, and minimal benefit on objective sleep measures in Parkinson’s disease (Trotti & Karroum, 2016).
- There is possible benefit with memantine and rivastigmine, but very limited evidence for zopiclone, benzodiazepines (other than clonazepam), desipramine, clozapine, carbamazepine, or sodium oxybate.

Slide 47:

- Sleep problems are common in older people and in persons with dementia; first line treatments are typically nonpharmacologic.
- There is some evidence suggesting possible improvements with melatonin on sundowning behavior in persons with Alzheimer’s disease and insomnia in persons with LBD; recommendations are for the lowest possible dose of immediate release formulation to best approximate normal physiologic patterns.
- Trazodone has shown some benefit for insomnia but has substantial adverse effects, including sedation, dizziness, orthostatic hypotension, arrhythmias, priapism, and psychomotor impairment. This side effect profile increases risk of falls. It is likely better tolerated than tricyclic antidepressants.

Slide 48:

- The adverse effect profile with benzodiazepines limits their use in older people, who are even more sensitive to the adverse effects of tolerance, withdrawal, oversedation, cognitive impairment, and falls. If they must be used, they are recommended for short-term durations with at low doses.

- Nonbenzodiazepine hypnotics, including zolpidem, zaleplon, zopiclone, and eszopiclone, may have benefit for management of insomnia, but elderly people may be more sensitive to motor and cognitive side effects due to their slower metabolism, medical problems, and polypharmacy.
- Sedating antidepressants may be used if the person has insomnia with depression. Tricyclic antidepressants are often used for this purpose but are not recommended for use in older people because of their poor tolerability profiles. Mirtazapine may be appropriate if the person has depression with insomnia, but there are no data for nondepressed older people with insomnia.
- A 2014 Cochrane report found no evidence of overall benefit with melatonin, trazodone, or ramelteon (a melatonin receptor agonist) on increasing total time spent asleep.

Slide 50:

- We now examine the pharmacologic management of medical comorbidities, beginning with the anticholinergic burden in persons living with dementia, and how it influences treatment of dementia and other medical concerns.

Slide 51:

- Individuals with dementia who receive primary care often have numerous chronic medical conditions.
- Management of these comorbidities is often influenced by or influences management of Alzheimer's disease or other dementias.
- Certain medications may exacerbate cognitive deficits—such as anticholinergics, antihistamines, narcotics, sedatives, and benzodiazepines.
 - Neuroleptic agents may exacerbate motor problems in persons with Lewy body dementias.
 - Sleep aids, anxiolytics, antipsychotics and other medications should be recommended only after a careful risk/benefit analysis has been done and nonpharmacologic strategies are unsuccessful in effectively managing the symptoms; this was discussed in Modules 5 to 7 and 12.
- It is important to align pharmacologic treatments with changing goals of care throughout the course of dementia. (See Module 15 for more information.) Goals may change from prolonging life in persons living with early-stage dementia to optimizing quality of life in persons with end-stage dementia.
- The American Geriatrics Society's Beers Criteria identifies medications with high likelihoods of negatively affecting cognition or inducing delirium in adults ages 65 and older. According to the Beers criteria, providers should generally avoid anticholinergics, benzodiazepines, hypnotics, and narcotics, which may worsen amnesia and confusion.

Slide 52:

- 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.
- Some are used specifically for their anticholinergic properties (antiparkinsonians, antispasmodics, antimuscarinics) and some have anticholinergic properties that are not

fundamental to their primary purpose (antihistamines, antipsychotics, and antidepressants, such as amitriptyline).

- Adverse effects of anticholinergics include blurred vision, constipation, dry mouth, impaired sweating, nausea, tachycardia, and urinary retention.
- Anticholinergics can also affect the central nervous system, causing agitation, confusion, delirium, hallucinations, and memory deficits, as well as leading to further cognitive function impairment in the elderly person with dementia.

Slide 53:

- Anticholinergic toxicity can result from the cumulative burden of multiple medications or metabolites.
- The combined use of a cholinesterase inhibitor with an anticholinergic agent may reduce the efficacy of the cholinesterase inhibitor.
- An estimated 10 percent to 33 percent of older adults with dementia living in community settings are taking anticholinergic medications that may be potentially inappropriate.
 - High anticholinergic burden is common among older persons who typically see multiple providers. A study estimated a 24-percent increased risk of high anticholinergic drug burden associated with every five additional physicians providing care to the person in the prior year (Reppas-Rindlisbacher et al., 2016). This study, which took place in Canada, notes U.S. Medicare beneficiaries see an average of seven providers a year—including five different specialists (Reppas-Rindlisbacher et al., 2016).
 - The most frequently prescribed anticholinergics were oxybutynin, solifenacin, paroxetine, tolterodine, promethazine, and cyclobenzaprine (Kachru et al., 2015).
 - Many prescribed drugs which have a high cholinergic burden have potentially safer alternatives—such as amitriptyline and oxybutynin. When possible, select a comparable agent with nonanticholinergic properties (Kachru et al., 2015).
- 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.

Slide 54:

- Cholinesterase inhibitors are the most widely prescribed agents for persons living with Alzheimer's disease. This puts them at high risk of adverse effects with concomitant use of antipsychotic drugs, even when taken in low doses. Other risks are associated with concomitant use of arrhythmics and acetylcholinesterase inhibitors.
- Rivastigmine is the only dementia medication that does not undergo hepatic metabolism and is therefore less likely to have pharmacokinetic interactions with other drugs.
- Memantine should not be administered alongside compounds acting upon the same receptor (NMDA) system (including amantadine, ketamine, and dextromethorphan) due to the risk of pharmacotoxic psychosis.
- Studies show a high proportion of persons living with Parkinson's disease are prescribed anticholinergic drugs—particularly antidepressants, antipsychotics, urological drugs, analgesics, and antihistamines.

- Prescribing medications with anticholinergic properties to persons living with Parkinson’s disease could aggravate some conditions—including dementia, urinary retention, and constipation—and can increase the risk of falls.
- Using anticholinergic drugs was associated with reduced physical functioning in health-related quality of life in older adults living with dementia.

Slide 56:

- The use of antibiotics in persons living with dementia is often related to the stage of dementia. Antibiotics are appropriate for persons in 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. This is discussed in greater detail in Module 12.
- 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. Antibiotics should be reserved for confirmed infections and when they are consistent with the preferences of the person living with dementia.

Slide 57:

- Lower urinary tract symptoms (LUTS) are common in older persons living with dementia.
- Some data indicate different types of LUTS occur at different stages with various dementias.
 - Persons living with Alzheimer’s disease may get urinary incontinence in late-stage dementia.
 - LUTS usually precedes severe cognitive impairment in persons living with LBD and vascular dementias.
- Cholinesterase inhibitors can lead to urinary incontinence, and urinary incontinence can occur with dementia.
- Common treatments of LUTS (including urinary incontinence) include antimuscarinic and anticholinergic agents—such as oxybutynin, tolterodine, solifenacin, trospium or darifenacin.

Slide 58:

- Common treatments of LUTS (including UI) include antimuscarinic and anticholinergic agents, such as oxybutynin, tolterodine, solifenacin, trospium, or darifenacin.
- The antimuscarinic agent oxybutynin has been associated with cognitive worsening and may not be appropriate for use in older persons living with dementia.
- Tolterodine appears not to have adverse central nervous system effects, but has been linked anecdotally with amnesia, hallucinations, and delirium.
- Darifenacin, fesoterodine, and trospium appear to have minimal or no effect on cognition.
- For persons with urinary retention, alpha-blockers such as tamsulosin, alfuzosin, and prazosin have no reported effects on cognition.

Slide 59:

- Pain is common in community-dwelling older adults living with dementia.

- It can be difficult to recognize, diagnose, and assess severity of pain in persons living with dementia, and there are no tests or guidelines for pain in this population.
- Pain may be the underlying cause of agitation in persons living with dementia.
 - It is unknown if opioids relieve or exacerbate agitation in persons with dementia (Brown, Howard, Candy, & Sampson, 2015).
- Many persons living with dementia rarely or never take any medications for pain, despite high levels of bothersome pain.
- In persons living with dementia who do use analgesics, evidence indicates pain remains prevalent, likely from suboptimal doses.

Slide 60:

- We conclude this module by looking at emerging options and participation in clinical trials.

Slide 61:

- 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 living with Alzheimer's disease already receiving cholinesterase inhibitors, although the clinical meaningfulness of these benefits is unclear.
- There is inconsistent evidence supporting the effects of vitamin E, vitamin B12, vitamin B6, folic acid, omega 3 in fish oil, and ibuprofen on cognition in dementia.

Slide 62:

- There is no apparent benefit on cognition in women living with Alzheimer's disease treated with the selective estrogen receptor modulator (SERM) raloxifene.
- There is no evidence of benefit of melissa oil.
- 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.
 - These mechanisms of action suggest cannabinoids may afford benefit for the management of agitation and aggression in Alzheimer's disease (Liu, Chau, Ruthirakuhan, Lanctôt, & Herrmann, 2015) as well as other dementia-related symptoms (Ahmed et al., 2015).
 - Clinical studies have not demonstrated promising results on cognitive impairments with dementia (Libro, Giacoppo, Rajan, Bramanti, & Mazzon, 2016), but have demonstrated significant improvement in quality of life scores in persons living with Parkinson's disease (Chagas, Zuardi, Tumas, Pena-Pereira, Sabreira, Bergamaschi, ... & Crippa, 2014).
 - Additional, larger studies are warranted.

Slide 64:

- 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.
- In contrast to clinical trials on other illnesses, people with more than mild symptoms or who have significant comorbidities usually cannot participate in clinical trials on dementia. The situation is the opposite of cancer trials, which begin testing treatments with advanced disease.
- Providers should explain the clinical trial and assess the person's capacity for consent to participate.
 - The resource section has several links to important clinical trials underway.

Slide 65:

Talking Points:

These items are provided to allow faculty to evaluate what students have learned. The items can be used in several ways including given at the end of the lecture to assess knowledge or as a pre-post test to assess knowledge gain. These items have face validity. Psychometric testing was not conducted on these items.

Answer:

1. d. Rivastigmine

Slide 66:

Answer:

2. a. Antidepressant agents

Slide 67:

Answer:

3. b. Minimizing the anticholinergic burden

Slide 68:

Answers:

4. c. For persons with pneumonia in end-stage dementia
5. c. **Neuroleptics**