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Alzheimer's Disease - A Review

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Epidemiology

The first case of pre-senile dementia with pathologic features of plaque formation and neurofibrillary degeneration was described in 1907 by Alois Alzheimer. Today, approximately 4 million Americans have Alzheimer's disease (AD). It is estimated to rise to 7 million by 2010 and that number is expected to reach 14 million by the year 2050.[1] The prevalence of Alzheimer's doubles every 5 years after the age of 65 years.[1] Ten percent of people older than 65 years and 50% of those older than 85 years have the disease. Rarely, patients in their thirties and forties are diagnosed with early-onset AD.[2] Alzheimer's is the most common form of dementia.[1] Both Alzheimer's and vascular dementia accounts to 90% of dementia. Average life expectancy for a patient with AD is 8 to 20 years from the onset of symptoms.[3] As of the year 2000, the annual deaths from Alzheimer's were 49,558 making it the eighth leading cause of death among Americans.[3] An interesting finding is that 70% of Alzheimer's patients live at home. And of those, 75% are cared for by a family member. One half of all nursing home residents have AD or a related disorder.[3] Dementia is the number one precipitator of nursing home placement.

The United States spends $100 billion a year on AD. American businesses lose approximately $36.5 billion annually because of the absenteeism of caregivers for Alzheimer's patients. Families pay about $12,500 per year for paid caregiver assistance. The average annual cost for nursing home care is $42,000.The lifetime healthcare cost per AD patient is $174,000.[2] With all these staggering statistics, Alzheimer's disease is truly a disease that one cannot ignore.

Pathophysiology

The pathophysiology of Alzheimer's dementia is the subject of significant research and debate. The two hallmark pathologic

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changes noted in the brains of Alzheimer's victims are senile plaques and neurofibrillary tangles. The plaques are composed of beta-amyloid peptides and may form due to a condition of excess beta-amyloid and/or its precursor protein.[4] Inflammation around these plaques may destroy neighboring neurons causing the general cerebral atrophy found in AD.[4, 5]

Neurofibrillary tangles are composed partly of the *tau* protein, which links together to form filaments and eventually, tangles.[4] The tangles compromise neuronal function and cause neuronal death.[4] Genetics influence the formation of forms of *tau* that are more likely to tangle.[6]

There is evidence that multiple mechanisms are responsible for the development of AD. Apolipoprotein E type 4 (ApoE-4) located on chromosome 19 increases the lifetime risk of developing AD from 9% to 29%.[7] ApoE-4 is a protein that is present in plaques in the brains of patients with AD and may trap amyloid in the brain parenchyma.[5] Another possible reason is reduction or deficiencies in the neurotransmitters like acetylcholine or adrenaline and glutamate. Acetylcholine plays a role in learning and short-term memory and in AD is markedly decreased in the cerebral cortex and hippocampus. Other neurotransmitters have been implicated in neurodegenerative disorders, including glutamate. Glutamate is the principle excitatory transmitter in the brain. Glutamate overstimulation of the N-methyl-D-aspartate receptor (NMDA) can lead to calcium overload and excitotoxicity.[8]

Risk Factors

One percent of the population older than 65 years has AD. The prevalence rates double every five years thereafter, to the point that 50% of the population older than 85 years may have AD.[1, 2] Therefore, the most significant risk factor for cognitive impairment is advanced age. Other risk factors include family history, head trauma, history of stroke, and Down syndrome.

Diagnosis

Dementia is defined as a progressive loss of nerve cells that are responsible for normal thought, memory, and daily functioning. The establishment of an AD diagnosis is accomplished by a detailed history and physical, neuropsychiatric testing and laboratory studies. Together, these methods accurately diagnose 90% of dementias. Unfortunately, the only definitive diagnosis of Alzheimer's disease can be accomplished antemortem by brain biopsy or postmortem by autopsy.

There are two established criteria for diagnosis of Alzheimer's disease that have been standardized. Both the DSM IV criteria (*Table 1*) and NINCDS – ARDA (*Table 2*) probable AD definitions have good sensitivity (81%) and a fair specificity (70%) for the diagnosis of AD.[9, 10]

Of the known cases of AD, approximately half are diagnosed with history and physicals completed by their primary care physician. First, reversible causes must be ruled out. Reversible causes include metabolic abnormalities, nutritional deficiencies, vasculitis, infection, intoxication, and anatomical causes (e.g., intracranial masses, bleeding and hydrocephalus). This exclusionary work-up is important, because approximately 10-15% of dementia diagnoses are due to a reversible cause. See Table 3 for suggested laboratory workup for potentially reversible causes of dementia.[11]

The best diagnostic tool for diagnosing Alzheimer's disease is a thorough history. In addition, several geriatric assessment tools are helpful. These include: a Mini Mental Status Exam (MMSE), Geriatric Depression Scale (GDS), Activities of Daily Living (ADL), and Instrumental Activities of Daily Living (IADL) inventories, a medication review, as well as hearing, vision, and nutrition screenings.

A widely accepted and standardized test for dementia is the MMSE.[12] Two U.S. studies show that the sensitivity is 49% with a specificity of 92% in detecting dementia.[13, 14] The MMSE is scored on a possible 30. A score of more than 24 is considered normal, 20-24 is mild, 10-19 moderate, and less than 10 indicates severe dementia. The clock drawing test (CDT) and Memory Impairment Screen are other useful screening tools.[15, 16] These tests need a baseline to which comparison can be made to establish the presence of a decline.

ADL and IADL are geriatric assessment tools that evaluate the degree of function for activities of daily living (*See insert.*). A total score of less than 9 of 25 indicates dependency in either inventory. Therefore, the lower the score the greater degree of dependence. The usual decline in AD patients starts with loss of IADL prior to loss of basic ADLs as more complex skills are needed to do IADLs.[17 - 21]

Depression is known to be a leading cause of pseudodementia. One study by Forsell showed that as much as 12% of patients with dementia also were depressed.[22] There are several accepted

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Table 1. DSM-IV Criteria

1. memory impairment, and
2. one or more of the following cognitive disturbances:
   - aphasia (language)
   - apraxia (motor skills)
   - agnosia (visuospatial)
   - loss of executive functioning (insight, planning, organization, sequencing,
   - abstracting)

Note: Patients are usually older than 65 years; however early onset can occur before age 65. There is gradual onset and continuing cognitive decline from previous level of functioning. The cognitive deficits impair social or occupational functioning.

Adapted from: Frances A, Pincess HA, et al. Diagnostic and Statistical Manual of Mental Disorder: 4th Ed. Washington DC: American Psychiatric Association; 2000: 147-171.

Table 2. NINCDS-ARDA Criteria

1. Dementia established by clinical exam and documented by the MMSE
2. Deficits in two or more areas of cognition
3. Progressive worsening of memory and other cognitive functions
4. No disturbance of consciousness
5. Onset between 40 and 90 years of age
6. Absence of systemic disorders other than brain disease that could account for the progressive deficits in memory and cognition

Adapted from: Knopman DS, DeKosky ST, et al. Practice Parameter: Diagnosis of Dementia (An Evidence-Based Review). Neurology 2001; 56:1143-1153.

GDSs: the Yesavage 30-point and Yesavage 15-point scales are the most widely accepted. On the 15-point scale, a score of more than 2 suggests depression. Additionally, the single question: *Do you often feel sad or depressed?* is statistically significant for the diagnosis of depression.[23-25] It is important to note that all these tests may be administered by any trained health professional, not necessarily a physician only.

The diagnosis of Alzheimer's disease is best accomplished with a thorough history and physical examination, and elimination of reversible causes. In certain cases, if the diagnosis is unclear, or the patient and/or family insists on further testing, there are several studies that can be performed that may help to support the clinical diagnosis. Presently, no laboratory test is appropriate for routine use in patients with suspected AD. The field of genetic testing is in infancy; therefore, centers with experience/expertise would be more apt to handle it. A cohort study shows that APO E4 allele has been shown to slightly increase the positive predictive value in Alzheimer's patient sfrom 90% to 94%.[26]

In recent years, examination of cerebrospinal fluid (CSF) markers has drawn a lot of interest and research. CSF ß amyloid 1-42 has been shown to be significantly decreased and CSF *tau* increased in patients with clinical AD.[27] The sensitivities and specificities of these results are reported to be 85% and 87%, respectively.[28-30] Kahle and associates showed that CSF AD7C had a specificity of 87% and a sensitivity of 70%.[31]

Radiological studies are another avenue in the array of options in diagnosing AD. A noncontrast computed tomography (CT) or magnetic resonance imaging (MRI) are useful to identify vascular dementia, neoplasms, subdural hematomas, or normal pressure hydrocephalus. MRI showing medial temporal atrophy has a sensitivity range from 77-92% and specificity range from 49% - 95%.[32, 33] Functional neuroimaging (e.g., single photon emission computed tomography [SPECT] scan) was noted to be of greatest value for a positive test in patients with mild dementia and low index of suspicion for the diagnosis of AD. In this setting, a positive SPECT scan would increase the posttest probability by 30%.[34, 35]

The positron emission tomography (PET) scan is the newest form of radiological imaging in the field of AD. It can detect early changes in the brain and may show decreased temporal/parietal activity. Two studies regarding comparison of PET vs SPECT show a higher sensitivity for the former.[36, 37] Additionally, combining a PET scan and MRI can create a three-dimensional brain image that may detect subtle brain abnormalities. Due to the high cost of functional imaging, further studies are needed to establish its role in the diagnosis of AD in light of a competent clinical diagnosis.

Although AD is the most common form of dementia, other causes of dementia may coexist with AD. Vascular dementia (VAD) is the second most common form of dementia. Currently, the four criteria that are used include the DSM-IV,[38] the California criteria,[39] the Haschinski Ischemic Score (HIS),[40] and the National Institute of Neurological Disorders and Stroke and the Association Internationale por la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN).[41] Comparison studies of the criteria and neuropathologic findings show a low sensitivity (43%) and high specificity.[42]

Dementia with Lewy bodies is another form of dementia. It is clinically defined as the presence of dementia, gait disorder, prominent hallucinations/delusions, fluctuation in alertness, and sensitivity to traditional antipsychotics.[43] However, all these features may occur in patients with AD, therefore these criteria give low sensitivity and high specificity when comparing with neuropathologic findings. [42]

Frontotemporal dementia (FTD) is less common than the above dementias.[44] Patients with FTD typically have deficits in frontal lobe tasks that include verbal fluency and executive function.[45] Early loss of personal and social awareness and perseverative behaviors are clinical criteria that are highly specific for FTD.[46]

Lastly, Creutzfeldt-Jakob disease is a disease that causes a

Table 3. Dementia Lab Work-up

Reversible Cause	Test
Metabolic	Chem 20 or CMP, TSH
Nutritional Deficiencies	B_{12}, RBC folate
Vasculitis	ESR
Infection	CBC. RPR, UA, HIV, CSF
Toxic Substances	ETOH, heavy metal, toxicolo-
Brain mass/bleed	MRI or CT scan
Hydrocephalus	MRI or CT scan

KEY: CMP = comprehensive metabolic panel.UA = urinalysis. TSH = thyroid stimulating hormone. HIV = human immunodeficiency virus. B_{12} = Vitamin B_{12}. CSF = cerebrospinal fluid studies. RBC Folate = red blood cell folate. ETOH = alcohol. CBC = complete blood count. MRI = magnetic resource imaging. RPR = rapid plasma reagin. CT: computerized tomography.

rapidly progressive dementia. Until recently, diagnosis is mainly through pathologic examination of brain tissue. Master has developed clinical criteria that are high in specificity (81%).[47, 48]

Clinical Course

The staging of AD can be quantified as mild, moderate, or severe. (*See insert.*)

Although death is usually a result of co-morbid conditions, end stage AD qualifies a patient for hospice services.[51, 52] The patient must score at or beyond stage seven of the Functional Assessment Staging (FAST) score. This includes: A) ability to speak limited to approximately a half a dozen intelligible different words or fewer in the course of an average day or in the course of an intensive interview, B) ability to speak is limited to the use of a single intelligible word in an average day or in the course of an intensive interview (the person may repeat the word over and over), C) ambulatory ability is lost (e.g., cannot walk without personal assistance), D) cannot sit up without assistance (e.g. the individual will fall over if there are not lateral rests [arms] on the chair), E) loss of ability to smile, and F) loss of ability to hold up head independently.[53]

Mild Cognitive Impairment

Mild cognitive impairment (MCI) describes a transitional stage between normal aging and clinical dementia. Patients with MCI have a measurable cognitive deficit—often strictly amnesia — but do not meet criteria for AD. Patients with MCI develop clinical AD at a rate of approximately 10% per year.[54] It is difficult to clinically separate MCI from normal aging without extensive neuropsychological testing. The Montreal Cognitive Assessment recently was developed as a brief screening tool for MCI and validated having a 90% sensitivity and 87% specificity.[55]

Prevention

Several options are available to reduce the likelihood of Alzheimer's: blood pressure control and avoidance of anticholinergic drugs are starting points for prevention. There is also evidence supporting Vitamin E supplementation, although one has to be careful in patients on anticoagulation medication due to its drug interaction properties with warfarin. Currently, there is no conclusive evidence that estrogen in women or nonsteroidals prevent AD.[56] Elevated levels of beta amyloid and *tau* have been observed in severe traumatic brain injury patients.[57] And, severe head trauma is known to double the risk for the development of AD.[58] Therefore, prevention of head trauma is important in decreasing the risk of developing AD.

Stimulating activities may reduce Alzheimer's risk. This is the "use it or lose it" concept. A recent study by the Rush Alzheimer's Disease Center found that more frequent participation in cognitively stimulating activities is associated with a reduced risk of AD.[59]

Treatment of Alzheimer's Disease

Cholinesterase inhibitors are the cornerstone of pharmacotherapy for Alzheimer's disease. These medications inhibit the action of the enzyme acetylcholinesterase, thereby increasing cholinergic activity in the central nervous system (CNS). This appears to improve cognition in some patients with AD. Elevated peripheral acetylcholine levels also results, which produces primarily gastrointestinal side effects.[60] These four agents have been shown to maintain cognitive function at or above baseline in six-month treatment studies.[61] Longer studies reveal a slowed decline compared with patients on placebo, delaying nursing home placement a year or more.[62]

In 1993, tacrine (Cognex) was the first cholinesterase inhibitor approved for treatment of AD. Tacrine causes liver enzyme level elevation in 40% of patients, therefore liver function assays are recommended every two weeks during dose titration and then every three months.[63] Due to the potential for liver toxicity and the short half-life requiring four times daily dosing, tacrine is now a second-line agent.

No large head-to-head studies have been completed comparing the remaining three cholinesterase inhibitors currently FDA approved in the United States. The three agents that are firstline in the treatment of AD and their characteristics are listed in the insert.[60, 63]

The newest pharmacologic agent for the treatment of AD, memantine, is in a new therapeutic class: NMDA receptor antagonist.[64] Memantine has been shown effective as monotherapy as well as an add-on to cholinesterase inhibitor.[65-67]

Randomized controlled trials have shown reliably that cholinesterase inhibitors produce small improvements on cognitive tests over 3-12 months in patients with mild to moderate AD. However, cholinesterase inhibitors are expensive, and the degree of clinical significance of these modest improvements in cognition is debatable. Physicians and families are left struggling to decide when (or if) to start these medicines in a patient with probable AD. The recent AD2000 randomized trial added weight

Table 4. Staging of Alzheimer's Disease

Mild Alzheimer's Disease

- Forgetfulness, unable to learn new information
- Difficulty managing finances, planning meals, taking medication on schedule
- Depression symptoms
- Still able to do most activities, drive car
- Gets lost going to familiar places

Moderate Alzheimer's Disease

- Forgetfulness extends to forgetting old facts (e.g., past career, names of friends)
  - Continually repeats stories
  - Makes up stories to fill gaps
- Difficulty
  - Performing tasks
  - Following written notes
  - Using the shower and toilet
- Agitation, behavioral symptoms common
  - Restlessness, repetitive movements
  - Wandering
  - Paranoia, delusions, hallucinations
- Deficits in intellect and reasoning (e.g., poor judgment, forgets manners)
- Concern for appearance, hygiene, and sleep become more noticeable

Severe Alzheimer's Disease

- May groan, scream, mumble, or speak gibberish
- Behavioral symptoms common
  - Refuses to eat
  - Inappropriately cries out
- Failure to recognize faces of family
- Difficulty with all essential activities of daily living (ADLs) (e.g., eating, toileting, walking)

Adapted from: Cefalu C, Grossberg GT. Diagnosis and Management of Dementia. *Leawood, Kan: American Academy of Family Physicians; 2001 (monograph). Gwyther LP.* Caring For People With Alzheimer's Disease: A Manual for Facility Staff. *2nd ed. Washington, DC and Chicago, Ill: American Health Care Association and the Alzheimer's Association; 2001.*

to the therapeutic nihilists among us. While some have argued that the trial design deviated from usual use, the AD2000 trial is one of the largest nonpharmaceutical funded studies to date.[68] The authors of the AD2000 study concluded that donepezil is not cost effective, with benefits below minimally relevant thresholds, based primarily on a lack of difference in time to institutionalization between treatment and placebo groups.[68]

The decision to start a cholinesterase inhibitor in a patient with mild AD is an individual choice. Some physicians recommend explaining cost, side effects, and potential benefit with patients and their caregivers. Some physicians believe that a cholinesterase inhibitor and/or memantine are useful particularly in patients who are cared for in the home by family members. This belief is supported by those trials that found a significant reduction in caregiver burden, reducing time spent caregiving as much as 46 hours per month.[64, 69] A second niche may be the demented patient, usually in moderate to severe stage, who has agitated or psychotic behaviors, as these medications may help control these behaviors with a safer side effect profile than an antipsychotic.

Memantine is only approved for patients with moderate-severe AD because it has failed to show efficacy in the mild AD group. Patients already on a cholinesterase inhibitor or those who could not tolerate a cholinesterase inhibitor are both candidates once they decline into the moderate stage (i.e., generally a MMSE score below 15). Similar to the cholinesterase inhibitors, memantine offers only a modest improvement in cognitive function. While it has very few side effects, it is also expensive, and therefore the potential benefits must be weighed against the significant cost. Treatment decisions are not easy, and it is worth keeping in mind that the most effective treatment for the AD patient may be caregiver support and education.

Recently, researchers have been exploring the use of cholinesterase inhibitors in MCI. One study investigated the efficacy of donepezil in MCI and failed to find a statistically significant difference in primary outcomes between treatment and placebo groups, however trends favored the donepezil-treated group.[70] Studies investigating galantamine in patients with MCI had a higher all-cause mortality in the treatment groups and a recent bulletin from the manufacturer cautions physicians against use of galantamine in MCI patients.

Other Pharmacologic Agents

Vitamin E at the dose of 1000 mg twice daily was found to be beneficial in slowing the progression of symptoms of Alzheimer's disease in the Alzheimer's Disease Cooperative Study. The same study also found that selegiline (Eldepryl) at a dose of 5 mg bid may slow cognitive decline, however current guidelines recommend vitamin E only as selegiline has a less favorable risk-benefit ratio.[71-73]

The over-the-counter herbal preparation ginkgo biloba is commonly used for dementia, however evidence of efficacy is lacking.[72] Epidemiologic studies previously showed a preventive benefit of estrogen, however multiple studies using estrogen to treat dementia have shown no benefit.[72, 74, 75] In addition, the Women's Health Initiative study showed in a randomized, placebo controlled fashion that estrogen increases the risk of cognitive impairment. Nicotine produced some improvement in patients with AD in one small study, but it also increased anxiety.[76]

Nonsteroidal anti-inflammatory medications have been proposed as a possible protective agent against cognitive decline in AD. Cyclooxegenase is an important mediator of signal transduction for excitotoxic cell death. However, while epidemiologic

studies have shown a protective benefit,[77] treatment trials show little benefit and high dropout rates due to adverse events.[78, 79]

Treatment of Behaviors Associated with Alzheimer's Disease

Behaviors such as paranoia, agitation, aggression, and wandering are common features of AD and increase as the disease progresses.[63] Nonpharmacologic interventions are the firstline treatment. Examples of environmental modifications to control behavior include utilizing clocks and calendars to orient the patient, avoiding overstimulation, placing safety latches on doors, and having a daily routine.[63,80] Behavioral modifications such as simplifying complex tasks with a step-wise approach, communicating with simple phrases, maintaining eye contact, and distracting or redirecting an agitated or confused patient are all important skills for caregivers.[63,80]

When nonpharmacologic interventions are inadequate, multiple medications are currently available to control behaviors associated with AD. Cholinesterase inhibitors produce some improvements in neuropsychiatric and functional outcomes in patients with AD and are sometimes started even in severe dementia to aid with these symptoms.[81] Analyses of multiple studies showed improvement in cooperation, delusions, pacing, and various other behaviors in patients treated with cholinesterase inhibitors compared with those on placebo.[80]

While the evidence is limited, the atypical antipsychotics have been used and found to be effective particularly for agitation with combativeness, delusions, and hallucinations.[82] The typical antipsychotics, while effective, are used for acute management of psychotic symptoms but are second-line agents for long-term use due to the side-effect profile and risk of tardive dyskinesia. The characteristics of the atypical antipsychotics and suggested dosages are listed on the insert.

Mood-stabilizers are also used to treat agitation, delusions, hallucinations, and combative behaviors in AD patients.[63] These agents can be used as firstline treatment or in addition to the atypical antipsychotics for long-term treatment of the behaviors.

The selective serotonin reuptake inhibitors (SSRIs) are generally safe and effective for depressive symptoms. Those with sedating effects can be helpful for aggression, confusion, irritability, and anxiety. Mirtazapine (Remeron) is an antidepressant that promotes sleep, appetite, and weight gain. Bupropion (Wellbutrin) and some of the activating SSRIs can be useful in patients with sedation associated with depression. Some antidepressant drugs and their characteristics are listed in the insert.

Education

Nonpharmacologic measures are often the most effective in changing or controlling behaviors in patients with AD. Care for 80% of AD patients is provided in the community by family members, and the median length of in-home caregiving before nursing-home placement is 6.5 years.[83] Therefore, caregiver education and support is critical. Some nationwide resources for those caring for AD patients are listed on the insert. Local organizations often provide the most immediate support.

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CME Questions

44. Which of the following cholinesterase inhibitors is considered second-line in the treatment of Alzheimer's disease due primarily to liver toxicity?
    A. Donepezil (Aricept)
    B. Galantamine (Reminyl)
    C. Tacrine (Cognex)
    D. Rivastigmine (Exelon)

45. Which of the following antidepressant medications promotes sleep, appetite, and weight gain?
    A. Mirtazapine (Remeron)
    B. Bupropion (Wellbutrin)
    C. Venlafaxine (Effexor)
    D. Fluoxetine (Prozac)

46. Current guidelines for the treatment of Alzheimer's disease recommend cholinesterase inhibitors plus which of the following medications?
    A. NSAIDs
    B. Estrogen
    C. Ginkgo biloba
    D. Vitamin E

47. Patient and caregivers can be advised that cholinesterase inhibitors in general have been shown to delay nursing home placement by approximately what period of time?
    A. Six months
    B. One year
    C. Two years
    D. Four years

48. Which of the following CSF markers is likely to correlate with AD?
    A. Decreased CSF beta amyloid 1-42 level
    B. Increased CSF tau level
    C. Abnormal level of CSF AD7C
    D. All of the above

49. Which of the following are risk factors for AD?
    A. Advanced age
    B. Down syndrome
    C. Head trauma
    D. A & B only
    E. All of the above

CME Answer Key

44. C; 45. A; 46. D; 47. B; 48. D; 49. E

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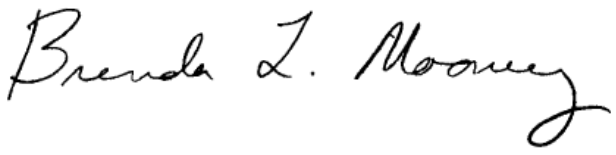

Brenda Mooney
Vice-President/Group Publisher
Thomson American Health Consultants

Atypical Antipsychotics in Alzheimer's Disease

Medication	Dosage	Comments
Olanzapine (Zypexa)	*Initial:* 2.5 mg qhs *Max:* 10-15 mg/day divided bid	May cause drowsiness, dizziness, weight gain, anticholinergic effects, and postural hypotension, rare EPS
Quetiapine (Seroquel)	*Initial*: 12.5 mg bid *Max:* 200 mg bid	Transient orthostasis, anticholinergic effects
Ziprasodone (Geodon)	10 mg IM acute	Not studied in geriatric population QT prolongation and EPS
Aripiprazole (Abilify)	5-15 mg/day	Not studied in geriatric population May cause nausea and sedation
Risperdone (Risperdal)	*Initial:* 0.25 mg qhs *Max:* 2-3 mg/day divided bid	Extrapyramidal symptoms may occur at 2mg/day May cause postural hypotension, blurred vision, drowsiness, dixxiness, headache, and weight gain

Characteristics of Mood Stabilizers and Anxiolytics

Medication	Dosage	Comments
Divalproex (Depakote)	*Initial:* 125 mg bid, titrate to therapeutic blood level (40-90 mcg/mL)	Monitor liver enzymes, platelets, PT and PTT
Carbamazepine (Tegretol)	*Initial:* 100 mg bid, titrate to therapeutic blood level (4-8 mcg/mL)	May cause bone marrow depression, avoid in renal or hepatic impairment
Trazodone (Desyrel)	*Initial:* 25 mg qd *Max:* 200-400 mg/day divided bid-tid	Caution in arrhythmias including PVCs, patients recovering from acute MI
Benzodiazepines (various)	Varies by agent	Use for acute management of agitation/anxiety, can lead to tolerance, depression, falls
Busipirone (BuSpar)	*Initial:* 5 mg bid *Max:* 20 mg tid	May take 2-4 wks to become effective, caution in renal or hepatic impairment

Resources for Patients with Alzheimer's Disease and Their Families

Alzheimer's Association
919 N. Michigan Avenue,
Ste 1100
Chicago, IL 60611-3900
800-272-3900
www.alz.org

American Association for Geriatric Psychiatry
www.aagpgpa.org

American Psychiatric Association
1400 K Street, N.W.
Washington, DC 20005
888-357-7924
www.psych.org

National Institutes of HealthBRAIN
(Brain Resource and Information Network)
P.O. Box 5801
Bethesda, MD 20824
800-352-9424
www.ninds.nih.gov

Administration on Aging
(Eldercare Locator)
800-677-1116
www.aoa.dhhs.gov

Family Caregiver Alliance
690 Market Street, Ste 600
San Francisco, CA 94104
800-445-8106
www.caregiver.org

International Psychogeriatric Association
www.ipa-online.org

National Family Caregivers Association
10400 Connecticut Avenue, #500
Kensington, MD 20895-3944
800-896-3650
www.nfcacares.org

Alzheimer's Disease Education and Referral (ADEAR) Center
800-438-4380
www.alzheimers.org/

National Association of Area Agencies on Aging
202-296-8130
www.n4a.org

ADLs and IADLs

ADLs	IADLs
Pneumonic "DEATH"	*Pneumonic "SHAFT"*
Dressing	**S**hopping
Eating	**H**ousekeeping
Ambulation	**A**ccounting
Toileting	**F**ood preparation
Hygiene	**T**ransportation

Antidepressants

Medication	Dosage	Comments
Bupropion (Wellbutrin	*Initial:* 37.5 mg bid *Max:* 150 mg bid	Activating, avoid in agitatd pts or seizure d/o, may cause insomnia
Mirtazapine (Remeron)	*Initial:* 7.5 mg qhs *Max:* ***30 mg qhs***	Promotes sleep, appetite, and weight gain
Fluozetine (Prozac)	*Initial:* 10 mg qod in AM *Max:* 20 mg qAM	Activating, very long half-life, GI side effects
Paroxetine (Paxil)	*Initial:* 10 mg qd *Max:* 40 mg qd	Less activating, anticholinergic
Sertraline (Zoloft)	*Initial: 25-50 mg qd* *Max:* 200 mg qd	Well tolerated
Citalopram (Celexa)	*Initial:* 10 mg qd *Max:* 40 mg qd	Well tolerated, some nausea and sleep disturbance
Fluvoxamine (Luvox)	*Initial:* 50 mg bid *Max:* 150 mg bid	Drug interactions with benzodiazepines
Venlafaxine (Effexor)	*Initial:* 37.5 mg bid *Max:* 225 mg qd divided bid	Potent, caution in impaired renal or liver function or seizure disorder

Cholinesterase Inhibitors

Drug	Dose and Titration	Side Effects	Special Considerations
Donepezil (Aricept)	Start 5 mg qhs, increase to 10 mg in 4-6 wks	Mild nausea, vomiting,diarrhea, and transient agitation	Some evidence of interactions with cimetidine, theophylline, warfarin, and digoxin
Galantamine (Reminyl/Razadyne)	Start 4 mg bid, increase by 4 mg bid q 4 wks as tolerated to max 12 mg bid	Mild nausea, vomiting, and diarrhea	Contraindicated in patients with renal or hepatic impairment
Rivastigmine (Exelon)	Start 1.5 mg bid, increase by 1.5 mg bid q 4 wks as tolerated to max 6 mg bid	Nausea, vomiting, diarrhea, headaches, dizziness, abdominal pain, fatigue, anxiety, and agitation	Side effects may cause weight loss. Interacts with procainamide and aminoglycosides.

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

Rifamixin for the Prevention of Traveler's Diarrhea?

Rifamixin, a nonabsorbed oral antibiotic, is effective for preventing traveler's diarrhea, according to new research. The study was done in 210 US students traveling to Guadalajara, Mexico. They were randomized to receive rifamixin 200 mg once a day, 200 mg twice daily, 200 mg 3 times a day, or placebo for 2 weeks. Rifamixin effectively prevented traveler's diarrhea for all doses. Overall, traveler's diarrhea developed in 14.74% of participants taking rifamixin and 53.70% of those taking placebo (rate ratio 0.27 [95% CI, 0.17 to 0.43]). All doses of rifamixin were superior to placebo in preventing diarrhea. In test subjects who did not report traveler's diarrhea, rifamixin significantly reduced the occurrence of mild diarrhea (P = .02) and moderate and severe intestinal problems, including pain and cramps (P = .009) and excessive gas (P = .02). Adverse reactions with rifamixin were comparable to placebo, and minimal change in coliform flora was found during rifamixin therapy. The authors conclude that rifamixin effectively prevents traveler's diarrhea in Mexico, with minimal changes in fecal flora. They also suggest that further studies should be performed to evaluate whether the drug is effective in preventing diarrhea in other areas of the world where *E. coli* is not the major pathogen, and whether rifamixin is effective in preventing postinfectious irritable bowel syndrome (*Ann Int Med.* 2005;142:805-812). The accompanying editorial suggests that rifamixin may not be appropriate for prophylaxis of all travelers, but rather selected patients at risk, and that rapid and judicious treatment of diarrhea is best recommended for most travelers (*Ann Int Med.* 2005;142:861-862). Rifamixin is currently only approved for the treatment of travelers diarrhea caused by *E. coli*. The drug is manufactured by Salix pharmaceuticals and marketed under the trade name Xifaxan.

Erectile Dysfunction and Visual Disturbance

Sildenafil (Viagra), Pfizer's blockbuster erectile dysfunction drug, has been implicated along with tadalafil (Cialis) and vardenafil (Levitra) in causing a relatively uncommon form of visual disturbance known as nonarteritic anterior ischemic optic neuropathy (NAION). The first reports of the relationship were published in March of this year. An ophthalmologist at the University of Minnesota noticed 7 patients in his practice who developed NAION within 36 hours after taking sildenafil (*J Neuroophthalmol*. 2005;25:9-13). Since that time, the FDA has received a total of 38 reported cases associated with sildenafil, 4 with tadalafil, and 1 with vardenafil. Pfizer is countering that review of 103 clinical trials

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5416. E-mail: leslie.hamlin@thomson.com.

involving over 13,000 patients. They say they found no reports of NAION and that there is no evidence that NAION occurs more frequently in men taking sildenafil than in men of similar age and health who did not take the drug. And while it is true that the risk factors for erectile dysfunction and NAION are similar and include hypertension and diabetes, the FDA may still require labeling changes for all 3 drugs, listing NAION as a possible risk. NAION results in loss of vision in parts of the visual field that are usually permanent. The FDA is continuing to evaluate the situation, and notes that there is no direct evidence relating erectile dysfunction drugs to NAION, but warns that patients who notice visual changes after taking one of these medications should report it to their physician immediately.

Mixed News on Statins

Good news and bad news about statins. First the good. It appears that statins are associated with a significant reduction in the risk of colorectal cancer. A population-based, case-control study from northern Israel of 1953 patients with colorectal cancer and 2015 matched controls, reviewed whether use of a statin between 1998 and 2004 reduced the risk of colorectal cancer. In comparison to patients who did not use statins, statin use was associated with a significantly reduced relative risk of colorectal cancer (odds ratio, 0.50; 95% CI, 0.40-0.63). This relationship remained significant after adjustment for aspirin use, NSAID use, physical activity, hypercholesterolemia, family history of colorectal cancer, ethnic group, and diet (odds ratio 0.53; 95% CI, 0.38-0.74) resulted in a 47% relative reduction in the risk of colorectal cancer. The authors admit that the absolute risk reduction is likely to be small, and further studies are needed (*N Engl J Med*. 2005;352:2184-2192). An accompanying editorial suggests it is too early to recommend statins as chemoprotective agents against cancer, but notes there is biologic plausibility to their use in this role. There is also the suggestion that statins may target many diseases of aging including osteoporosis and dementia, as well as cardiovascular disease by similar mechanisms (*N Engl J Med*. 2005;352:2238-2239).

Bad news for rosuvastatin (Crestor), AstraZeneca's high-potency statin. The drug has been under scrutiny after related reports of high rates of toxicity in premarketing and some post-marketing studies, compared with other statins. The drug has been a favorite target of the watchdog group Public Citizen, which has petitioned the FDA to withdraw rosuvastatin from the market. Now a report in the May 23rd online version of *Circulation* confirms a higher level of adverse events associated with the drug. Researchers from Tufts University reviewed all rosuvastatin related adverse events reported to the FDA in the drug's first year of marketing. Higher rates of rhabdomyolysis, proteinuria, nephropathy, and renal failure were seen with rosuvastatin, when compared with atorvastatin ($P < 0.001$) , simvastatin ($P < 0.001$), and pravastatin ($P < 0.001$). Adverse events generally occurred early in the course of treatment and at recommended doses. The authors conclude that there are safety concerns associated with rosuvastain, and that healthcare providers should consider other statins as first-line therapy.

FDA Actions

Pegasys, Roche's pegylated interferon, has been approved for the treatment of chronic hepatitis B infections, including both HBeAg-positive and HBeAg-negative disease. The drug was previously approved for the treatment of chronic hepatitis C.

Infliximab (Remicade) is approved for the treatment of psoriatic arthritis affecting at least 5 joints. The biologic agent is a monoclonal antibody that targets tumor necrosis factor alpha. It is also approved for ankylosing spondylitis, Crohn's disease, and rheumatoid arthritis.

Pfizer has received approval to market sildenafil citrate for the treatment of pulmonary arterial hypertension. Sildenfil, which is the active ingredient in Viagra, will be marketed under the trade name Revatio, in a 20 mg tablet that looks different from Viagra tablets to avoid confusion. Sildenafil as Revatio is dosed 3 times a day.

The FDA has approved an extended-release form of dexmethylphenidate for the treatment of attention deficit, hyperactivity disorder. The once daily formulation is approved for adults, adolescents, and children. It will be marketed as Focalin XR by Novartis Pharmaceuticals.

Canadian drug maker Depomed has received approval to market a once a day form of metformin for the treatment of type 2 diabetes. Glumetza will be marketed in 500 and 1000 mg doses. The formulation employs the company's Gastric Retention technology that slows transit and controls drug delivery. ■