DEMENTIA

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Week 7

Educational Objectives:

1. Recognize the signs of dementia and mild cognitive impairment and separate them from confounding diagnoses (e.g., depression) in primary care patients
2. Review the diagnostic criteria for dementia, and when referral to a specialist or neuroimaging is indicated
3. Briefly discuss pharmacologic and non-pharmacologic treatment options for dementia, and more specifically Alzheimer's disease
4. Review special considerations for the care of patients with dementia such as caregiver burden, safety, and behavioral disturbances

CASE ONE:

Mr. RP is a 72-year-old male with a past medical history of atrial fibrillation on rivaroxaban, hypertension, COPD and an active tobacco user who is seen in clinic with his wife for a yearly visit. He reports he is doing "great," has no concerns and is only here because his wife made him come. His wife states that he has become forgetful and no longer helps with chores around the house. He does not interact with his adult children when they come to visit and prefers to watch TV and sleep. She also reports he is having urinary accidents because he is "too lazy to go to the bathroom." She notes these behaviors have been ongoing for about six to 12 months. When asked about this, Mr. RP just smiles, shrugs his shoulders and says "maybe." Of note, he is very hard of hearing and is not wearing his hearing aids.

Questions:

1. **Should Mr. RP be screened for dementia and what screening tools exist that can be used in the primary care setting? What other diagnoses should be considered?**
   Memory loss or forgetfulness is a frequently encountered chief complaint in primary care and yet there is evidence that 40% (Chodosh, 2004) to 65% (Valcour, 2000) of mild cases of dementia are missed by their primary care doctors until they reach a moderate to severe level. Symptoms that may be reported include inability to learn new tasks, forgetting locations or friends' and family members' names, decreased ability to perform tasks at home, and changes in personality. Dementia (or major neurocognitive disorder) is defined by the Diagnosis and Statistical Manual of Mental Disorders-5 (DSM-5) as "a significant decline in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual motor function and social

cognition) that interferes with a person's independence in daily activities." It also must represent a change from the patient's prior level of functioning, occur outside of the setting of delirium, and cannot be better accounted for by another mental disorder. In comparison, patients with mild cognitive impairment also have a measurable deficit in at least one of the above listed domains, however, it is not severe enough to affect the patient's activities of daily living. According to a prospective longitudinal study including 1,011 participants followed over on average 2.5 years, the annual rate of conversion from MCI to dementia was 3-10% in community settings and 10-15% in specialty clinics (Farias, 2009).

Please note that the terminology surrounding dementia is somewhat confusing as the diagnostic criteria has changed over time. As more evidence emerges, previous definitions of dementia are no longer accurate as the various subtypes now have individual criteria, while they were previously combined into one generalized category of dementia. The DSM-III and DSM-IV referred to this category as "Delirium, Dementia, Amnestic and Other Geriatric Cognitive disorders" and it was changed to "major and mild neurocognitive disorders" with several subtypes in DSM-5. In DSM-IV, a diagnosis of dementia required both memory impairment and impairment in one of the following: aphasia, apraxia, agnosia or decline in executive function. In DSM-5 the requirement for memory impairment has been removed as it is recognized that non-amnestic forms of dementia exist, although less commonly. The DSM-5 criteria for neurocognitive disorder requires impairment in only one or more of the six domains listed above (complex attention, executive function, learning and memory, language, perceptual motor function and social cognition). In addition, the terms "dementia" and "Alzheimer's" are often used interchangeably but do have separate diagnostic criteria. The National Institute on Aging-Alzheimer's Association workgroup on diagnostic guidelines for Alzheimer's disease released in 2011 defines "probable AD" and "possible AD" as impairment in two or more of the following: memory, reasoning, visuospatial abilities, language functions or changes in personality.

The United States Preventive Services Task Force (USPSTF) in February 2020 reiterated its prior recommendations that there is insufficient evidence to screen all asymptomatic community-dwelling adults (older than age 65) for cognitive impairment. Certainly, if a person exhibits signs or symptoms of cognitive impairment based on their history or input from friends or family, it is reasonable to proceed with screening tests for dementia. One reason the USPSTF cites for insufficient evidence for universal screening at all encounters is the lack of evidence that current pharmacologic and non-pharmacologic treatments for dementia have shown a clinically significant benefit for patients or caregivers. However, the Centers for Medicare & Medicaid Services (CMS) does cover a "cognitive impairment assessment" as part of their yearly wellness exam (Medicare.gov).

There are several validated screening tests for dementia that are designed to test a combination of attention, memory, recall, language, fluency, executive function, and orientation. To be effective in a primary care setting, they must be quick, easy to administer, valid, reliable, and reproducible. The most widely recognized screening test is the Mini Mental Status Exam (MMSE); this is a 30-point assessment which can be

completed in less than 10 minutes. Despite clinicians' familiarity with the MMSE, it is less commonly used now, after it was copyrighted in 2011. A systematic review of 149 studies estimated the sensitivity and specificity of the MMSE in the detection of dementia to be 81% and 89% respectively (Tsoi, 2015). The St. Louis University Mental Status Exam (SLUMS) and the Montreal Cognitive Assessment (MoCA) are alternatives to the MMSE and both also have a maximum score of 30 points. Both are considered superior to the MMSE in detecting mild cognitive impairment. The disadvantage of the MoCA (sensitivity 91% and specificity 81% of detecting dementia) (Tsoi, 2015) is that it is longer to administer (approximately 15 minutes in duration) than the MMSE. The Mini-Cog (sensitivity 91% and specificity 86% of detecting dementia) (Tsoi, 2015) is the shortest of the tests to administer and incorporates a three-word registration, clock drawing and recall. On all tests, if the patient scores below a predetermined cut-off, it is indicative of possible cognitive impairment but must be interpreted in context as it is not diagnostic of dementia alone. Low scores can also be attributed to intellectual disability, language barriers, mood disturbances, hearing difficulties and low education levels. The scores on these exams can be recorded and followed over time and may help detect a pattern of decline; it is important to note that patients may score higher than their "true" level on subsequent testing due to previous experience with the test or patients may score lower without reflecting true clinical changes. It has been suggested that a test-retest difference of greater than 2-3 points may represent "true" clinical change while smaller differences may be as a result of chance (Hensel, 2007).

Dementia must be distinguished from other conditions which can exist concurrently or confound the diagnosis of dementia. It is not uncommon with normal aging processes to experience a change in cognitive abilities; this is usually manifested by decreased ability to form new memories (although retention of old memories is not usually affected) and a decrease in processing and speed response. Many patients will verbalize worry over behaviors such as misplacing objects or struggling to remember names of infrequent acquaintances however they can be reassured this is not pathologic if it does not rise to the level of interfering with their ability to function independently, and if it is not evident on objective cognitive screening tests. Subjective memory complaints may still be a precursor to the later development of dementia, but this area is still being explored.

Dementia must also be differentiated from depression, which has an estimated prevalence of 2-14% (Beekman, 1999) in adults older than 65 years old. Many patients ultimately diagnosed with depression first present to the clinic with subjective memory complaints and thus it should always be in the differential. In contrast, many patients diagnosed with dementia will lack insight into any change in their cognition and are often brought to medical attention by their family members. A common screening tool for detecting depression in the elderly adult is the Geriatric Depression Scale or the Patient Health Questionaire-2 (PHQ2).

Although less commonly seen in the outpatient setting, delirium (defined as decreased attention and concentration, fluctuating course and impairment in cognition) must also be considered and ruled out.

2. **You administer the MoCA screening test in clinic and Mr. RP scores 11/30, consistent with moderate cognitive impairment. You decide to gather more information from the patient and his spouse. What other information regarding Mr. RP's home life and ability to care for himself should you inquire about?**
Once you have established a positive screen for dementia, it is important to gather more information before you can make a diagnosis of dementia. It is imperative to conduct a thorough history including the patient's past medical, social, and family history as you would for any other encounter. A screen for any contributing medications (especially sedatives, opioids, benzodiazepines, anticholinergics) is also prudent.

   It is critical to obtain collateral information regarding cognitive and behavioral changes from family, friends, or close contacts as they are usually the first to notice subtle changes. The decline in function related to dementia often occurs gradually and can be overlooked (or attributed to normal aging) by close contacts for years prior to coming to the attention of the patient's physician.

   It is necessary to ascertain how the patient is functioning at home and any changes from their prior cognitive status. This will include assessments of a patient's ability to carry out activities of daily life (ADLs) and self-care such as continence, bathing, toileting, grooming, feeding, and also instrumental activities of daily life (IADLs) which include more complex tasks such as shopping, preparing food, housekeeping, laundry, using the telephone, administering medications, and paying bills. These can be assessed using the Katz Index of ADLs and the Lawton Instrumental Activities of Daily Living Scale. It is important to determine if a patient is still able to work and if they are still driving.

CASE ONE CONTINUED:

You ask the patient and his wife how he is managing at home. You ask about ADLs and IADLs. He is fully dependent in IADLs and needs cueing and assistance with some ADLs (toileting, reminder to eat), but is independent in ambulation and feeding. You feel comfortable diagnosing him with dementia based on his MoCA scoring and impairment in ADLs/IADLs.

3. **What types of dementia exist? Do you need any additional information before deciding what is the etiology of Mr. RP's dementia?**
The classes of dementia can be divided into those caused by: neurodegenerative disorders (Alzheimer's, Dementia with Lewy Bodies (LBD), Parkinson's, Frontotemporal); substances (alcohol-related); vascular dementia (VD); those associated with other chronic illnesses (HIV-related, hypothyroidism); nutritional deficiencies (B12, folate, copper); and structural abnormalities (after traumatic brain injury, subdural hematomas, normal pressure hydrocephalus [NPH]). The most common subtype is Alzheimer's dementia (AD) which accounts for approximately 43% of all cases of dementia (Goodman, 2017).

A complete physical exam including neurological exam is necessary and can sometimes help narrow down the etiology of the dementia. Specific findings to look for include: gait disturbances (asymmetrical walking pattern in LBD, shuffling and impaired balance in VD, ataxic gait in NPH); presence of resting tremors or cogwheel rigidity (Parkinson's); bradykinesia, focal deficits suggestive of prior strokes (VD); or frontal release signs (primitive reflexes) in frontotemporal dementia.

Dementia is often a clinical diagnosis and a presumptive diagnosis can be made based on consistent symptoms, a low score on an objective and validated screening tool, and history supporting impairment in functional activities. The majority of patients will be presumed to have AD if they fit the typical pattern: gradual onset, lack of insight into loss of memory, decreased ability to form new memories with relative preservation of long-term memory, and minimal changes in personality. As the disease progresses, many will develop difficulty with words, language, and recognizing objects. If the symptoms that the patient experiences are not typical of AD, then a different specific etiology should be investigated.

Table 1. Comparison table of most common types of dementia

	History	Physical	Imaging and Pathology
Alzheimer's Disease (60-80%)	Gradual onset, progressive decline	Prominent memory loss, especially short-term memory. Normal gait. No focal deficits. Possible aggression.	Generalized atrophy (mostly in medial temporal lobe). Beta amyloid plaques. Neurofibrillary tangles.
Vascular dementia (10-20%)	Hx of CVAs, HTN, DM, smoking. Can be abrupt or gradual onset. Often stepwise decline.	Focal neurologic deficits to suggest prior infarcts. Problems with concentration, communication and following directions. Memory (especially short term) usually intact early on.	Generalized volume loss. Evidence of prior infarcts. White matter lesions.
Frontotemporal (5%)	Usually gradual onset but can often be rapidly progressive after onset.	Disinhibition, inappropriate behaviors. Apathy. Language difficulties (aphasia). Memory usually intact early on. Can have increased appetite/weight gain.	Frontal and temporal atrophy. Left to right asymmetry.
Dementia with Lewy Bodies (5%)	Gradual onset	Prominent visual hallucinations, parkinsonian features (shuffling gait, increased tone, tremors). Cognition can fluctuate hour by hour.	Generalized atrophy. Lewy bodies in cortex and midbrain.
NPH	Incontinence, gait imbalance	Wide based and shuffling gait	Enlarged ventricles with obstruction

CASE ONE CONTINUED:

Mr. RP's wife requests a referral to a specialist and inquires what other work-up, bloodwork and imaging is needed.

4. **Is routine bloodwork and imaging necessary in the work-up of dementia?**
According to the guidelines set forth by the National Institute on Aging and Alzheimer's Association and supported by the American Academy of Neurology (AAN) in 2011 (McKhann, 2011), the basic laboratory work-up should include complete blood cell count, electrolytes, glucose, BUN/creatinine, serum B12, thyroid function tests, and liver function tests. Other sources also recommend HIV and syphilis testing, as these are all potentially reversible causes.

   The AAN recommends routine neuroimaging for all patients with dementia. Other guidelines reserve imaging for those who are young (age < 60), have acute decompensations, rapid symptom progression, equivocal presentations or unexplained symptoms, or if a reversible cause is thought likely (e.g., NPH, subdural hematoma). If neuroimaging is performed, MRI is the preferred imaging modality, however, a non-contrast CT is reasonable if the patient is claustrophobic, has metal implants or has another reason they cannot have a MRI performed. The most common findings on imaging include: cortical atrophy, ventricular enlargement with evidence of obstruction (NPH) or without evidence of obstruction (hydrocephalus ex vacuo), prior cerebral infarctions and cerebrovascular disease, and microhemorrhages. At some centers, the use of PET/SPECT imaging is being incorporated as an adjunct in the diagnosis of AD. The American College of Radiology (ACR) appropriateness campaign states that non-contrast MRI or CT is "usually appropriate" in most cases (ACR, 2019). In addition, the ACR states that FDG-PET and PET-amyloid scans are indicated in the assessment of progressive dementia and assessment of neurodegeneration in subjects with MCI (ACR, 2015). FDG-PET is most useful for identifying early AD especially when the diagnosis is unclear (early MCI) or ruling out other causes of dementia. The classic findings for AD on FGD-PET is bilateral temporoparietal and posterior cingulate cortex hypometabolism.

   Neuropsychiatric testing is a much longer and more detailed battery of tests evaluating many of the same domains as the screening tests. The testing will usually take two to six hours and will provide a more detailed report of specific levels of functioning in multiple domains, as well as the possible etiology of the impairment and recommendations for management. These tests can be helpful to diagnose dementia versus MCI in equivocal cases and can sometimes help point to the etiology of the disease when it is not clear. It is not indicated in all cases of dementia. Unfortunately, neuropsychiatric testing uses many hours of a clinician's time (one-two hours for preparation, six hours to perform the testing, several hours for interpreting the results, writing a report and then sharing the results with family) which greatly reduces the availability of these tests. Neuropsychiatric testing is sometimes covered, in part, by insurance companies for specific indications

(ADHD, dementia, intellectual disability, etc.) but often will only be covered for the testing portion (and not reviewing the findings with the patient). In addition, many insurance companies will only cover the referral if it is "medically necessary to make the diagnosis" and usually requires preauthorization. Without insurance, cost ranges from several hundreds to several thousand dollars.

In select cases, a lumbar puncture or other invasive testing may be needed (for example to rule out infection; support a diagnosis of AD with low amyloid and high tau levels; confirm oligoclonal bands in multiple sclerosis; or monitor response to large volume spinal tap in NPH). This is usually reserved for dementia in younger patients or those with rapidly progressive forms of dementia.

Referral to a specialist should be considered (neurologist, geropsychologist) if the diagnosis is uncertain or the primary care physician is not comfortable managing the symptoms. This usually occurs with early or severe behavioral changes, Parkinsonian features, language problems, hallucinations, or a young age at diagnosis.

CASE TWO:

Mr. DR is a new patient to your clinic. He comes with his wife who does the majority of the talking during the interview. She states he was formally diagnosed with Alzheimer's disease six months ago, however, in hindsight, she now realizes it probably was gradually developing over the last several years. She states his former doctor told him he could no longer drive but did not offer any other treatments. She is wondering what treatment options are available for him.

5. **What pharmacological treatment options are available for AD?**
   The treatment of AD (and dementia more broadly) should focus on improving the most troubling symptoms and improving quality of life for the patients and caregivers. If any reversible causes of dementia are detected, they should be corrected. Unfortunately, only limited therapies are available for the treatment of AD and the benefit is modest at best. All patients with MCI or dementia can be offered tools to help compensate for memory loss such as writing lists, setting reminders/timers (e.g., to take medications), pre-filling medication pill boxes, etc. Consultation with an occupational therapist can be helpful in this regard.

   Most patients with AD should be offered a trial of a cholinesterase inhibitor (CEIs). The currently available cholinesterase inhibitors include donepezil (GoodRx monthly cost $6), rivastigmine (GoodRx monthly cost $25 oral, $100 patch) and galantamine (GoodRx monthly cost $20-45). The data regarding their efficacy is mixed. A 2003 meta-analysis including 29 placebo-controlled trials of patients with mild-moderate AD treated for at least one month with a cholinesterase inhibitor determined a "modest beneficial impact on neuropsychiatric and functional outcomes for patients with AD" (Trinh, 2003) as

judged by improvement in ADL/IADLs and improved scores on neuropsychiatric inventory testing. A 2006 Cochrane Review which included 13 randomized, double-blinded, placebo-controlled studies also showed a modest benefit in improvement of both ADLs and cognitive testing after the use of cholinesterase inhibitors for a period of six months (Birks, 2006). This improvement was determined using a 70-point Alzheimer Disease Assessment Scale-Cognitive Subscale (ADAS-Cog). Importantly, most clinicians will not be able to see noticeable differences at follow up visits with patients taking CEIs and will need to rely on caregiver's determination of benefit in the patient's daily activities. Although all three CEIs are similar in terms of effectiveness and side effects, they do have some notable differences. Donepezil, the first of these medications marketed, is still the most widely prescribed due to its once daily dosing, whereas both rivastigmine and galantamine need to be administered twice daily if taken orally. Rivastigmine has the advantage that it is available in a patch formulation if a patient is unwilling or unable to take it by mouth. One limiting side effect of all CEIs is they can lead to gastrointestinal (GI) side effects including nausea, vomiting, diarrhea, and anorexia; this is more commonly seen with galantamine than donepezil, and very infrequently seen using the transdermal patch formulation of rivastigmine. In addition, the CEIs increase vagal tone and must be used cautiously and/or discontinued in patients with bradycardia, atrioventricular blocks, and syncope. Donepezil (more so than the others) can also lead to vivid dreams or sleep disturbances but this can be minimized by morning administration or switching to a different CEI if needed. Ultimately, patients' dementia symptoms will progress and as the CEIs are not disease-modifying they can be stopped (tapered) if they are not helping or an adverse side effect develops.

The only other FDA-approved medication class for the treatment of AD is memantine, a NMDA-receptor antagonist. It has shown benefit in patients with moderate or severe AD, but not in mild cases. Memantine is thought to be neuroprotective (prevents ongoing damage to brain neurons and possibly restores function of damaged neurons) by preventing pathological stimulation of NMDA receptors. It can be used alone (if a patient cannot tolerate CEIs) or in conjunction with a CEI (a combination pill exists in two doses as well). The major side effects noted are dizziness, and some people can experience agitation, confusion, or hallucinations. In most cases, memantine is continued as long as the patient is not developing side effects, even if no clinical improvements are noted, as it may be disease-modifying.

CASE TWO CONTINUED:

He is started on memantine and donepezil and Mr. DR and his wife return three months later. His wife thinks he is doing "about the same or maybe a little better" but also reports she is exhausted because he is not sleeping at night and she is awake all night long caring for him. She also reports she is preparing his favorite foods, but he doesn't seem to have an interest in eating any longer. She asks if you can prescribe a medication to improve his sleep?

6. **Should an antidepressant be prescribed? What are the options for treating the behavioral symptoms and sleep disturbances that often occur with AD?**
The first thing to recognize in this case is that his caregiver is experiencing some fatigue with his care. It can be very overwhelming to care for a spouse or family member with dementia. Caregiver burnout should not be taken lightly, and community resources and education should be offered to caregivers when needed. Attending adult daycare or respite care is an option for some patients with AD in order for their caregivers to have a reprieve. In general, caregivers should aim to speak in calm tones, limit the number of choices they offer to the patient, follow a daily routine, encourage scheduled voiding, offer frequent small meals high in protein, and plan on taking extra time with all activities and trips out of the house. Additional caregiver information can be found at: https://www.alz.org/help-support/caregiving.

One of the most challenging aspects of care is treating the behavioral and sleep issues associated with dementia. It is important when new symptoms arise to evaluate for evidence of a new medical condition (e.g., infection) that might be contributing. If none is found, there should be a careful analysis for changes in prescription or over-the-counter medications, other substances used, and assessing for worsening depression and/or pain. Additionally, special attention should be paid to whether the patient has any hearing or vision loss and whether appropriate corrective measures have been taken if deficits are present (e.g., providing hearing aids or glasses).

The neuropsychiatric symptoms that occur are often more troubling to the caregivers than the cognitive symptoms. Examples include agitation, hallucinations, delusions, and sleep-wake disorders. Many caregivers ask for the use of medications to treat these symptoms. The data on SSRIs are mixed: early data from Depression in Alzheimer Disease Study (DIADS) supported the use of SSRIs for the treatment of agitation and delusions in patients with AD, however, data from the HTA-SADD study published in 2011 (Brodaty, 2011) showed conflicting reports. In the latter study, 300 patients with moderate dementia were randomized to placebo, sertraline, or mirtazapine and all showed improvement on the Cornell Score for Depression and Dementia (CSDD), however, there were no significant differences between the groups. In 2014, the randomized, placebo-controlled, double-blinded CitAD trial showed a reduction in agitation in patients with probable AD (excluded patients with a major depressive episode as defined by DSM-IV) treated with citalopram vs placebo (Porsteinsson, 2014). SSRIs are indicated for patients with co-existing AD and major depression; at times it may be difficult to separate the signs and symptoms of depression from dementia as they often overlap.

For all of these behaviors, it is important to optimize non-pharmacologic options prior to considering pharmacologic options. This is notably important before considering using anti-psychotics in the population. In 2005, the FDA released a warning that the use of anti-psychotics in patients with dementia has an increased rate of mortality. The American Psychiatric Association guideline from 2015 recommends non-emergent antipsychotic use only "when symptoms are severe, are dangerous, and/or cause significant distress to the patient" (Reus, 2016). In addition, haloperidol should be avoided as a first-line agent (preference for olanzapine, risperidone or quetiapine).

Anti-psychotics should be used only as a last resort if non-pharmacologic options have failed or the behavior is severe or unsafe.

Many patients with AD will experience sleep-wake disorders. As with sleep-wake disordered patients without AD, the hallmark treatment includes increasing sunlight exposure during day (lifting up blinds and curtains), encouraging activity during the daytime, limiting oral intake late at night to prevent needing to urinate during sleep hours, and avoiding alcohol or caffeine in the evening. If behavioral interventions do not work, trazodone can be considered as an adjunct to helping with sleep latency (prescribed in the lowest possible dose).

The most important consideration is to maintain the safety of both the patient and to prevent any aggression that may harm the caregiver. At times, higher levels of care (nursing homes, inpatient psychiatric units) are necessary temporarily or long-term in order to control the behaviors or as patients decline and need more assistance with ADLs. It is also important to discuss with the caregivers other safety measures at home including door locks to prevent wandering, clearing out walkways, and removing rugs to prevent falls, installing handrails and non-stick mats. Dangerous items such as knives and medications should be kept locked up.

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Knowledge Questions:

1. **All patients with dementia should be put on a cholinesterase inhibitor (e.g., rivastigmine, donepezil) early after diagnosis as it can prevent progression of Alzheimer's' disease.**

    a. True
    b. False

2. **All patients with suspected dementia should be referred for a neuropsychological evaluation to diagnose dementia.**

    a. True
    b. False

3. **Haldol is the preferred antipsychotic agent to use if a patient is exhibiting signs of aggression or harm to self or their caretaker.**

    a. True
    b. False

4. **Which of the following is NOT a potential common side effect of donepezil?**

    a. Vivid dreams
    b. Nausea or vomiting
    c. Diarrhea
    d. Tachycardia

Answers:

1. **b** *Cholinesterase inhibitors may be useful for symptom control (improvement in cognition), however, they are not known to be disease modifying.*
2. **b** *Dementia can be diagnosed based on scoring below a pre-set cutoff in a validated screening test (SLUMS, MoCA, MMSE, etc.) combined with an impairment in functional activity.*
3. **b** *Haldol should be avoided. Preferred anti-psychotics are olanzapine, risperidone or quetiapine and they should only be used after non-pharmacologic treatments have been attempted and/or if the patient is a danger to themselves or others.*
4. **d** *Tachycardia. All cholinesterase inhibitors can increase vagal tone and can lead to bradycardia.*