"So We Have Alzheimer's Disease. Now What?" The Primary Care of Patients with AD

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Introduction

Over the past few years scientific advances have added to our understanding of Alzheimer's disease (AD). Recent published reviews have discussed the diagnosis, pathophysiology, and treatment of dementia.[1-4]

This review will focus on the primary care of AD after the diagnosis has been established. The primary care physician is now, and will continue to be the primary provider of medical care to this rapidly growing population of patients, and by the nature of the disease to their families and caregivers. Furthermore, the management of AD is the quintessential geriatric care problem in that in addition to the biological result, social and other medical factors interact to determine the functional state of the patient.

AD, the most common cause of progressive irreversible intellectual loss (dementia) in aging humans, affects an estimated 4.5 million Americans.[5] The estimated annual incidence of AD approximately doubles every 5 years after age 65. The rate is 0.6% for persons aged 65 to 69 years, 1.0% for persons aged 70 to 74 years, 2.0% for person aged 75 to 79 years, 3.3% for persons aged 80 to 84 years, and 8.4% for persons aged 85 years and older.[5,6] The prevalence of AD increases from approximately 5-7% at age 65-74 to approximately 40% for those 85 and older.[7] The impact of this disease will only grow considering that the 85 and over age group is the fastest growing segment of the population.

The estimated annual cost of caring for AD patients is approximately $100 billion.[8,9] More than 70% of affected individuals live at home and 75% of them receive care from family members and friends.[7] As the disease progresses families frequently need long-term paid care. The cost of this care averages $19,000 annually and is mostly paid out of pocket.[10] AD costs American businesses an estimated $61 billion a year; $24.6 billion covers AD health care and $36.5 billion covers costs related to caregivers of AD individuals, (lost productivity, absenteeism, and worker replacement).[11]

The brains of patients with AD contain numerous extracellular amyloid plaques composed of 40 and 42 amino acid β-amyloid proteins surrounded by dystrophic neurites (axons and dendrites), activated microglia (monocyte- or macrophage-derived cells from within the brain) and reactive astrocytes.[3] The less soluble 42-residue β-amyloid protein is more prone to aggregation.

Another characteristic lesion is the neurofibrillary tangle consisting of

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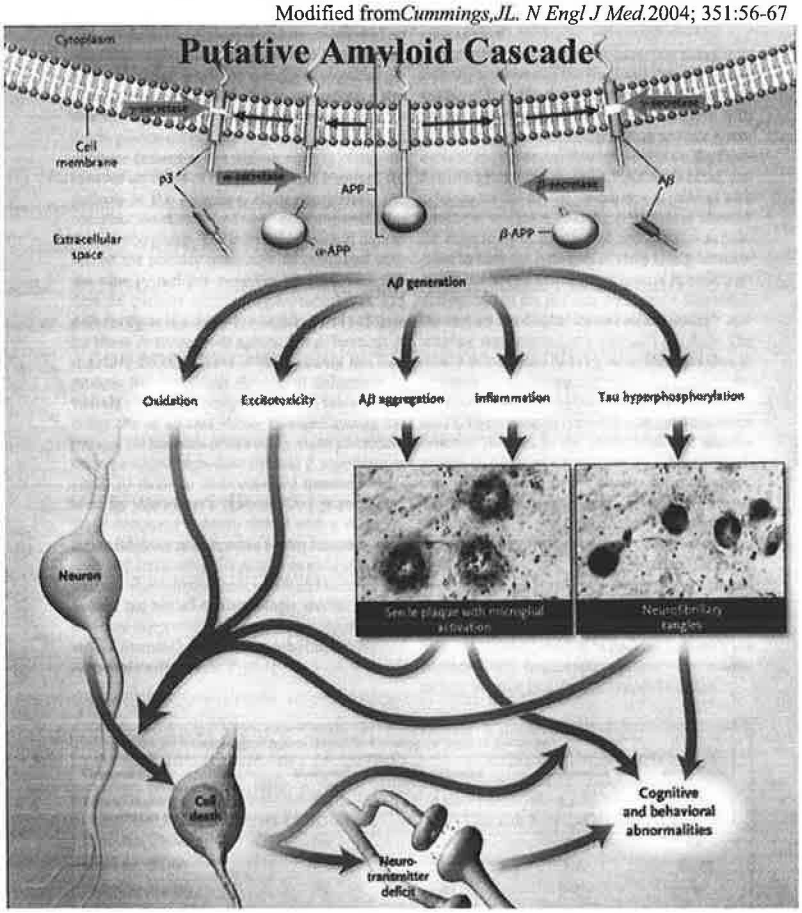

This hypothesis of the amyloid cascade, which progresses from the generation of the β-amyloid peptide from the amyloid precursor protein, through multiple secondary steps, to cell death, forms the foundation for current and emerging options for the treatment of AD. APP denotes amyloid precursor protein, and Aβ beta-amyloid.

intraneuronal intracytoplasmic masses of tau protein.[12,13] Tau normally binds to and stabilizes the microtubules that comprise the cytoskeleton of neurons. In AD, the tau protein becomes hyperphosphorylated, unfastens from microtubules and begins to combine with other tau proteins forming tangles and leading to impairment and collapse of the neuron's transport system. This ultimately leads to loss of communication between neurons and cell death. In AD neurofibrillary tangles usually occur in large numbers in the entorhinal cortex; hippocampus; amygdala; association cortices of the frontal, temporal, and parietal lobes; and certain subcortical nuclei that project to these regions. Neurofibrillary tangles can occur in other degenerative brain diseases in the absence of amyloid protein deposition (for example, in frontotemporal dementia, subacute sclerosing panencephalitis, and progressive supranuclear palsy).[3] A third pathologic feature of AD is profound synaptic loss and disconnection between neurons causing dysfunction and ultimately, cellular death.

AD pathology spreads overtime from the temporal and limbic cortices into parietal and frontal brain regions, largely sparing the occipital cortex and not impinging on the motor cortex.[14] As more areas of the brain are involved, more and varied symptoms develop.

Initially patients with AD experience memory loss and confusion. These impairments result in functional decline such as difficulty managing home finances, getting lost while driving in familiar places, and difficulty with food preparation. With time, cognitive losses progress to affect multiple cognitive domains (e.g. language, visuospatial relationships, judgment, calculation).[1] Progressive functional decline ensues, often accompanied by behavioral problems. Late in the disease loss of language and praxis cause patients to become dependent on others for assistance with all basic activities of daily living.

The criteria for dementia most often used are outlined in the *Diagnostic and Statistical Manual of Mental Disorders,* fourth edition (DSM-IV).[15] The specific diagnosis of AD is most often based on the criteria developed by the National Institute of Neurologic and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA).[16] The diagnosis is classified as definite (clinical diagnosis with histologic confirmation), probable (typical clinical syndrome without histologic confirmation), or possible (atypical clinical features but no alternative diagnosis apparent; no histologic confirmation). A variety of diagnosis and treatment guidelines have been published.[17-19]

Table 1: DSM-IV-TR Dementia of the Alzheimer's Type

A. The development of multiple cognitive deficits manifested by both
   (1) memory impairment (impaired ability to learn new information and to recall previously learned information)
   (2) one (or more) of the following cognitive disturbances:
      (a) aphasia (language disturbance)
      (b) apraxia (impaired ability to carry out motor activities despite intact motor function)
      (c) agnosia (failure to recognize or identify objects despite intact sensory function)
      (d) disturbance in executive functioning (i.e., planning, organizing, sequencing, abstracting)
B. The cognitive deficits in Criteria Al and A2 each cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.
C. The course is characterized by gradual onset and continuing cognitive decline.

Table 1 continued

D. The cognitive deficits in Criteria A1 and A2 are not due to any of the following: (1) central nervous system conditions that cause progressive deficits in memory and cognition (e.g., cerebrovascular disease, Parkinson's disease, Huntington's disease, subdural hematoma, normal-pressure hydrocephalus, brain tumor) (2) systemic conditions that are known to cause dementia (e.g., hypothyroidism, vitamin B12 or folic acid deficiency, niacin deficiency, hypercalcemia, neurosyphilis, HIV infection) (3) substance-induced conditions
E. The deficits do not occur exclusively during the course of a delirium.
F. The disturbance is not better accounted for by another Axis I disorder (e.g., major depressive disorder, schizophrenia).

Table 1 outlines diagnostic criteria for AD. Since memory loss is a common complaint in older patients, it is helpful to emphasize two requirements which may be overlooked when assessing memory and other cognitive complaints: (1) significant impairment in social or occupational functioning representing a significant decline from a previous level of functioning and (2) the deficits do not occur exclusively during the course of a delirium.

Education is critical and the process should begin once the diagnosis is made. Frequently patients have had a thorough evaluation (neuroimaging, standard laboratory studies to rule out reversible causes of dementia) and although diagnosed with AD, have very little understanding of what the diagnosis means and what to expect.

The understanding and diagnosis of a dementing illness in general and AD in particular is arguably more difficult for patients and families to comprehend than most medical diagnoses. It is essential that time is spent discussing what for many is a nebulous and difficult concept. The investment in time to educate families and patients will avoid excessive frustration, misunderstanding, and a host of potential problems in the future. To some family members some of the behaviors of patients may seem volitional or of a "psychiatric" basis. We often use the paradigm of stroke since most people can relate to the idea of a brain injury that could affect function, for example the loss of movement in an extremity. If the behaviors can be explained in a similar manner, i.e. specific areas of the brain have been injured (from the pathophysiology of AD) and that these injured circuits can no longer function, patients and families get a better understanding of the medical nature of the problem. Also, it becomes more apparent why, for example, it is hopeless to expect that repetitive exercises will help to remember a person's name or that "Dad keeps telling the same story over and over within 10 minutes" is not volitional. Just as we would not ask a patient to walk who has a flaccid paralysis from a CVA, likewise, we would not quiz mom "What is my name".

In addition to appropriately "medicalizing" the impairments of AD patients, giving some specifics regarding the basis of brain dysfunction can be helpful for many people and can help make some sense of what the family and patient are experiencing. For example, executive control function is the cognitive domain that includes the ability to plan, initiate, sequence, and monitor complex goal-directed behavior. Anatomically executive function is thought to reside in the frontal cortex and its basal ganglia-thalamic connections.[20] Many of the symptoms and behaviors of patients with AD can be explained by impairment in this domain rather then memory per se. A patient may be able to retain unimpaired, the motor sequencing for driving a car (a form of so-called procedural memory that is probably mediated by the cerebellum)[21] but the actions taken to avoid a collision when one is cut off in traffic or to avert hitting a child that steps out into traffic is an executive function. In fact, there are studies suggesting that functional impairment is more closely linked to impairment in this domain than from impaired memory.[22]

The patient (when appropriate) and family should be counseled with regard to the general course of the disease. Although there are daily fluctuations in the cognitive state of the patient (good days and bad days), decline is generally gradual. Family members should be counseled that abrupt changes in a patient's cognition should not be attributed simply to the disease but as a warning sign that an acute medical process may have supervened (acute on chronic process) or that an adverse effect has occurred of a prescription or over-the-counter medication. Therefore, a sudden worsening of the patient's functional status should prompt a call to their physician.

Limiting Excess Disability by Optimal Management of Comorbid Conditions

The value of a complete medical evaluation of a patient with AD is to ascertain the overall medical status of the individual. This helps the family understand the overall health status of the individual and to optimally manage other problems that may have an impact on the individual's functional state. Reversible conditions should be treated.

Polypharmacy and adverse drug reactions

Patients with AD are particularly vulnerable to the adverse effects of anticholinergic drugs. Loss of the cholinergic synapses and neurons that support memory function is one of the cardinal features of AD. A prudent therapeutic strategy is to eliminate all non-essential medications and in particular to shun anticholinergic agents which may further impair cholinergic and cognitive function. Furthermore, the use of unproven treatment guidelines in older patients with comorbidity may lead to polypharmacy and unintended consequences.[23]

Besides avoiding adverse drug effects, fewer medications reduce the burden and responsibilities for the caregiver. In addition, administering medications to some patients results in confrontations in irritable or easily agitated patients.

Many commonly used medications have anticholinergic properties. This is true for both over-the-counter agents (e.g. Tylenol PM®) and prescription drugs (e.g. amitriptyline and antimuscarinic agents for urge incontinence and overactive bladders).[24] If an anticholinergic drug is used, the potential benefits and risks should be carefully weighed and families should be warned regarding potential for worsening cognitive function.

Sensory Impairment

Attention to sensory losses is important. If the patient has not had a visual assessment, this should be completed and refractive errors corrected. Hearing loss is common and what is not heard cannot be remembered. However, hearing aids are generally not recommended. In addition to their high cost, they often are lost; patients have difficulty applying and adjusting them; and they forget to use them. Appropriate communication for hearing impaired individuals (speaking face-face) is more useful and families should be counseled in this regard.

Cardiovascular Disease and AD Risk

Hypertension and other cardiovascular risk factors are common in the aged with and without AD.[25,26] There is some evidence that cerebrovascular disease can aggravate dementia in AD and also be a direct cause of dementia. It makes inherent sense to avoid additional cerebral injury in the

brain of an AD patient who is already being ravaged by neuronal loss and injury. The former may be preventable even though the latter currently is not. The diagnosis of Mixed Dementia (AD plus vascular dementia) is also a common clinical and pathologic entity. The development of AD may be accelerated by ischemia resulting from cerebrovascular disease.[27-30] A number of observational studies have shown a relationship between hypertension and increased risk for cognitive impairment, in addition to a protective effect of antihypertensive therapy.[31,32]

Forette et al.[33] reported antihypertensive therapy reduced the risk of developing dementia by 50% (21 vs. 11, P=0.05) but the estimate of benefit was of limited value because of few total cases (n=32). In an extended two-year open label trial following a double-blind randomized trial,[34] 41 of the 64 incident cases of dementia were due to AD. The authors concluded that the findings from the extended trial supported the trend seen in the closed label trial since antihypertensive therapy reduced the risk of dementia by 55%. After controlling for various factors (age, sex and entry blood pressure) they estimated that treatment of 1000 patients for 5 years can prevent 20 cases of dementia.

The Systolic Hypertension in the Elderly Program[35] found that treatment reduced the incidence of cardiovascular events but not dementia. However an inadequate analysis of dropouts may have obscured a protective effect of treatment.[36] The Medical Research Council Trial in Older Adults study also failed to demonstrate any effect on cognition.[37]

Vermeer et al.[30] reported an association between silent brain infarcts and risk of dementia and cognitive decline in a prospective population base study in patients 60-90 years of age free of dementia at baseline. Those with silent infarcts had a steeper decline in cognitive function than those without silent infarcts. The decline was confined to people who had additional silent brain infarcts. There was no association between the presence of silent infarct at baseline and decline in MMSE score. The study also found that decline in cognition varied with location of the infarct on MRI. Infarcts in the thalamus were associated with worse performance in memory tasks, probably because the thalamus is involved with short-term memory and long-term storage.

Population based studies have shown an association between elevated cholesterol and increased risk of AD.[26,38] However, randomized controlled trials have not confirmed that statins reduce the incidence of AD.[39] Findings from the PROSPER study found that pravastatin given for 3 years reduced the risk of coronary disease in elderly individuals but did not slow cognitive decline.[40] Similarly, the Heart Protection Study found significant cardiovascular and cerebrovascular benefits over 5 years of follow-up for at risk patients for coronary or cerebrovascular disease treated with 40 mg/d of simvastatin, but no evidence for a decreased incidence of cognitive impairment or dementia.[41] These studies, however, do not answer the question whether there is a role for statins as a treatment to slow the rate of disease progression in people with AD. An NIH supported trial initiated in 2003 is currently evaluating the efficacy of statins in approximately 400 AD participants at 40 sites nationwide.

Depression

Patients should be evaluated for depression for two reasons. It is a common problem that can clinically present with cognitive symptoms such as marked inability to concentrate (dementia of depression; pseudodementia) and should be identified and treated appropriately. Furthermore,

patients with dementia can develop depression and to the extent the depression can be treated, the patient's functional state can improve. Patients with dementia may not be able to offer a history of depression, but caregivers seem to serve as reliable surrogate reporters of depression.[42]

Distinguishing, depression from dementia can be challenging. In AD and depression, patients can appear apathetic and withdrawn. In AD this can be especially true once executive function is impaired. This is common in settings where patients receive little external stimulation or encouragement. Patients may just sit because they are unable to self initiate. When encouraged they may become much more engaged. Nonetheless, since depression is treatable, and modern antidepressants are relatively benign agents, clinicians should have a low threshold in treating patients suspected of being depressed.

A Cochrane systematic review was conducted to determine whether antidepressants are clinically effective in the treatment of patients with depression and dementia.[43] There were strikingly few studies of sufficient design quality or data quantity to enter the meta-analysis. Based on the available data, the authors concluded there is "weak support to the contention that antidepressants are effective for patients with depression and dementia." The main finding was the scarcity of research and evidence in this area. Data from a 12-week trial found improved depression scores in the treatment group (SSRI) vs. placebo; and responders had less behavioral disturbances and caused less caregiver stress. Cognitive scores did not change.[44]

A CASE

MJ is an 81-year-old man with AD. The patient's wife reported that he had over the preceding week started complaining of anxiety over their lack of money and that they were destitute. He would not accept any assurances by his wife and family that there were no financial problems. He stated he understood what his family was saying but assured his physician that he knew he had no money and that his family was just wrong. He had difficulty sleeping, and began to lose weight because he declined eating – feeling he had no money to pay for it. This was poignantly demonstrated one day when he was sitting at a country club but refusing to eat. His Mini-mental State Examination, (MMSE) score six months earlier had been 25 and was now 19. His clock drawing, normal one year earlier, was now impaired. The initial impression was that his AD was progressing and he had now developed delusions. He was started on an atypical antipsychotic in an attempt to treat his delusion. However he became more confused and distraught and his oral intake declined further. A week later he continued to have delusions about being penniless and having no clothes or food in the house; he was having trouble sleeping at night. He stated he was going to kill himself and his spouse. At this point he was brought to the emergency room; a CT scan and laboratory studies were unremarkable. On discharge from the ER, the atypical antipsychotic was discontinued and he was given a hypnotic for sleep. His mood remained melancholic, he was preoccupied with his financial state, and he had a 10-pound weight loss over 4 weeks. The hypnotic was discontinued and he was started on an SSRI. Within three weeks he had stopped complaining about financial problems, his appetite increased substantially, and he was consuming 3 meals a day. At eight weeks on the SSRI he was back to baseline – pleasant, cooperative, well-groomed, with an excellent appetite. His short-term memory remained impaired but his MMSE had improved to 23. The final assessment was that the patient was suffering from a psychotic depression in addition to his baseline AD. The depression was treatable and a reversible process. Although the AD remained, his functional state improved dramatically.

Health Maintenance

The appropriateness of ongoing health maintenance measures should be considered. Routine vaccinations should generally be continued and other screening measures should be considered in the context of co-morbidity and the clinical state of the patient.

Disease Progression and Survival

Families frequently inquire about the life expectancy of their relative diagnosed with AD. Larson et al.[45] found the median survival from initial AD diagnosis of 521 patients enrolled in a managed care organization was 4.2 years for men and 5.7 years for woman, equal to about half that predicted using U.S. Census life tables. Predictors of mortality included an MMSE of 17 or less and a Blessed Dementia Rating Scale score of 5 or greater,[46] presence of frontal lobe release signs, presence of extrapyramidal signs, gait disturbance, history of falls, congestive heart failure, ischemic heart disease, and diabetes at baseline. A rapid decline in the first year predicted a more malignant course. A MMSE decline of 5 points or more in a one year follow up was associated with a 60% increased risk of death.

Similarly others have found that disease severity and rate of progression to be a predictor of time course.[47] Doody et al.[48] determined the time for a clinically meaningful decline in cognitive state (defined as a fall in MMSE score of 5 or more points) could be grouped into slow (<2 points per year), average or medium (2-4.9 points per year) or rapid (>5 points per year). The rate of decline was related to their preprogression rates (patients typically have had symptoms 3-4 years before clinical presentation). In other words, patients tend to stay on the slope they had when they initially presented with AD. Furthermore, if population derived estimates are used (3 points per year), an individual patient's decline can be over or underestimated.

Family Risk

Children of people with AD are often concerned about their risk of developing the disease. Increasing age, female sex, family history, and presence of one or two copies of the apolipoprotein E ε4 allele are risk factors for AD.[49]

Autosomal dominant AD beginning before 60 years of age accounts for less than 1% of AD patients worldwide. Fifty percent of these cases are thought to involve mutations in the presenilin 1, 2 or the amyloid precursor protein (APP) gene.[50] The lifetime risk of AD at age 65 in a person without a family history of AD is approximately 15%.[51,52] Seshadri et al.[52] has estimated the lifetime risk of developing AD with an APOE ε4 allele increases to 29% but risk is reduced to 9% in those without an APOE ε4 allele. A number of studies have suggested the baseline risk of developing AD is greater in African Americans but the relative increased risk related to first degree relatives or female sex is similar in whites of European descent and African Americans.[53,54] Risk estimates appear to be 2 to 3 times higher in first-degree relatives of patients with AD compared to non-relatives. The presence of at least one ε4 allele doubled the adjusted risk among Whites and tripled the risk among African Americans. While the number of ε4 alleles increase risk in an individual, the ε3 allele conveys neutral risk and ε2 reduced risk[54,55] Studies have suggested the ε4 allele is a risk factor for AD before 70 years of age but the effect is diminished afterward.[49,55]

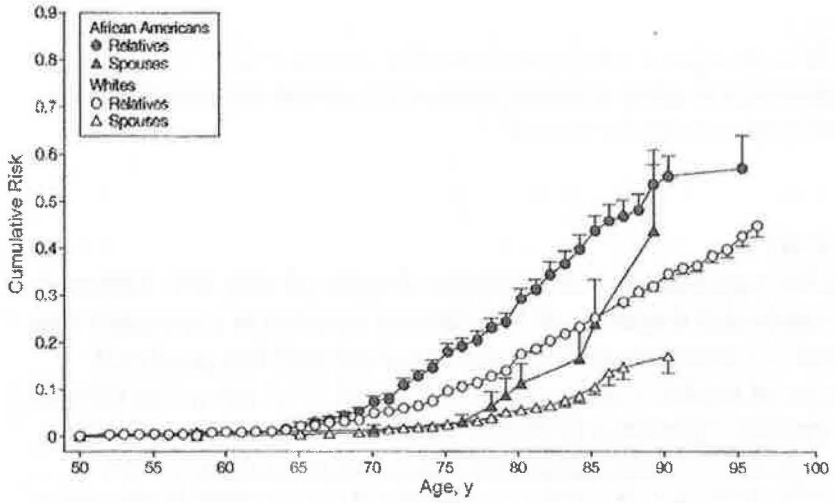

Fig. 2: Cumulative risk of AD in 1° relatives and in spouses of AD probands, stratified by proband's ethnicity.[54]

Figure 2 shows the cumulative risk of dementia in first-degree biological relatives and in spouses of probands (an approximation of the general population). The number of African American spouses is low and caution is strongly advised interpreting this line.

Figure 3 provides the cumulative risk of dementia in first-degree biological relatives of AD probands stratified by APOE genotype and ethnicity. The authors caution that these findings are for scientific interest and should not be used for clinical counseling. To reinforce this position genetic testing for AD has no role in clinical practice today.[56]

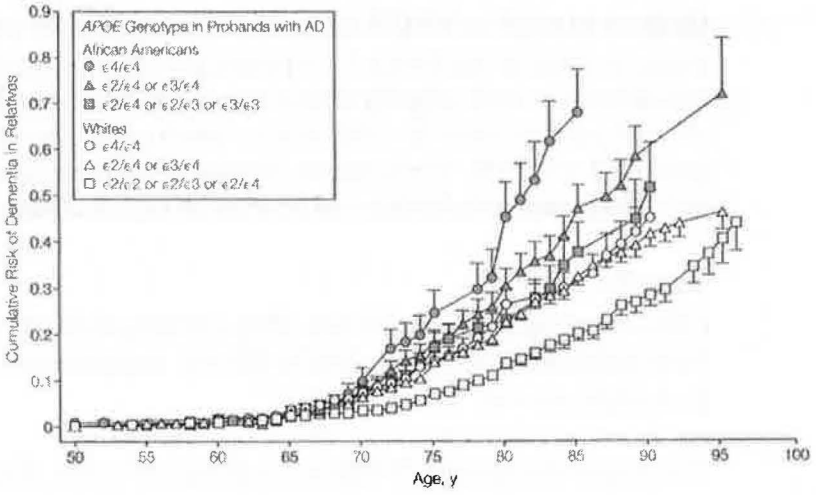

Fig. 3: Cumulative risk of AD in 1° relatives of AD probands, stratified by proband's APOE genotype/ ethnicity.[54]

Outcome Scales Used To Assess Interventions in AD

A variety of scales are used to evaluate the efficacy of pharmacologic interventions for AD. They can be grouped into four major domains: cognition, behavior, function, and global assessment. Some understanding is necessary to interpret the significance of findings in intervention trials and to appreciate the magnitude of effect size. There are a myriad of different assessment tools but the following is a summary of some commonly used. Examples of the actual tools are readily available in related textbooks and on the web.[57]

Cognition

ADAS-cog: Probably the most common tool to assess cognition in mild to moderate disease is the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog).[58] This tool is used to measure selective elements of cognitive function – specifically memory, orientation, language, reasoning, and practices. The scoring ranges from 0-70 with higher scores indicating increased magnitude of cognitive impairment. There are 11 individual tests. Spoken language ability (0-5), comprehension of spoken language (0-5), recall test instructions (0-5), word finding difficulty (0-5), following commands (0-5), naming objects (0-5), instruction drawing (0-5), ideational praxis (0-5), orientation (0-8), word recall (0-10) and word recognition (0-12).

A 4-point difference in the ADAS-cog score is often used as a cutoff to suggest a clinically meaningful response in clinical trials although the validity of this number is debated.[59,60]

MMSE

The Mini Mental State Examination® (MMSE)[61] evaluates cognition in five areas: orientation, immediate recall, attention and calculation, delayed recall, and language. The score ranges from 0 (severe impairment) to 30 (normal). Typically mild disease has a score of 20-30, moderate 10-20, and severe < 10. Mod-severe is generally classified as <14.

The US Food and Drug Administration has suggested that a reversal of the natural history of cognitive decline by 6 months constitutes a clinically important difference.[62] This change equates to 1.4 MMSE points since the mean annual rate of decline in AD is reported to be about 2.8 points (range 1.8–4.2).[63] A survey of clinicians found that 45% judged a 3-point change as the minimum clinical benchmark.[63]

SIB

The severe impairment battery (SIB) is a 40-item test developed for evaluation of cognitive dysfunction for patients with severe AD. Six subscales assess memory, orientation, language, attention, visuospatial ability, and praxis. Scores range from 0-100; higher scores reflecting higher levels of cognitive abilities.[64]

Global assessment

The Clinician's Interview-Based Impression of Change scale (CIBIC-plus)[65] provides a global rating of patient function in four areas: general, cognitive, behavioral, and activities of Daily Living (ADL). Measurements are derived through independent, comprehensive interviews of the patient and caregiver by a trained clinician who is blinded to all other patient assessments and outcomes. Patients are scored on global severity at baseline and subsequent assessments on a scale of 1-7 are relative to baseline, with 1 showing marked improvement, 7 marked worsening with 4 representing no change. Results are often presented in a Likert-like scale (ranging from 1 markedly improved) to 4 (no change) to 7 (marked worsening), and in a dichotomized mixed form, for example, improved compared with unchanged or worse.

Physical Function

Overall physical function is assessed by evaluating activities of daily living (ADLs). A variety of tools have been used. Some include:

The ADCS (AD Cooperative Study-Activities of Daily Living inventory) ADL_{19} is a 19-item inventory of items appropriate for evaluating later stages of dementia. The tool can be administered as an interview of patient's caregivers. Scores range from 0-54. Higher scores reflect higher levels of functioning.[66]

The Progressive Deterioration Scale (PDS)[67] is a disease specific measure of changes in nine items of the activities of daily living. Each item is scored on a visual analogue scale of 0-100 (a higher score is better), and the final score is the mean score of the items. The interview is conducted with the caregiver.

The Disability Assessment for Dementia (DAD)[68] scale is based on an interview with a caregiver to assess activities of daily living (self care activities, instrumental (complex) activities of daily living, planning and organization, leisure, effective performance, initiation). 46 questions are used and has a score range of 0-100 (higher scores indicate better functioning).

Behavioral assessments

The Neuropsychiatric Inventory (NPI)[69] is a 12-item, caregiver administered instrument, used to evaluate behavioral and neuropsychiatric symptoms, including delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy, disinhibition, irritability, aberrant motor behavior, night-time behavior, and appetite/eating disorder. Frequency is rated from 1 (occasional, less than once a week) to 4 (very frequent) and severity from 1 (mild) to 3 (severe). The product of frequency and severity ranges from 1 to 12, with a total score ranging from 12 to 120 for the 10 domains summed. A lower score indicates improvement.

Primary Treatment Considerations for AD

Vitamin E and Anti-inflammatory Agents

Although it has been common clinical practice to recommend vitamin E on the basis of an antioxidant effect to treat AD, there is little evidence to support this recommendation. A Cochrane systematic review concluded that there is currently insufficient evidence to recommend vitamin E treatment.[70] The one trial suggesting a benefit used 2000 IU per day. After adjusting for a significant baseline difference in MMSE score across the vitamin E and placebo groups, those taking vitamin E had a significant delay to the combined end point of death, institutionalization, loss of ability to perform at least 2 of 3 ADLs, or progression to severe dementia.[71] No benefit from vitamin E was found for cognitive function as measured by the MMSE, the ADAS-Cog, or the Blessed Dementia Scale (BDS). Some investigators have interpreted these results as supporting vitamin E treatment to slow institutionalization in AD. The median time to this end point was 670 days in the vitamin E group vs 440 days in the placebo group (P=.001). Therefore the estimated increase in median time to end point was 230 days (RR, .47). Significantly fewer patients taking vitamin E were institutionalized during the study period (26% vs 39%, P=.003; RR, .42). More participants taking vitamin E suffered a fall (12/77 compared with 4/78; odds ratio 3.07, 95% CI 1.09 to 8.62). Considerable attention has surrounded vitamin E and cardiovascular events.[72] This was not found to be the case in patients with AD. Likewise selegiline, a neuroprotective agent, is ineffective in the treatment of AD irrespective of the outcome measure evaluated (i.e. cognition, emotional state, activities of daily living, and global assessment).[73]

Epidemiological surveys suggest a lower prevalence of cognitive impairment in patients receiving long term treatment with NSAIDs. Animal and cell culture studies have also suggested that inflammatory processes may be involved in the pathogenesis of AD and have fueled interest in non-steroidal antiinflammatory drugs. However, No evidence exists from randomized double-blind, placebo-controlled trials that either Cox-I or II inhibitors are effective in the treatment of AD.[74-77]

Cholinesterase Inhibitors

The cholinergic hypothesis of memory dysfunction[78] is the basis of pharmacologic interventions to ameliorate cognitive decline in AD. Acetylcholine is an essential neurotransmitter associated with memory. In AD loss of neuronal function and cell death leads to diminished levels of acetylcholine. The inhibition of acetylcholinesterase (AChE) by ChEIs is a strategy to reduce breakdown of acetylcholine in the synaptic cleft thereby helping to maintain cholinergic neurotransmission. In 1997 Tacrine was the first FDA approved ChEI but is no longer marketed because of a difficult dosing schedule and because it induced hepatitis in about a 50% of patients. The "second generation" ChEIs (donepezil, rivastigmine, and galantamine) have slightly different pharmacologic properties but all work by inhibiting the breakdown of acetylcholine. The newer ChEIs have superior properties in terms of specificity of action, ease of administration, and fewer side effects. Hepatic monitoring is not indicated for these newer agents.

Donepezil is a specific and reversible inhibitor of AChE.[79] Rivastigmine has acetylcholinesterase and butyrylcholinesterase inhibitor activity.[80] Galantamine is a selective, competitive, and reversible inhibitor of AChE. Galantamine also enhances the intrinsic action of acetylcholine on nicotinic receptors, probably through bonding to the allosteric receptor sites.[81]

A recent review of cholinesterase inhibitors (13 randomized double blind placebo control trials with donepezil, galantamine, and rivastigmine at recommended doses for people with mild, moderate, and severe dementia due to AD produced improvements in cognitive function on average [2.7 points (P=<0.00001) on the 70 point ADAS-Cog scale and 1.37 on MMSE (0-30) P=<0.00001].[82] Studies using the NPI to assess behavioral disturbances favored ChEI [-2.44 (P=0.004)] Global clinical states also improved. The 7-point CIBIC-Plus scale was dichotomized by counting those showing no change or decline against those showing improvement and analyzed using the odds ratio. After approximately 6 months of treatment 428/1755 (24%) improved vs. 277/1647 (17%) improvement in the controls, OR 1.56, 95% CI 1.32 to 1.85, P=<0.00001). Analysis was performed by intention to treat and last observation carried forward. The findings were similar across the three ChEIs. When the CIBIC-Plus scale was dichotomized (showing decline compared to showing improvement or no change) and analyzed by the ITT-LOCF analyses using the odds ratio, after approximately 6 months of treatment numbers improved or remained unchanged 425/645 (ChEI) vs 340/661 (placebo), OR 1.84, 95% CI 1.47 to 2.30, p.0.00001. One trial used the Gottfries-Bråne-Steen (GBS)[83] global assessment scale and found no evidence of benefit or risk associated with donepezil after one year of treatment.[84] Benefits were seen on measures of ADL and behavior but none of the treatment effects were large. More patients leave ChEI treatment groups because of adverse events than leave placebo groups (29% vs 18%).[82]

There are four studies comparing two ChEIs, all supported by pharmaceutical companies. Two studies compared donepezil with galantamine[85,86] and two compared donepezil with rivastigmine[87,88] In three studies patients were not blinded; in the fourth, donepezil compared to rivastigmine was

double-blinded. Two of the studies were only 12 weeks duration, just enough time for dose titration. There is no evidence of a treatment difference between donepezil and galantamine at 52 weeks for cognition, ADLs, or side-effects.[85] There is no evidence that donepezil vs rivastigmine was different in terms of cognitive function, ADLs, or behavioral disturbance at two years[87] Fewer patients suffered adverse drug reactions on donepezil vs rivastigmine.[82]

There is some evidence that slow titration with galantamine and rivastigmine over three months has similar tolerability to donepezil. Some investigators have recommended the 5 mg dose of donepezil because of better tolerability and the small difference in efficacy between the 5 and 10 mg dosing. There are fewer data on measures of behavioral disturbances and ADLs, but there are findings of benefits in these domains as well.

Although there is slight variation in the mode of action of the three ChEIs, there is no evidence of any difference between them with respect to efficacy; this is generally in agreement with most clinicians' experience.

Rivastigmine (6-12 mg daily) improved cognitive function in patients with mild – moderate probable AD over a maximum of 26 weeks as measured by MMSE (0.8 points), and ADAS-Cog by 2.1 points both results using ITT analysis. There was a benefit in the 6-12 mg dose on the PDS rating scale. The CIBIC-Plus results, when dichotomized to compare the number of patients who improved with numbers who showed no change or whose condition had deteriorated, showed that those in the 12 mg daily group were significantly better than those on placebo. Some studies have shown fewer side effects with thrice daily rather than twice daily dosing.[80] The effective dose of rivastigmine is 6-12 mg a day. There is little evidence that less then 6mg a day is effective.

A prolonged release formulation of galantamine has similar efficacy and side effect profile as the equivalent twice daily regimen. Data from a galantamine mild cognitive impairment trial showed a marginal clinical benefit but unexplained excess in death rate (unpublished clinical research report Gal-Int-11 Dekosky). In nine AD trials none found a higher death rate in treatment compared to control group. Galantamine effect on severely impaired AD subjects has not been assessed. The recommended dose is 8-12 mg bid or 16-24 mg once per day of the longer acting agent. Starting dose on the latter should be 8 mg increased by 8 mg every 4 weeks to 24 mg if tolerated. The approximate retail price is $158.00/month; for bid dosing, approximately $150.00/month. Donepezil dosing is approximately $132.00/month. Rivastigmine pricing is approximately $160.00/month.

The National Institute for Health and Clinical Excellence (NICE), which reviews the clinical as well as economic data for health care recommendations in the U.K., suggests that when an MMSE score falls below 10, patients should no longer be prescribed any ChEIs.[89]

Open label trials have been conducted which suggest that cholinesterase inhibitors may delay nursing home placement, with an accompanying economic benefit.[90] However, the open label format and potential for recruitment bias has led many investigators to criticize the studies' conclusions.[91-94]

Most clinical trials have been supported by the pharmaceutical industry or marketing companies. The AD2000[95] is a large, randomized, placebo-controlled trial of donepezil independently funded in the UK. Participants were "typical" patients seen in clinical practice and referred to memory clinics by

local doctors. This study was not included in the Cochrane review of ChEIs because of a complex study design and the manner in which the results were reported. Initially 3000 patients were to be recruited but ultimately only 566 were enrolled with significant dropout due to introduction of ChEI during the trial period. In the first year more than 40% of subjects were lost, but dropout was similar in experimental and control groups. Overall the AD2000 results comparing donepezil to placebo over the first two years found that MMSE averaged 0.8 points better ($P < 0.001$) and functionality had a one point improvement [basic ADL ($P<0.0001$)]. They found no differences in institutionalization or progression of disability at 3 years. However, only 117 subjects were enrolled at year three compared to 565 at baseline, although dropouts were analyzed and accounted for. The number of dropouts was similar in both groups There were no differences in behavior, psychological symptoms, psychopathology or formal care costs. Their conclusion was that donepezil was not cost effective. Also, during the study period there was also a second randomization at baseline and at 12 weeks. There was no worsening of cognitive function in those who were on donepezil and then switched to placebo. This is in contrast to the common clinical experience that sudden withdrawal of ChEI's is often accompanied by severe confusion which can be reversed by restarting the drug. Therefore, if medication is discontinued, it should be withdrawn slowly.

The authors of AD2000 also believe that they had problems recruiting because of "difficulty securing placebo and drug supplies from relevant pharmaceutical companies who opposed the trial" and patient withdrawal after publication of the NICE (National Institute for Health and Clinical Excellence) guidance in 2001 that made donepezil available via the U.K. health service. The editorial accompanying the paper argued for needed long term randomized trials.[96] However many in the scientific community deemed this as being unethical. The authors state that "a rational strategy for those who believe that cholinesterase inhibitors produce worthwhile benefits might be to treat all their patients, whereas those who believe the benefits are dubious should treat none." The editorial goes on to state "based on the results, clinicians and health care funders can validly question whether other uses of scarce resources allocated to dementia care would provide better value than routine prescriptions of cholinesterase inhibitors". In some circumstances families may decide the $150 per month may be better spent in other areas of care (caregiver support, respite care) than on medications with small overall benefit. This decision may be influenced by who is paying for the medication.

Memantine

L-glutamate, the main excitatory neurotransmitter in the central nervous system, is implicated in neurotransmission, learning, and memory processes.[97] Neuronal injury is believed to occur by over stimulation of receptors of excitatory amino acids.[98] The term "excitotoxicity" has been used to describe what might be a final common pathway for neuronal injury in stroke or degenerative neurologic processes.[99] However, physiologic glutamate activity is required for normal brain function so glutamate cannot be abolished completely. Memantine acts as a low affinity NMDA type receptor antagonist and may prevent excessive excitatory amino acid activity without interfering with the necessary physiologic actions of glutamate.

Memantine was first synthesized by Eli Lilly as a hypoglycemic agent, but was ineffective. In 1978 the German pharmaceutical company Merz was granted a patent for memantine as a potential treatment for neurologic disorders. Memantine was approved by the FDA for the treatment of moderately severe-severe AD in 2003. In July 2005 a non-approvable letter for memantine to treat

mild AD was announced. This was based on negative unpublished data from mild-moderate AD disease studies.

A Cochrane Review to determine the efficacy and safety of memantine with AD, vascular dementia, and mixed dementia was performed in 2005.[100] The principle published AD trials enrolled moderate-severe AD patients with an MMSE of 3-14[101] and an MMSE of 5-14.[102] Patients in the latter trial were also receiving stable doses of donepezil. Both studies showed a small beneficial effect of memantine. At 6 months improvement in cognition (4.12 points on the 100 point SIB, P<0.00001), ADLs (1.27 points on the 54 point ADCS-ADL sev., P=0.0003), and behavior (2.76 on 144 NPI, P=0.004) were supported by clinical impression of change (0.28 points on 7 point CIBC-plus). MMSE and ADAS-cog are not used in studies of subjects with severe dementia given the insensitivity of these tools to detect change at this level of impairment. A 6-month trial of memantine in mild-moderate AD patients showed a beneficial effect on cognition (1.9 ADAS-Cog points), behavior (3.50 NPI points), and CIBIC-plus 0.3 points but no effects on ADLs or observed case analysis of cognition.[100,103] However, two unpublished studies showed no significant benefit. The Cochrane review notes that studies showing no effect of memantine were made available by Forest Laboratories over two years after its completion in contrast to wide distribution and publication of positive findings for moderate to severe AD.

The summary conclusion of the systematic Cochrane analysis is that in moderate-severe dementia there was a reduction in the incidence of agitation although the effective reduction is small. Twenty-five patients would need to be treated for six months to prevent one occurrence of agitation. There is no evidence that treatment reduced existing agitation. In the United Kingdom, NICE recommended that memantine should not be publicly funded for the treatment of moderately severe AD except to study long-term outcomes, diseases progression, and quality of life cost.

Overall memantine has a small beneficial effect at six months in moderate-severe AD, for which it is approved. The FDA issued a non-approvable letter for memantine to treat mild AD in July 2005. Memantine appears to be well tolerated; the therapeutic dose is 20mg a day usually given in divided doses, although pharmacologically it could be administered once a day (based on half life). A titrating dose schedule is recommended at 5mg a day and titrating weekly over 4 weeks. Memantine costs approximately $136.00/month.

Table 2. Clinical Pharmacology and Cost of Agents Approved for AD

Characteristic	Donepezil	Rivastigmine	Galantamine	Memantine
Time to maximal serum concentration (hr)	3-5	0.5-2	0.5-1	3-7
Absorption affected by food	No	Yes	Yes	No
Serum half-life (hr)	70-80	2**	5-7	60-80
Protein binding (%)	96	40	0-20	45
Metabolism	CYP2D6, CYP3A4*	Nonhepatic	CYP2DD6, CYP3A4*	Nonhepatic
Dose (initial/maximal)	5 mg daily/ 10 mg daily	1.5 mg twice daily / 6 mg twice daily	4 mg twice daily / 12 mg twice daily 24 SR daily	5 mg daily / 10 mg twice daily
Mechanism of Action	Cholinesterase inhibitor	Cholinesterase inhibitor	Cholinesterase inhibitor	NMDA-receptor Antagonist
Cost / Month***	$132	$160	$150 once daily / $150 twice daily	$136

*CYP2D6 denotes cytochrome P-450 enzyme 2D6, CYP3A4 cytochrome P-450 enzyme 3A4, and NMDA *N*-methyl-D-aspartate.
**Rivastigmine is a pseudo-irreversible acetylcholinesterase inhibitor that has an eight-hour half-life for acetylcholinesterase inhibition in the brain.
*** Source: Drugstore.com Modified from Cummings et al.[1]

Ginkgo Biloba

The maiden hair tree, aka ginkgo biloba, has been widely used for medicinal purposes. References can be found regarding its use in neoplasms, headache, asthma, vascular disorders, and memory loss. It is purported to have antioxidant and vasodilatory properties. The active component of ginkgo biloba consists of flavonoids, terpenoids, and terpene lactones. An extract, EGb 761, is produced from the leaves. EGb 761 is one of the top prescription medicines in Germany. In the US it is marketed as a food supplement. There is some controversy whether components of ginkgo biloba inhibit platelet activating factor and there have been case reports of excessive bleeding and subdural hematoma associated with high doses.[104-106] Ginkgo biloba has been recommended for age-related cognitive decline and slowing the progression of AD. A Cochrane review[107] found no significant differences between Gingko and placebo groups. However, overall there were findings that were promising and suggested improvement in cognition and function with Gingko. However, the trials used unsatisfactory methods, were small, and publication bias could not be excluded. Three more recent trials show inconsistent results. The findings support the need for larger trials, modern methodology, and an intention-to-treat analysis.

One favorable trial included in the Cochrane review was that of Le Bars et al.[108] This study enrolled both patients with AD and vascular dementia. Patients that appeared to be declining could be dropped from the study and be offered an open label humanitarian protocol. There were a large number of dropouts, a difference in the proportion completing the study in each group and data missing at 52 weeks was replaced by last evaluable assessment after 20 weeks brought forward.[106] Nonetheless, they reported the Gingko group had a favorable 1.4- point difference on the ADAS-cog compared to placebo (P=0.04). No difference was seen in the Clinical Global Impression of Change (CGIC).

The NIA and the National Center for Complementary and Alternative Medicine (NCCAM) are co-funding a prevention trial comparing gingko to placebo in 3,000 cognitively healthy people over age 70. The NCCAM is also recruiting patients to see if gingko improves short-term memory losses associated with electro-convulsive therapy. A study was completed to assess whether adding ginkgo biloba extract enhances the effects of donepezil. There are currently no published results. A phase III trial has completed enrollment to see whether gingko will delay cognitive decline in people aged 85 or older. Another study to determine the effects of 240mg/day Ginkgo biloba in decreasing the incidence of AD, slowing cognitive decline and functional disability, reducing incidence of cardiovascular disease, and decreasing total mortality has completed enrollment. This study is expected to be completed in 2009.

Pharmacologic Agents for the Treatment of Agitation and Other Behavioral Symptoms Associated With Dementia

Agitation is a common problem associated with demented patients, occurring in as many as 70% of patients.[109] Agitation can be defined as "inappropriate verbal, vocal, or motor activity that is not explained by needs or confusion per se."[110] Agitation may be manifest by wandering, crying out, assault, hostility, suspiciousness, or aggression. A number of agents are used in clinical practice to treat agitation including benzodiazepines, neuroleptics, antidepressants, beta-blocking agents, anti-

convulsants and anticholinergic inhibitors – none of which are approved for treating agitation in AD. Their efficacy is limited, adverse effects are frequent and can be serious.

A systematic Cochrane review found some evidence that haloperidol was useful in reducing aggression but was associated with adverse effects; the authors concluded there was no evidence to support routine use for management of agitation in dementia.[109] This assessment was based on five randomized trials. Side effects noted were over sedation, hypotension, and involuntary movements, Parkinsonian manifestations such as rigidity and tremor, and rarely malignant neuroleptic syndrome.

A study by Teri et al.[111] compared the effects of haloperidol, trazodone, behavioral management techniques (BMT), and placebo on agitation in AD. The BMT intervention consisted of eight weekly and three bi-weekly structured sessions, which provided information about AD, strategies for decreasing agitated behaviors, structured in-session and out-of-session assignments including the use of videotape training programs. There were no significant differences in outcomes obtained between haloperidol (mean dose 1.8 mg per day), trazodone (mean dose 200 mg per day), BMT, or placebo. Significantly fewer adverse events (bradykinesia and Parkinsonian gait) were evident in BMT. Overall, 34% of subjects improved with a range from 31% (placebo) to 41% (Trazodone). Earlier studies of neuroleptics in the treatment of agitation also reported similar response rates of 40-60%.[112]

Trinh et al.[113] evaluated the efficacy of cholinesterase inhibitors in the treatment of neuropsychiatric symptoms and functional impairment in AD. They reviewed randomized double-blind placebo-controlled trials lasting at least a month in patients with mild–moderate AD with baseline MMSE of 10-26. The neuropsychiatric inventory showed a small improvement in favor of cholinesterase inhibitors (ChEIs) of 1.72 points (120 point scale) compared to placebo. Using the ADAS-Noncog, ChEIs improved 0.03 points (0-50 scale) (95% CI 0.00-005 points). They also reviewed 14 trials evaluating activities of daily living finding a trend favoring ChEIs 0.10 SDs compared with placebo (05% CI 0.00-019). Of the 14 studies reviewed, in 12 the confidence interval cross 1.Thirteen trials included IADL (instrumental activities of daily living) reflecting higher level physical function favored ChEIs by 0.09 SDs compared with placebo (95% CI 0.01-0.79), in this instance showing a borderline statistically significant benefit. In this analysis 12 of the 13 studies the confidence intervals crossed 1. There was no difference in efficacy among the ChEI used. They conclude that based on the 29 trials reviewed that ChEIs have a modest beneficial role in reducing neuropsychiatric symptoms and reducing functional impairment in patients with mild-moderate AD living in the community. Cummings et al. have reported that an approximately 2 point improvement on the NPI is equivalent to a decrease in frequency or severity of a particular neuropsychiatric symptom.[69] Their findings are also similar to trials using valproic acid and atypical antipsychotics.[114,115] The authors further point out that some have suggested that results of functional outcomes in SD units require an effect size of 0.20 to be clinically detectable. The result in the meta-analysis was 0.10 SD[116] suggesting the results although statistically significant may not be clinically significant.

A recent Cochrane Review[117] on the effectiveness of atypical antipsychotics for treatment of aggression and psychosis in AD found nine studies with sufficient data to evaluate and of those, five were published in full in peer review journals. They found significant improvement in aggression with risperidone and olanzapine treatment compared to placebo. There was significant improvement in psychosis among risperidone treated patients. There was a significantly higher incidence of serious adverse vascular events (including stroke), extrapyramidal side effects, and other adverse outcomes in

patients treated with risperidone and olanzapine. There were insufficient data to evaluate the impact on cognitive function. Because of the adverse effects, the authors recommended that neither risperidone nor olanzapine be used routinely to treat dementia patients with aggression or psychosis unless there is marked danger to the person or the environment or severe distress.

A recent meta-analysis of atypical antipsychotics in patients with dementia showed an increase in death as compared to placebo.[118] Fifteen trials evaluated aripiprazole (n=3), olanzapine (n=5), quetiapine (n=3), risperidone (n=5). A risk ratio of approximately 1.5 (range 1.3 – 1.9) was found for all second generation drugs although the results were significant only when all studies were combined. The meta-analysis did not exclude first generation antipsychotics from the same risks as there was a study showing a similar trend. There is insufficient data available to fully evaluate the findings in non-atypical antipsychotics. An accompanying editorial aptly suggests that the findings from the study do not contraindicate antipsychotic drugs but alters the risk benefit analysis making it clear that there needs to be an identifiable risk to the patient or harm to others when considering such therapy and that any therapy should be minimized both in terms of dose and duration.[119]

A variety of other agents including carbamazepine,[120] trazodone and divalproex sodium[115] have been used to treat agitation in AD. Short-term studies have shown some efficacy. None of these agents, however, are approved for this purpose. Benzodiazepines are generally not recommended in part out of concern that symptoms may worsen because behavioral can become more disinhibited. Trazodone is commonly recommended as a hypnotic agent in patients with dementia because of its sedative properties and minimal anticholinergic effects. However for treatment of behavioral and psychological manifestations of dementia, there is currently little evidence for its efficacy and trazodone cannot be recommended based on current literature.[121] Selective serotonin reuptake inhibitors (SSRIs) are also used by clinicians for patients with moderate to severe behavioral symptoms of dementia even in the absence of depression.

There is increasing interest in the role of serotonergic function in cognitive impairment in AD. It is felt that serotonergic dysfunction may be potentially responsible for a significant portion of the behavioral aspects of the disease.[122] There are some studies supporting the use of SSRIs in this setting.[123,124]

Patients with AD who develop agitation or psychotic symptoms should be carefully assessed for factors other than dementia. Delirium, undertreated or overtreated medical conditions, medications, environmental factors, unrecognized disorders, and maladaptive interactions between the patient and caregiver(s) should all be considered. Patients with hallucinations that are not disturbing to the patient or others should not be treated with antipsychotic drugs. When an antipsychotic agent is prescribed patients should be re-evaluated frequently to see if the medication can be stopped. For patients living in a nursing home, the Omnibus Budget Reconciliation Act (OBRA) regulations of 1987 requires careful assessment and documentation of the need for continued use.[125]

Non-Pharmacologic Interventions

Behavioral and psychological problems should initially be managed by non-pharmacologic interventions which can be very effective. Emotional, behavioral, ideational, and perceptual disturbances are common. Teri et al. have described the ABC approach to assessing these problems.[126] "A" refers to antecedents of "B", the behavior and "C", the consequences of the behavior. Very commonly the problematic behavior or disturbance can be linked to circumstances related to a non-

therapeutic interaction between the caregiver and patient with a predictable outcome. Table 3 is a list of general management principles in patients with AD[127]

Table 3: General Principles of Managing Dementia Patients	
Correcting sensory impairment	Reinforcement
Non-confrontation	Reducing choices
Finding optimal level of autonomy	Optimal stimulation
Simplification	Avoiding new learning
Structuring	Determining and using over-learned skills
Multiple cueing	Minimizing anxiety
Repetition	Distraction
Guiding and demonstration	

With permission MF Weiner[127]

A variety of non-pharmacologic interventions have been used to treat a variety of behavioral problems in patients with dementia and AD. Light therapy or bright light therapy (BLT) has been used for managing sleep, behavioral, mood, and cognitive disturbances associated with dementia. However, currently available studies provide insufficient evidence supporting the effectiveness of this intervention in patients with dementia.[128] Further research with appropriately designed studies is needed to adequately assess the efficacy of this intervention.

Verbally disruptive behaviors (VDB) are defined as verbal or vocal behaviors that are inappropriate to the circumstances which they manifest (disruptive vocalizations include screaming, abusive language, moaning, and repetitious verbalizations). Cohen-Mansfield et al.[129] studied four non-pharmacologic interventions to treat VDB in nursing home residents with dementia. All patients underwent a medical examination focused on identification of an underlying cause for discomfort. The interventions provided were: (1) no treatment, (2) presentation of a family-generated video tape, (3) one to one social interaction, (4) exposure to music with the selection from input of family members. Interventions were developed because of theoretical origins of VDB. These include (1)VDB from neurologic changes and damage associated with AD which cause disinhibition or directly activate screaming;. (2)VDB as a natural response to pain and/or exacerbated in persons who are unable to communicate and therefore try to communicate through screaming; (3)VDB related to sensory deprivation and social isolation; and (4) VDB as an operant behavioral reinforced by attention from staff and other residents. VDB behaviors decreased 56% during social interaction, 46% with videotape, 31% during music, and 16% with no intervention. The study supports the need to provide a more stimulating and richer environment in AD patients in a nursing home setting.

Mittelman et al.[130] studied the long-term effectiveness of comprehensive support and counseling for spouses, caregivers, and families in postponing or preventing nursing home placement of persons with AD. In a randomized controlled trial, caregivers were provided six sessions of individual and family counseling within four months of enrollment in the study and in addition they were required to join support groups; counselors were available for further counseling if needed. The control group received standard services but no structured individual or family counseling. Time to nursing home placement was 329 days longer in treatment than control. Furthermore, caregivers were two-thirds as likely to place their spouses in a nursing home at any point in time if they were in the treatment group compared to the control group. The effects were particularly noted in patients in early to middle stages of dementia. The intervention required at least the spouse and one relative living in the area. The outcome

was also reported to be income dependent, and thus this highly selected sample limits generalization to other populations. Furthermore, an accompanying editorial notes that specific or individual components of the process could not be directly related to the "outcome".[131]

Cognitive rehabilitation and cognitive training have been suggested as interventions to improve memory function. A Cochrane systematic review assessed the evidence for their efficacy in early AD and VD.[132]

Cognitive rehabilitation is an individualized approach to helping people with cognitive impairments in which affected people work with a professional to identify personally relevant goals and devise strategies for addressing them. No RCTs of cognitive rehabilitation were available making it impossible to determine if individualized cognitive rehabilitation is effective in early AD.

Cognitive training involves practice of standard tasks designed to reflect particular cognitive functions such as memory, attention, and problem-solving or executive function. The hope is that practice has the potential to improve or maintain functioning in the domain under question and enhance function beyond the immediate training context. Cognitive training is more generalized; cognitive rehabilitation more specific and goal oriented.
Six studies of cognitive training were analyzed. None of the studies reported significant effects. There were positive trends in some domains. Since there were methodological problems (e.g. selection and performance bias) and relatively few studies, better designed studies would provide more definitive evidence. There was no evidence that cognitive training resulted in a significant increase in depression for people with dementia or their caregivers, which had been a concern with using this technique.

Long term planning
The diagnosis of AD presents the opportunity for the primary care physician, patient, and family to review their goals of care. It is important to identify a power of attorney for health care if one has not already been appointed. Table 4 is a summary of important care issues that should be reviewed. As much as possible the patient should participate in these decisions. It is an opportunity for the patient to discuss (in early AD) and document their long-term desires regarding durable power of attorney for healthcare, directive to physicians and in some instances out-of-hospital DNR status. Appropriate living arrangements and long-term plans need to be evaluated. These decisions will weigh heavily on the financial and human resources available to the patient and family. Referral to a qualified social worker can be invaluable in these circumstances.

Safety issues are a major source of concern and depending on circumstances, immediate decisions may need to take place (e.g. living alone, driving, cooking, administering medications, or behavioral problems like wandering). Discussion regarding driving should be initiated. The physician can bear the brunt of the decision to stop driving. There is often great resistance to cease driving. However, the family as well as the patient should be strongly advised to discontinue driving when persons with AD meet criteria for dementia. In addition to concern for safety of the patient and others, the patient and their family also assume potential legal liability and negligence. The educational needs of the family are immense and are an ongoing process. Community resources are critical to provide information, support, and counseling for the road ahead. Alzheimer's Associations and a variety of web-based resources are available.

Table 4: AD Caregiver Resources

Living Arrangements/Long Term Plan:
Discuss your long-term care desires with your family and children. Recommend adult children read Caring for Aging Parent by Donna Cohen and Carl Eisdorfer (1993) and How to Care for Your Parents: A Practical Guide to Eldercare by Nora Levin (1997). Both books provide a planning and action guide for initiating long-term care plans.

Safety Issues:
Home safety principles for the Alzheimer's patient. Think prevention: checking the safety of the home helps the caregiver take control of potentially hazardous situations. It is more effective to change the environment than it is to change most patient behaviors. By minimizing danger you can maximize independence.

Suggestions include:

Have emergency numbers and home address displayed near all phones.
Use an answering machine for incoming calls, silence the ringer.
All outside doors and windows need secure locks.
All rooms need adequate lighting.
Handrails on stairways.
Keep ALL medications and alcohol locked in a cabinet.
Lock up household cleaning products, matches, sharp knives and scissors.
Remove scatter rugs.
Place non skid mats in tub and shower, install grab bars and elevated toilet seat with hand rails.
Adjust the water heater to avoid scalding.
Minimize clutter, keep walkways clear of furniture.
Remove all firearms from home.
Eliminate access to a swimming pool by fencing it off with a locked gate.
Consider a "NO SOLICITATION" sign on the front door

Preventing Wandering/Getting Lost (Alzheimer's Association):
Wandering is one of the most frequent and challenging problems that caregivers face. Establishing a daily routine that includes meaningful activities and physical exercise is critical to minimizing wandering. Staying engaged is essential.
The Alzheimer's Association Safe Return program is the only nationwide system that helps identify, locate and return individuals with dementia. It provides:
1. 24 hour toll free number
2. Identification projects that include a bracelet, necklace, clothing labels and ID card.
3. Registration is in a national database that includes personal, medical information.
4. Applications acquired by contacting (800) 272-3900 or www.alz.org

Table 4 continued

Behavioral Issues:
Caregivers and family benefit from reading The 36 Hour Day: A Family Guide to Caring for Persons with Alzheimer's Disease and related Dementing Illness by Nancy Mace and Dr. Peter Rabins. This book provides practical management suggestions as well as education about the Alzheimer's disease process.

Coping with Your Difficult Older Parent: A Guide for Stressed-Out Children by Grace Lebow and Barbara Kane (1999) is particularly beneficial for those families dealing with the emotional drain of trying to help parents who don't want help. It also addresses conflictual family dynamics and underlying personality traits.

Steps to Understanding Challenging Behaviors (Alzheimer's Association)
Proposes that changes in behavior can be caused by: physical discomfort, over stimulation, unfamiliar surroundings, complicated tasks and frustrating interactions. The key is to identify and examine the behavior, explore potential solutions and try a different response in the future. Recommendations are given on how to respond to repetitive actions, aggressive behaviors, suspicious thoughts, recognition difficulties and anxious and agitated feelings (for a complete brochure, contact http://www.alzdallas.org

Health Maintenance
Emphasis on the importance of general health maintenance. Recommend a pneumovax for all patients over 65 and yearly flu vaccination for patient and caregivers. The appropriateness of yearly well woman exams, mammograms and colonoscopy screenings assessed on a case by case basis. Reinforce the importance of dental hygiene and maintenance of dentures if applicable.

Table 4 continued

Community Resources: Provide geographic specific resources for patients/families: Alzheimer's Association; Caregiver Classes; Caregiver Support Group; Individual/Family Counseling Referrals; Geriatric Care Management; Safe Return Program; Driving Assessments; Books on Tape; Lighthouse for the Blind; Callier Center; Private duty agencies for sitters/caregivers; Home Health Care: Durable Medical Equipment Companies; Emergency Response Systems; Adult Day Care; Continued Care Retirement Centers; Alzheimer's Units; Elder Law Attorneys; Advocacy Groups; Meals on Wheels; Handirides/Transportation Resources; TDHS for entitlement programs; Social Security Administration; http://www.medicare.gov for Medicare D enrollment; Nursing Home Medicaid Eligibility. Dallas Aging Information Office 214.379.4636 or 211 in Texas. Alzheimer's Association home page: http://www.alz.org. Alzheimer's Foundation of America home page: http://www.alzfdn.org Legal/Financial: Recommend execution of durable power of attorney documents. Strongly recommend completion of all health care directives to include directive to physicians and power of attorney for health care; Discuss and review appropriateness of out of hospital DNR. Provide referrals to Elder law attorneys for estate planning and future Medicaid planning if eligible.

Caregiver Issues

Caregivers are likely to encounter many challenges that may affect their own health and well-being and ultimately affect the AD patient. Not surprisingly, depression and anxiety are commonly found in caregivers. The use of psychotropic drugs is higher among caregivers than non-caregivers. Being female, exposure to stresses and lack of a supportive social network are risk factors for caregiver burden and depression. Spouses are more likely to be distressed than other family members. The patient characteristic in studies that most consistently predicted caregiver depression was the presence of behavioral problems such as wandering, screaming, or destroying property. In all, two demographic variables most consistently predicted depression in caregivers: socioeconomic status and the caregiver's relationship to the patient.[133] Likewise, poorer health status in the caregiver was most consistently associated with low financial adequacy, high psychological distress, low social support, and high levels of cognitive impairment in the patient.

Caregiver/patient dynamics and burden and should be assessed by the primary care physician. Caregiver burden should be acknowledged and the primary care physician can serve as the point of entry in getting assistance for the caregiver. Referral to support groups, education, and counseling services is essential.[134,135]

Future Directions

Vaccinations: Over the past couple of decades there has been increasing understanding of the biology of AD. Recent investigations have revolved around attempts to develop a vaccine to reduce or eliminate the accumulation of amyloid plaques [composed of amyloid-β-peptide (Aβ), a 40-42-amino-acid fragment of the β-amyloid precursor protein (APP)]. Amyloid plaques are thought by many to be the cause of cognitive decline in AD. In 1995 Games et al.[136] reported that production of transgenic mice that express high levels of human mutant APP progressively develop many of the pathologic hallmarks of AD, including neuritic plaques, synaptic loss, astrocytosis, and microgliosis. Schenk et al.[137] immunized transgenic animals with $A\beta_{42}$ either before the onset of AD-type neuropathology or at an older age (11 months) when Aβ deposition and other neurologic changes were established. The immunization of the young animals prevented the development of β-amyloid plaque formation, neuritic dystrophy, and astrogliosis, thus raising the possibility of immunization against amyloid-β in prevention and treatment of AD in humans. Subsequently Bayer et al.[138] in a phase I trial immunized 80 study patients with differing doses of synthetic $A\beta_{42}$ (AN1792) plus adjuvant for up to 84 weeks. An antibody response (anti-AN1792) was elicited in more than half of subjects. One patient developed meningoencephalitis diagnosed after death. Four efficacy scales were used. In three scales no treatment effect was observed (ADAS-Cog, MMSE, AD Cooperative Study-Clinical Global Impression of Change). A functional disability scale,

Disability Assessment of Dementia (DAD), showed less decline in treatment compared to controls at week 84.

Nicoll et al.[139] have reported the human neuropathology findings after Aβ immunization. Compared to unimmunized cases of AD, they found: (1) areas in the neocortex with very few Aβ plaques; (2) areas devoid of plaques contained densities of tangles, neuropil threads, and cerebral amyloid angiopathy similar to unimmunized AD but lacking plaque associated to dystrophic neurites and astrocyte clusters; (3) in some regions devoid of plaque, Aβ-immunoreactivity was associated with microglia; (4) T-lymphocyte meningoencephalitis was present; and (5) cerebral white matter showed infiltration by macrophages. These findings were similar to changes seen after immunotherapy in mouse AD models. They concluded that the immunologic response was responsible for clearing Aβ plaques and that T-lymphocyte activity likely resulted in meningoencephalitis in some patients. It has been suggested that the inflammatory T-cell response may be related to the adjuvant and not the development of antibodies. Passive immunization studies are currently underway.

Gilman et al.[140] reported the clinical effects of Aβ immunizations (AN1792) in 300 patients with mild-moderate AD participating in a multicenter randomized, placebo-controlled trial. The trial was interrupted after meningoencephalitis developed in 6% of immunized patients. Aβ immunizations resulted in antibody response in 20% of subjects. No significant differences were found between antibody responder and placebo groups for ADAS-Cog, DAD, clinical dementia rating, MMSE, or clinical global impression of change (CGIC). In the Neurological Test Battery (NTB) there was no difference between groups in 7 of 9 subtests. However, there was less decline in the NTB composite analysis in the antibody responders at 12 months.

In summary, the development of vaccines offers an exciting possibility to intervene, prevent, and treat AD. Vaccination appears to reduce some but not all of the pathologic findings found in AD.[141] If the serious complication of meningoencephalitis can be avoided, patients and the scientific community will be eager to see if this form of treatment can result in meaningful clinical improvements. [141]

A variety of other agents are under investigations. Some include; beta and gamma secretase inhibitors which may block the formation of amyloid at the earliest stage of development in the presenilin complex.[142,143] Huperzine A, derived from the Chinese club moss used in China as a traditional medicine to treat various disorders including dementia, has been isolated. It is a competitive and reversible inhibitor of acetyl cholinesterase and may protect cells against oxidants, glutamate, and apoptosis. Patients are currently being recruited by the Alzheimer's disease center to evaluate its efficacy in AD[144]. Clioquinol is a heavy metal chelator that crosses the blood-brain barrier and may promote the dissolution of plaques. However, initial clinical studies have not been favorable.[145]

Conclusion

Unfortunately Alzheimer's disease is an all too common disease affecting millions of people world-wide. Comprehensive medical care is essential to maximize function and limit disability. Treatable and reversible comorbid problems should be identified and optimally managed. Family and caregiver education and support are a critical component of care. Currently available medications have a small clinical effect but should be considered. They may improve global and cognitive symptoms and slow progress of disease. However, if there is no clinical response their continued use should be reconsidered. Our understanding of the biology of Alzheimer's disease is rapidly advancing. In the near future vaccines and secretase inhibitors appear to hold the greatest promise for treatment.

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