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May 2007 "Pharmacist's Perspective; Alzheimer's Disease" 707-000-07-005-H01

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**THIS MONTH--
"Alzheimer's Disease"**

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This month's lesson presents a topic that is becoming more prevalent in our society--Alzheimer's. Our primary goal is to discuss therapeutic options. This lesson provides 1.25 hours (0.125 CEUs) of credit, and is intended for pharmacists in all practice settings.

The program ID # for this lesson is 707-000-07-005-H01.

Pharmacists completing this lesson by May 31, 2010 may receive full credit.

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The objectives of this lesson are such that upon completion the participant will be able to:

1. Differentiate among the various types of dementia.
 2. Describe symptoms associated with AD.
 3. Discuss etiological theories associated with AD.
 4. Identify tests used to diagnose or rule out AD.
 5. Compare and contrast cholinesterase inhibitors.
 6. Discuss drug treatment options for AD, including "off-label" options.
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INTRODUCTION DEMENTIA

The initial concept that needs to be addressed in any discussion of AD is dementia. This is characterized by total progressive cognitive impairment.¹ Patients with dementia have short-term memory difficulties, and, to a lesser extent, long-term memory difficulties.¹ The memory disturbances may be associated with deficiencies in abstract thinking, and judgment, or personality change.² The cognitive changes are significant, and potentially interfere with work and social interactions.²

There are numerous etiologies of dementia.¹ **AD** is the most common cause of dementia.¹ Short-term memory loss is seen early in AD, while the inability to perform activities of daily living (ADLs), such as eating and toileting, occur later in AD.³ **Vascular dementia** is due to ischemic cerebral injury, and is the second most common cause of dementia.⁴ Patients with vascular dementia present with a sudden onset of cognitive impairment symptoms and progressive step-wise deterioration.³ Dementia can also be substance-related, such as **alcoholic dementia**.¹ This becomes apparent after many years of heavy drinking, and is often associated with a personality change.¹ Some additional causes of dementia include **Parkinson's disease and Acquired Immunodeficiency Syndrome**.¹ Early prominent symptoms of Parkinson's disease dementia include executive dysfunction, where patients have difficulty paying attention and planning, and visuospatial impairments, such as difficulty recognizing faces.⁵ Patients with HIV-associated dementia complex often present with movement disorders and depressive symptoms in addition to cognitive impairment.⁶

DEMENTIA OF THE ALZHEIMER'S TYPE

In 1907, Alois Alzheimer described the cognitive and behavioral symptoms of what is now known as Alzheimer's disease.⁷ AD has an extremely insidious onset that is nearly impossible to pinpoint.⁷ Cognitive impairments occur gradually and are present all through the course of AD, whereas behavioral impairments are not as predictable.⁷ Patients with later stages of AD are often unable to perform ADLs and usually suffer from psychological problems.^{7,8} In the later stages of AD, both functional deterioration and psychological difficulties dominate over cognitive symptoms.⁸

Some of the memory symptoms include: impaired ability to recall information, impaired ability to comprehend new information, and misplacing items.^{7,9} At least one of the following cognitive symptoms are also seen in AD: aphasia (language disorder), apraxia (voluntary movement disorder), agnosia (impaired ability to recognize objects), or executive dysfunction.⁹ Some behavioral symptoms of AD include depression, hallucinations, delusions, aggression, wandering, and repetitive mannerisms.⁷ Additionally, patients with later stages of AD are often unable to perform ADLs.⁷

In 2000, it was estimated that 4.5 million people had AD.^{7,10} While the vast majority of patients are diagnosed after age 65, approximately 5% of diagnoses are made in patients as early as 40 years of age.⁷ Therefore, there are two AD age classifications: early-onset (40 to 64 years of age), and late-onset (65 years of age and older).⁷ Females are two times more likely than males to be diagnosed.⁷ Patients who have a family history of AD are up to four times more likely to be diagnosed.⁷ Other risk factors include previous head injury and low educational status.⁹ Once a patient presents with symptoms, the average survival time is 8 years, ranging from 3 years to 20 years.⁷ Most fatalities are indirectly related to AD, such as via predisposition to infections like pneumonia and sepsis.⁷ In the United States, AD represents the eighth most common cause of death.⁷

ETIOLOGY AND PATHOPHYSIOLOGY

CE PRN® (ISSN 0199-5006) is owned and published by W-F Professional Associates, Inc. 400 Lake Cook Road, Suite 207, Deerfield, Illinois 60015.

William J. Feinberg, President *CE PRN*® is published eleven times per year, monthly, January through November. Subscription rate is \$99.00 per year. Second-Class Postage paid at Deerfield, Illinois 60015 and at additional mailing offices. © 2007 by W-F Professional Associates, Inc. All rights reserved. None of the contents of this publication may be reproduced in any form without the written permission of the publisher.

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May 2007

Currently, there is no cure for AD.⁷ Furthermore, the exact etiology and pathophysiology are unknown.⁷ Neuropathologic and clinical criteria define the disease.⁷ It destroys neurons involved in memory, higher learning, behavior, and emotional regulation.⁷ Neurofibrillary tangles (NFTs) and neuritic plaques (NPs) are two hallmark lesions that may cause neuronal destruction.⁷ NFTs and NPs are in very high concentration among patients with AD. Essentially, AD does not occur without NFTs and NPs.⁷ Beta-amyloid protein (β AP) comprises the center of NPs.⁷ β AP likely initiates both the NP formation process and neuronal destruction.⁷ Both genetics and the immune system may play a role in the development of NPs and NFTs.^{7,11}

A variety of neurotransmitters are detrimentally effected by NPs, with cholinergic neurons being the most extremely effected.^{7,11} Glutamate is an excitatory neurotransmitter that may be a neurotoxin in AD.⁷ Blocking N-methyl-D-aspartate (NMDA) receptors may decrease the severity of cellular damage in AD by lessening glutamate activity.⁷

Estrogen may help to advance neuronal growth and inhibit oxidative cellular damage, which would be beneficial to neurons exposed to NPs.^{2,7} Estrogen may also play a key role in the normal maintenance of cholinergic neurotransmission and increase the number of NMDA receptors in the brain.⁷

A theory exists that cholesterol may be associated with the incidence of AD.^{3,7} Cholesterol inside the cellular membrane may be involved with the eventual formation of NPs; therefore, cholesterol depletion may impede or delay NP formation.⁷

DIAGNOSIS

Presently, no laboratory tests exist that verify the presence of AD. In fact, conclusive diagnosis can only be determined via autopsy or biopsy of brain tissue.^{3,7} Laboratory tests are performed to rule out other conditions, such as cyanocobalamin (vitamin B₁₂) deficiency, folate deficiency, and hypothyroidism.⁷ Neuroimaging tests of the brain, like computed tomography (CT) and magnetic resonance imaging (MRI), also serve as helpful aids to rule out conditions other than AD.¹⁰ It is recommended that a CT or MRI be performed at least once during the course of dementia.¹⁰

AD is clinically diagnosed.³ Typical clinical features are amnesia-like memory impairment, language degeneration, and visuospatial inadequacies.¹⁰ Functional, behavioral, and psychological disturbances may progress through the course of AD as well.¹⁰ Both the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) and the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, Text Revision (DSM-IV-TR) have established diagnostic criteria for AD.^{3,7} The NINCDS-ADRDA criteria allow for probable AD diagnoses, thereby reducing the percentage of AD misdiagnoses to under 10%.⁷ While the NINCDS-ADRDA criteria continue to be the standard, the DSM-IV-TR criteria are also appropriate to utilize for diagnosis.⁷ An important step is obtaining a thorough patient history via interviews with the patient and caregivers.^{7,12} During a history, the healthcare provider should note information regarding signs and symptoms of potential AD, other diseases, social history, substance abuse, and medication history.¹² Many medications may cause cognitive changes, particularly those with anticholinergic properties.¹² Additionally, the presence of dementia may be confirmed by employing a scale, such as the Mini-Mental Status Examination (MMSE).^{7,8} Some of the MMSE measurements include orientation, short-term memory, attention, recall, and language.⁷ The MMSE has a maximum score of 30 points; scoring between 10 and 26 points is typically reflective of mild or moderate AD. Scoring less than 10 points is typically indicative of severe AD.^{7,8}

TREATMENT APPROACH AND NONPHARMACOLOGIC THERAPY

Presently, there are no curative treatments for AD.⁷ Furthermore, it is unknown if any of the current treatments can directly reverse or stop the progressions of the disease.⁷ Consequently, the primary therapeutic objective is to treat the cognitive impairment symptoms while conserving and prolonging patient function.^{7,12} Secondary treatment objectives include reacting to the behavioral and psychological symptoms resulting from AD.⁷

Nonpharmacologic therapy is the primary treatment.⁷ However, both nonpharmacologic and pharmacologic therapies are necessary. This is because AD not only has an extreme effect on the patient, but also on the patient's caregivers.^{7,10} It is important for both the patient and his or her caregivers to be educated about the course of AD and the available treatment options.^{7,10} This improves the knowledge and confidence of the caregivers, which may postpone institutionalization.⁷ Communication between caregivers and the patient is also

necessary to reduce stress and frustration.⁷ Providing frequent reminders, simplifying instructions, and demonstrating activities are all helpful ways for caregivers to improve communication.⁷ Some nonpharmacologic interventions to treat the behavioral symptoms include: music, walking, and light exercise.^{10,12} As AD progresses, the life of the patient must become more simplified and organized. This is to compensate for cognitive impairments and to optimize safety.⁷

The physician must provide guidance to the family of the AD patient to assign a power of attorney capable of executing financial and medical resolutions once the patient is no longer competent.⁷ The most difficult decision for the caregiver is likely to be whether or not the patient needs to be institutionalized.⁷ Patients with AD are typically institutionalized due to either behavioral disturbances or incontinence. Caregivers find these problems to be especially hard to manage at home.⁷ When deciding whether or not to institutionalize a patient, it is critical that caregivers are provided physician support, as well as assistance from social services and related organizations.^{7,10}

Table 1. Resources for the Caregivers of Alzheimer's Disease Patients

Organization	Website	Phone Number
Alzheimer's Disease Education and Referral Center	http://www.alzheimers.org	800-438-4380
Alzheimer's Association	http://www.alz.org	800-272-3900
Administration on Aging	http://www.aoa.dhhs.gov	202-619-0724
Eldercare Locator	http://www.eldercare.gov	800-667-1116

**CURRENT PHARMACOLOGIC THERAPIES
COGNITIVE SYMPTOMS**

Cholinesterase Inhibitors (ChEIs)

AD detrimentally effects neurotransmitters. Acetylcholine is the neurotransmitter associated with the most extreme and consistent deficit.² Cholinergic deficit has been correlated with cognitive impairment, psychiatric symptoms, and AD severity.⁸ For over 20 years, the hypothesis that cholinergic deficit accounts for the distinctive memory impairment of AD provided the foundation for drug development.² ChEIs decrease acetylcholine metabolism; thus, acetylcholine activity is prolonged at cholinergic brain synapses.¹³ ChEIs are utilized for symptomatic treatment of AD. These medications are dependent on the production of some endogenous acetylcholine.¹⁴ **Currently, there are 4 ChEIs** with FDA approval for the treatment of AD: **tacrine (Cognex®), donepezil (Aricept®), rivastigmine (Exelon®), and galantamine (Razadyne®, formerly Reminyl®).**² Please refer to Table 2 for a summary of the commonly used ChEIs.

Tacrine was the first ChEI approved by the FDA, and the first medication approved for treatment of AD.^{7,15} It is dosed initially at 10 mg orally four times daily, with a maintenance dose range of 20 to 40 mg orally four times daily.⁷ Tacrine has a poor adverse reaction profile, with hepatotoxicity being the most notable.⁷ Since tacrine requires qid dosing, and is associated with significant adverse reactions, it has fallen out of favor, and is not marketed in the United States anymore.^{2,7}

On October 13, 2006, the FDA approved the tablet formulations of donepezil for treatment of severe AD. Prior to this, ChEIs were only approved for mild to moderate AD treatment.^{10,16,17} Donepezil is a reversible ChEI, with specificity for inhibiting centrally-active acetylcholinesterase, compared with inhibiting centrally-active butyrylcholinesterase.^{7,17} Butyrylcholinesterase is an enzyme believed to play a key role in acetylcholine breakdown once acetylcholinesterase is depleted.^{7,12} Donepezil is available as 3 formulations: tablet, orally disintegrating tablet (ODT), and oral solution.¹⁷ The recommended initial dose is 5 mg orally once daily.⁷ Once a patient has been tolerating the drug for 4 to 6 weeks, if necessary, the donepezil dose may be adjusted to 10 mg orally once daily.⁷ The purpose of the 4 to 6 week period between dose adjustments is to reduce gastrointestinal intolerance and other cholinergic adverse reactions.¹⁷ For patients with severe AD, the recommended maintenance dose is 10 mg orally once daily.¹⁷ Effects on ADLs and behavior were noticed with donepezil 10 mg orally once daily.⁸ The drug may be administered either with food or without food.¹⁷ The package insert recommends administering in the evening.¹⁸ However, for those patients experiencing vivid dreams and nightmares while taking donepezil (frequency of abnormal dreams is 3%), early afternoon administration decreases the probability of these reactions.^{12,18} As a specific inhibitor of centrally-active acetylcholinesterase, donepezil has minimal peripheral activity.^{7,17} Additionally, the specificity of donepezil to inhibit acetylcholinesterase rather than

butyrylcholinesterase may cause fewer peripheral adverse reactions than a nonspecific cholinesterase inhibitor like tacrine.⁷ Some of the peripheral adverse reactions, which are also cholinergic adverse reactions, observed with donepezil include: nausea, vomiting, and diarrhea.⁷ Donepezil is metabolized in the liver by the cytochrome P450 (CYP450) system, specifically isoenzymes 2D6 and 3A4 (otherwise known as CYP2D6 and CYP3A4, respectively).⁸ Ketoconazole and quinidine are inhibitors of both CYP2D6 and CYP3A4; therefore, the metabolism of donepezil may be inhibited when administered concurrently with either ketoconazole or quinidine.¹⁷ Patients taking donepezil and either ketoconazole or quinidine should be monitored for cholinergic toxicity.¹⁷ A synergistic effect may be seen if donepezil is administered to patients taking a cholinergic agonist, like bethanechol. These patients should be monitored for augmented cholinergic adverse reactions.¹⁷ Succinylcholine, a depolarizing neuromuscular blocking agent, works similar to acetylcholine.¹⁷ Succinylcholine should be dispensed with extreme caution for a patient receiving donepezil, and the patient needs to be monitored for prolonged neuromuscular blockade.¹⁷ Lastly, patients taking anticholinergic medications may experience decreased efficacy of donepezil.¹⁸

Rivastigmine is approved for mild to moderate AD treatment.¹⁹ Rivastigmine is a nonspecific reversible ChEI, inhibiting both centrally-active acetylcholinesterase and centrally-active butyrylcholinesterase.^{7,8} There are 2 formulations of rivastigmine, capsule and oral solution. Rivastigmine capsules should be swallowed whole.^{19,20} The recommended initial dose of rivastigmine is 1.5 mg orally twice daily.⁷ After at least 2 weeks of well-tolerated therapy at that dose level, the drug can be titrated up to 3 mg orally twice daily.¹⁹ Rivastigmine titration can continue to a maximum of 6 mg orally twice daily.^{7,19} Slow titration of rivastigmine reduces gastrointestinal intolerance.¹² Rivastigmine should be taken with food to improve tolerability.⁷ As a centrally-active ChEI, the drug has minimal peripheral activity.⁷ The central activity of rivastigmine may result in fewer peripheral adverse reactions.⁷ Cholinergic and gastrointestinal reactions, including diarrhea, loss of appetite, weight loss, nausea, and vomiting, are common.^{7,19} However, as rivastigmine treatment progresses, the frequency of adverse reactions usually decreases.¹⁹ Rivastigmine is predominantly metabolized by acetylcholinesterase and butyrylcholinesterase, with minimal CYP450 system metabolism.⁸ Since rivastigmine undergoes minimal metabolism via the CYP450 system, there is low drug interaction potential with this medication.⁷ However, as with donepezil, caution should be exercised when dispensing succinylcholine, and the patient must be monitored for prolonged neuromuscular blockade.¹⁹ Additionally, like donepezil, a synergistic effect can occur when rivastigmine is administered concurrently with a cholinergic agonist, such as bethanechol.¹⁹

Galantamine is approved for mild to moderate AD treatment.²¹ Galantamine is a reversible ChEI with specificity for inhibiting both centrally-active acetylcholinesterase and peripherally-active acetylcholinesterase compared with inhibiting butyrylcholinesterase.^{8,22} Additionally, galantamine acts as a nicotinic cholinergic receptor agonist, improving cholinergic function.^{7,12} Galantamine is available as an immediate-release tablet, an immediate-release oral solution, and an extended-release capsule.²² The recommended initial dose is 8 mg per day, either 4 mg orally twice daily of immediate-release galantamine or 8 mg orally once daily of extended-release galantamine.²² Galantamine titrations should occur after a minimum of 4 weeks, with each titration interval increasing the total daily dose by 8 mg.^{7,22} The galantamine patient package insert recommends a maximum total daily dose of 24 mg.^{7,21} The 4-week titration interval of galantamine is recommended to improve tolerance.⁷ Galantamine usage has shown improvements in ADLs, while both psychological and behavioral AD symptoms were demonstrated to remain stable with galantamine usage.⁷ Galantamine is best given with food; this measure may decrease nausea and vomiting.²¹ Patients with moderate hepatic or renal impairment generally should not exceed a total daily dose of 16 mg.²¹ Galantamine is not recommended for patients with severe hepatic or renal impairment.²¹ Gastrointestinal adverse reactions, such as diarrhea, weight loss, nausea, and vomiting, are common.²¹ The majority of adverse reactions occur during dose titration periods.²¹ Like donepezil, galantamine is metabolized in the liver by both the CYP2D6 and CYP3A4 systems.⁷ As with donepezil, the metabolism may be inhibited when administered concurrently with either ketoconazole or quinidine, and patients should be monitored for cholinergic toxicity.²² Additionally, the metabolism of galantamine can be inhibited with co-administration of paroxetine, a CYP2D6 inhibitor. Again, patients should be monitored for cholinergic toxicity.²¹ A synergistic effect may result when galantamine is taken concurrently with a cholinergic agonist, such as bethanechol. Patients should be monitored for augmented cholinergic adverse reactions.²¹ Extreme caution should be exercised when dispensing succinylcholine for a patient taking galantamine. The patient must be monitored for prolonged neuromuscular blockade.²¹

For an anti-dementia agent to become FDA approved, two well-designed clinical trials must demonstrate

significant differences between patients given the active drug and patients given placebo via results of cognition and global function scales.¹⁰ The scale usually employed to measure cognition in clinical trials of ChEIs is called the Alzheimer's Disease Assessment Scale-Cognitive portion (ADAS-Cog). This scale evaluates areas including language, memory, movement, and visuospatial skills.¹⁵ The scale commonly employed to measure global function in clinical trials of ChEIs is called the Clinical Interview-Based Impression of Change with caregiver input (CIBIC-plus). Clinicians utilizing this scale interview patients and caregivers separately to evaluate change from baseline.^{10,12} Efficacy is found to be similar when comparing donepezil, rivastigmine, and galantamine via the ADAS-Cog and CIBIC-plus scales.¹⁰ The major differences between ChEIs seem to be dosing regimen convenience and the incidence of adverse reactions. The incidence of adverse reactions may be controlled by dose titrations.^{2,12} Donepezil is often the preferred ChEI due to the lowest incidence of adverse reactions, the convenient once-daily dosing regimen, and the FDA approved indication for treatment of severe AD.^{2,16}

When considering the efficacy of ChEIs for the symptomatic treatment of AD, treatment responses should be evaluated with respect to all treatment domains.¹⁴ As a multifaceted disease, it is appropriate to evaluate patients with AD by treatment domains, including cognition, global function, ADLs, behavioral and psychological symptoms, quality of life, and caregiver burden.¹⁴ Besides cognitive benefits, beneficial effects on behavioral symptoms and ADLs were noticed with donepezil, rivastigmine, and galantamine.^{7,8,12} Demonstrating benefit in any one treatment domain may be significant for both the AD patient and the caregiver.¹⁴ Since AD is progressive, benefits may be demonstrated not only by improvements in treatment domains, but also by both disease stabilization and delaying disease progression.¹⁴ While the optimal ChEI treatment duration is unclear, patients exhibiting benefits within 6 months of ChEI therapy should probably continue therapy for 1 or 2 years at minimum.^{10,14} If further benefit is doubtful after 1 or 2 years of ChEI therapy, the ChEI should be tapered off and discontinued.^{12,14} Upon follow-up with the AD patient, if the patient's status rapidly declines within several weeks of ChEI therapy discontinuation, the same ChEI should be re-initiated and the patient should be monitored for benefits.^{12,14} However, if upon follow-up with the patient, the status does not change within several weeks of ChEI therapy discontinuation, changing to a different ChEI or another AD therapy, such as memantine, may be considered.^{12,14}

Table 2. Summary of the Cholinesterase Inhibitors.^{7,8,10,12,15-17,19-22}

Drug	Donepezil	Rivastigmine	Galantamine
FDA Approval*	Mild Moderate Severe†	Mild Moderate	Mild Moderate
Activity/Specificity	Central Acetylcholinesterase	Central Acetylcholinesterase Butyrylcholinesterase	Central and Peripheral Acetylcholinesterase‡
Formulations	Tablet ODT Oral solution	Capsule Oral solution	IR tablet IR oral solution ER capsule
Initial Daily Dose	5 mg	3 mg	8 mg
Maintenance Daily Dose	5 mg - 10 mg	6 mg - 12 mg	16 mg - 24 mg
Daily Dosings	One	Two	IR: Two ER: One
Minimum Interval between Dose Adjustments	4 - 6 weeks	2 weeks	4 weeks
Administration with Food	With or Without	With	With
Common ADRs (Frequencies)	Vomiting (5%) Diarrhea (10%) Nausea (11%)	Weight Loss (3%) Loss of Appetite (17%) Diarrhea (19%) Vomiting (31%) Nausea (47%)	Weight Loss (5%) Diarrhea (9%) Vomiting (13%) Nausea (24%)
Metabolism via CYP450 System	Yes CYP2D6 and CYP3A4	Minimal	Yes CYP2D6 and CYP3A4

*Alzheimer's disease severity

†Tablet formulations only

‡ Additional mechanism of action as a nicotinic cholinergic receptor agonist

ODT = orally disintegrating tablet; IR = immediate release; ER = extended release; ADRs = Adverse drug reactions; CYP = cytochrome P450

NMDA (N-Methyl-D-Aspartate) Receptor Antagonist

NPs (Neuritic Plaques) increase the release of the major excitatory neurotransmitter, glutamate.²³ AD patients also experience significantly lower uptake of glutamate compared with patients without dementia.²³ Glutamate stimulates NMDA receptors.⁸ Under normal physiological conditions, NMDA receptors are involved in learning and memory processes; however, NMDA receptors pathologically activated by glutamatergic overstimulation may contribute to the neuronal destruction of AD.²³ Memantine (Namenda®) is a novel AD agent. It is a NMDA receptor antagonist.^{7,12} The drug is FDA approved for moderate to severe AD treatment.²⁴ Memantine is available as loose tablets, tablets in a titration package, and oral solution.²⁴ The recommended initial dose is 5 mg orally once daily.⁷ Dose titration intervals should be at least one week in duration, and titrations should increase the total daily dose by 5 mg.²⁴ Total daily doses of greater than 5 mg should be given in 2 divided doses.²⁴ The recommended maintenance dose is 10 mg orally twice daily.²⁴ Memantine may be taken either with food or without food.²⁴ For patients who have severe renal impairment, the recommended dose of memantine is 5 mg orally twice daily.²⁴ Generally, memantine is well-tolerated. Some of the more frequently observed adverse reactions include headache, dizziness, and constipation.^{7,24} Memantine is excreted unchanged by the kidneys, undergoing minimal hepatic metabolism.^{7,12} As a weak base, the drug may accumulate if the patient's urine becomes alkalinized. Medications that may cause alkalinized urine include carbonic anhydrase inhibitors and sodium bicarbonate.^{12,24} Due to memantine's partial elimination via tubular secretion, other drugs using the same transport system may cause altered memantine plasma levels.^{12,24} Some of these are cimetidine, hydrochlorothiazide, quinidine, and ranitidine.^{12,24} Caution should be exercised when dispensing memantine to a patient taking another NMDA antagonist, such as amantadine, dextromethorphan, or ketamine, since there is a theoretical additive effect.^{12,24} Memantine may be used as monotherapy or in combination with a ChEI.⁷ When evaluating the efficacy of memantine compared with placebo, global function, cognitive, and ADL benefits were all observed.⁸ A randomized, double-blind, placebo-controlled clinical trial comparing memantine in combination with donepezil to donepezil alone found benefits in cognition, global function, and ADLs for patients taking combination therapy compared with donepezil alone.⁸

Antioxidants

Post-mortem studies of patients who had AD have revealed markers of oxidative brain injury.²³ Antioxidants most likely work by decreasing oxidative brain damage.²⁵ Vitamin E is an antioxidant often recommended as adjunctive therapy for the treatment of AD; however, vitamin E has not been FDA approved for this indication.^{7,26} A randomized, double-blind clinical trial comparing vitamin E 1000 International Units twice daily, selegiline (Eldepryl®; monoamine oxidase inhibitor, type B) at a dose of 5 mg twice daily, the combination of vitamin E and selegiline, and placebo, showed benefits with all active treatments in patients with moderate AD.^{10,25-27} The benefits seen with vitamin E monotherapy, selegiline monotherapy, and combination therapy included delayed time to the following: death, institutionalization, impaired ability to perform ADLs, and development of severe AD.^{10,25} Like vitamin E, selegiline is not FDA approved for the treatment of AD.^{26,27} Vitamin E is utilized more often than selegiline due to a more favorable adverse reaction profile and a lower cost.²⁵ However, a recent meta-analysis showed an increased risk of all-cause mortality for patients taking high dose vitamin E therapy, defined as greater than 400 International Units daily.^{12,28} Therefore, since the beneficial results seen with vitamin E have not been supported with other evidence, and high dose vitamin E therapy may cause an increased risk of all-cause mortality, the use of vitamin E for the treatment of AD is questionable.¹²

Estrogen

While the exact mechanism for beneficial effects of estrogen in AD is not understood, estrogen has been proclaimed to have over 200 actions on neurons. These actions include neurotransmitter regulation and antioxidant effects.¹² Most epidemiological studies demonstrated a decreased occurrence of AD in patients taking postmenopausal estrogen replacement therapy. Additionally, these findings encouraged researchers to evaluate

estrogen therapy for prevention and treatment of cognitive deterioration.⁷ However, 2 randomized clinical trials of conjugated estrogens for the treatment of cognitive deterioration did not show any benefit.^{7,10} The Women's Health Initiative Memory Study evaluated patients taking estrogen and progestin therapy compared with placebo and found women taking active treatment had an increased risk of dementia compared with those taking placebo.^{7,10} Additionally, health risks are associated with the use of estrogen and progestin, including increased risk of breast cancer, strokes, heart attacks, and blood clots.^{7,12,23} Since the efficacy of estrogen as an AD treatment has not been demonstrated and serious health risks are associated with its use, estrogen is not recommended for the treatment of AD.⁷

Anti-inflammatory Agents

Inflammatory markers have been discovered in the post-mortem brain tissue of AD patients. Inflammation may result in neuronal damage.^{2,23} Epidemiologic studies proposed associations of decreased risk of AD occurrence and improved cognition with the use of nonsteroidal anti-inflammatory drugs (NSAIDs).²³ However, clinical trials of NSAIDs, such as naproxen sodium (Aleve[®]) and diclofenac sodium/misoprostol (Arthrotec[®]; diclofenac is an NSAID, and misoprostol is a prostaglandin E1 analogue, providing gastric protection), demonstrated no significant benefits versus placebo for AD patients.^{10,12,23,29} Selective cyclooxygenase-2 (COX-2) inhibitors, such as rofecoxib (Vioxx[®]; voluntarily withdrawn from market) and celecoxib (Celebrex[®]), have also failed to show benefit compared with placebo in clinical trials of AD patients.^{7,12,23,30} Additionally, prednisone (Deltasone[®]), a corticosteroid, has not shown beneficial outcomes compared with placebo for the treatment of AD.^{7,10} Therefore, due to insufficient supporting evidence and increased risk of significant adverse reactions, anti-inflammatory agents are not recommended for the treatment of AD.^{7,10}

3-Hydroxy-3-Methylglutaryl-Coenzyme A (HMG-CoA) Reductase Inhibitors

Rodent studies suggest cholesterol may regulate β AP production.²³ Epidemiological data demonstrated a decreased risk of AD with HMG-CoA reductase inhibitor usage.²³ The protective mechanism of HMG-CoA reductase inhibitors for AD patients may involve numerous pathways, including cholesterol reduction and the alteration of β AP regulation.^{12,23} Pravastatin (Pravachol[®]) and lovastatin (Mevacor[®]) were associated with decreased prevalence of AD.⁷ A small, randomized, double-blind clinical trial of patients with mild or moderate AD received either atorvastatin (Lipitor[®]) 80 mg orally daily or placebo. A significant improvement in ADAS-Cog scores at 6 months was observed, favoring atorvastatin.³¹ Larger randomized clinical trials of HMG-CoA reductase inhibitors for the prevention or treatment of AD are necessary.^{7,23} Furthermore, issues such as treatment duration, optimal dosing, and whether or not all HMG-CoA reductase inhibitors have similar efficacy and safety profiles in AD patients need to be addressed.^{7,23} At this time, HMG-CoA reductase inhibitors are not recommended for the prevention or treatment of AD.^{7,12}

Ginkgo Biloba

While the mechanisms of action of ginkgo biloba extracts are unclear, this herbal supplement is thought to exert antioxidant and anti-inflammatory effects.^{7,23} A meta-analysis of ginkgo biloba extract, with doses ranging from 120 to 240 mg daily, compared with placebo revealed a modest, but statistically significant, cognitive benefit favoring ginkgo biloba extract.^{7,10,23} There have been case reports of hemorrhaging, which may be associated with its antiplatelet properties.^{7,23} Herbal supplements are inadequately standardized. There may be significant variation in the active ingredient content of herbal supplements between lots and manufacturers.⁷ Additionally, information is scarce regarding the drug interactions, adverse reactions, and long-term toxicity associated with herbal supplements.⁷ Therefore, caution should be exercised when considering their use.⁷

NONCOGNITIVE SYMPTOMS

Antipsychotics

Antipsychotics are used to treat noncognitive symptoms of AD patients. These include psychosis, such as hallucinations and delusions, and disruptive behaviors, such as agitation.⁷ Prior to the availability of atypical antipsychotics, typical antipsychotics, such as haloperidol (Haldol[®]), were commonly used.^{7,25} In double-blind, placebo-controlled clinical trials, haloperidol has shown to reduce agitation in AD patients.^{10,12,25} Typical antipsychotics have an unfavorable adverse reaction profile with regards to extrapyramidal effects, such as tardive

dyskinesia and Parkinsonism.^{10,12} Since atypical antipsychotics are less likely to produce extrapyramidal effects than typical antipsychotics, atypical antipsychotics may be better tolerated by AD patients.^{10,12,25} Atypical antipsychotics became the preferred medications to manage psychosis and disruptive behaviors of AD.^{10,12} However, antipsychotics are not FDA approved for dementia-related psychosis treatment.^{25,32} Moreover, atypical antipsychotics have a "black-box" warning, stating that when compared to placebo, patients using atypical antipsychotics for the treatment of dementia-related psychosis are at a greater risk of death.^{12,32,33} For patients with dementia-related psychosis, the increased risk of death associated with atypical antipsychotics is approximately 4.5% versus approximately 2.6% with placebo. While causes of death varied, most were of either a cardiovascular or infectious nature.³⁴ In randomized, placebo-controlled clinical trials, the atypical antipsychotics, risperidone (Risperdal[®]) and olanzapine (Zyprexa[®]), modestly reduced psychosis and disruptive behavior symptoms in AD patients.^{7,25} However, a recent randomized, double-blind, placebo-controlled clinical trial comparing the atypical antipsychotics risperidone, olanzapine, and quetiapine (Seroquel[®]), suggested that while the active medications were more efficacious than placebo, adverse reactions restricted their overall effectiveness.³³ Therefore, atypical antipsychotics are best reserved for AD patients where the benefits of these medications outweigh the risks.^{12,33}

Mood-stabilizing Agents

Since antipsychotics may cause serious adverse reactions and have shown only modest efficacy for the treatment of psychosis and behavioral disturbances in the AD patient, alternative therapies, such as mood-stabilizing agents, have been used.⁷ The mood-stabilizing agent and anticonvulsant carbamazepine (Tegretol[®]) showed agitation improvement for patients with AD.^{7,10,12} In addition, carbamazepine was well-tolerated by AD patients.^{7,12} Another mood-stabilizing agent and anticonvulsant, divalproex sodium (Depakote[®]), may have minimal efficacy for the treatment of AD patients with agitation.^{7,10,12} However, both carbamazepine and divalproex sodium are not FDA approved for the treatment of behavioral disturbances in the AD patient.^{35,36}

ChEIs

ChEIs have demonstrated modest efficacy for the improvement of psychosis and behavioral disturbances in AD patients.^{7,12} Further research is necessary to understand the exact roles of ChEIs for the non-cognitive symptoms of AD.⁷ AD patients who recently began ChEI therapy should be monitored for non-cognitive benefits before additional psychotropic medications are initiated.¹²

Antidepressants

Since some symptoms of dementia and depression overlap, depression may be difficult to diagnose in a patient with AD.⁷ Some depressive symptoms a patient with AD might exhibit include crying spells, reduced food intake, and remaining in bed.⁷ Most literature evaluating the use of antidepressants in AD patients is comprised of uncontrolled studies and case reports, and the results of these data are mixed.⁷ Selective serotonin reuptake inhibitors (SSRIs), such as citalopram (Celexa[®]), sertraline (Zoloft[®]), and fluoxetine (Prozac[®]), have been shown to improve depressive symptoms of AD patients.^{7,25} Tricyclic antidepressants, such as clomipramine (Anafranil[®]), have also shown efficacy in AD patients with depressive symptoms.⁷ However, tricyclic antidepressants are associated with significant undesirable anticholinergic adverse reactions, which can exacerbate the cognitive disturbances of AD patients and limit their usefulness.^{7,10,12} Conversely, the favorable adverse reaction profile and efficacy of SSRIs has led them to be the most utilized class of medications for depressive symptoms of AD patients.^{7,10} Of note, none of the aforementioned medications have been FDA approved for the treatment of depression in AD patients.^{10,37-40}

CONCLUSION

Many etiologies of dementia exist, with the most common cause attributed to AD.¹ AD has a very slow onset.⁷ Cognitive impairment is gradual and evident early in AD, while functional, behavioral, and psychological disturbances are less predictable and tend to dominate later in the disease.^{7,8} Presently, no cure exists for AD, and its pathophysiology is not fully understood.⁷ The primary therapeutic goals for an AD patient are to treat cognitive impairment symptoms and preserve and prolong functionality.^{7,12} The secondary therapeutic goals for an AD patient are to treat behavioral and psychological symptoms.⁷ While nonpharmacologic therapy is the primary treatment for AD, pharmacologic treatment is also necessary.^{7,10} Currently, ChEIs and memantine are the only FDA approved medications for the treatment of AD.^{2,24}

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Please fill out this section as a means of evaluating this lesson. The information will aid us in improving future efforts. Either circle the appropriate evaluation answer, or rate the item from 1 to 7 (1 is the lowest rating; 7 is the highest).

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- | | | |
|---|-----|----|
| Differentiate among types of dementia | Yes | No |
| Describe symptoms of dementia | Yes | No |
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| Identify tests used to diagnose or rule out AD | Yes | No |
| Compare & contrast cholinesterase inhibitors | Yes | No |
| Discuss drug treatment options for AD | Yes | No |

2. Was the program independent & non-commercial Yes No

	Poor			Average		Excellent
3. Relevance of topic	1	2	3	4	5	6 7

4. What did you like most about this lesson? _____

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Please Select the Most Correct Answer

- | | |
|--|---|
| <p>1. In addition to Namenda, are any of these approved for severe AD?
 A. Exelon
 B. Razadyne
 C. Aricept
 D. None of these</p> <p>2. In AD there is thought to be too much glutamate, which may be associated with cognitive impairment. Namenda blocks glutamate stimulation.
 A. True
 B. False</p> <p>3. AD may be diagnosed with laboratory tests.
 A. True B. False</p> <p>4. Of the following types of dementia, which etiology is the most common?
 A. Vascular
 B. Alcoholic
 C. Alzheimer's disease
 D. Parkinson's disease</p> <p>5. Which of these may be involved with the pathophysiology of AD?
 A. AD detrimentally effects neurotransmitters, including acetylcholine & glutamate
 B. Adenylate cyclase causes neuronal destruction
 C. Gamma-amyloid protein initiates neuronal destruction
 D. None of these</p> | <p>6. What is the treatment approach for AD?
 A. No cure; no treatment
 B. Treat behavior & psychological symptoms
 C. Treat cognitive symptoms & conserve patient function
 D. None of these</p> <p>7. The ChEIs are recommended to have titration intervals between dose adjustments to improve tolerance.
 A. True
 B. False</p> <p>8. Which of these have been used "off-label" for the treatment of either cognitive or non-cognitive AD symptoms?
 A. Vitamin E
 B. Citalopram
 C. Carbamazepine
 D. All of these</p> <p>9. The most arduous decision for caregivers is likely to be whether or not the AD patient needs to be institutionalized.
 A. True B. False</p> <p>10. Which of these is not a typical symptom of AD?
 A. Impaired ability to comprehend new info
 B. Misplacing items
 C. Personality change
 D. Impaired ability to recognize objects</p> |
|--|---|

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