

Dementia Update 2005

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This update reviews selected recent clinical advances in dementia that have been published (online and in print) in peer-reviewed journals through January 2005. It reflects the author's interests and biases and is far from comprehensive.

Alzheimer disease (AD), the most common cause of dementia in older adults, is the main focus of this Update. As AD has become better understood and potential risk factors have been identified, clinical methods now accurately diagnose the disorder and allow initiation of appropriate therapy with approved symptomatic drugs. Truly effective therapies, however, may need to be initiated prior to the onset of symptoms as the cerebral changes of AD likely begin many years before dementia is diagnosed. Considerable interest in putative prodromal states of AD, such as mild cognitive impairment (MCI), has stimulated earlier recognition of the disorder. In addition to AD, other neurodegenerative dementing illnesses, including Dementia with Lewy bodies (DLB), Frontotemporal lobar degeneration (FTLD), and prion disorders, appear to be linked mechanistically by the conversion of normal proteins into insoluble aggregates, forming either cerebral deposits or neuronal inclusions, which in turn prompt neurotoxic biochemical cascades that attempt to recycle or remove the misfolded proteins. Elucidation of the pathophysiology of abnormal protein aggregation may yield targets for potentially disease-modifying therapeutic interventions. To address these and other topics, this update is organized as follows:

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ALZHEIMER DISEASE

Epidemiology and Risk Factors

Prevalence and incidence

The prevalence of AD, defined as the proportion of living cases in the population, reflects both the duration of the disorder and its incidence (defined as the rate of occurrence of new disease). Based on 2000 census data, there are 4.5 million people in the United States with AD. Of these, approximately 7% are age 65 to 74 years, 53% are between 75 to 84 years, and 40% are 85 years or older; the severity of AD is mild in 48%, moderate in 31%, and severe in 21%.¹ Both the overall prevalence of AD and the proportion of severe cases increase with age, and thus the challenges of AD also will increase as older age groups increase in size (nearly 19 million Americans will be 85 years or older by year 2050).

Incidence estimates allow assessment of potential risk factors for AD. Confirmed risk factors are age, family history, and the presence of the apolipoprotein E (*APOE*) ϵ 4 allele. Incidence rates for AD consistently demonstrate exponential growth as a function of age such that the incidence of AD doubles every 5 years after age 65, at least until 85 to 90 years of age.² In 1994, the national cost of AD was estimated to be as much as \$100 billion a year.³ If no preventive treatments become available, population trends ensure that the already substantial societal and public health burden of AD soon will reach enormous proportions.

Alzheimer disease results in disability, dependency, and death. Its malignancy is underscored by the poorer survival for individuals with AD compared with the life expectancy of a comparably aged population. The median survival from time of diagnosis in one study was 4.2 years for men and 5.7 years for women; predictors of mortality included dementia severity at time of diagnosis, abnormal neurologic findings (gait disturbance; extrapyramidal dysfunction), and the presence of medical problems such as heart disease and diabetes.⁴ In a

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population-based study of individuals over age 65, dementia was the strongest risk factor for mortality, surpassing heart disease, stroke, diabetes, and cancer.⁵

Genetics

The influence of genetic factors in AD varies as a function of age at onset of dementia. An age at onset below 55 years of age (early-onset AD) is characteristic for cases of dominantly inherited familial AD caused by mutations in at least one of three genes (amyloid precursor protein, APP; presenilin 1, PS1; presenilin 2, PS2).⁶ These mutations are rare and together account for only about 1% of all individuals with AD.

Although insufficient to cause AD, the *APOE* ϵ 4 allele increases risk for late-onset AD in a dose-dependent manner.^{2,7} The *APOE* ϵ 4 allele effect, which is strongest before age 75 years, is similar for men and women and for whites and African Americans.⁷ Relatives of African Americans with AD may be 1.6 times more likely to become demented before age 85 years than relatives of whites with AD, a finding that appears to be associated with ethnicity.⁸ Only about 50% of individuals with AD carry the *APOE* ϵ 4 allele, suggesting that other genes also affect risk for AD or modify its age at onset. Candidate susceptibility genes for AD include those encoding for the insulin-degrading enzyme on chromosome 10⁹ and for glyceraldehyde-3-phosphate dehydrogenase on chromosome 12,¹⁰ but to date only *APOE* ϵ 4 has been confirmed by multiple independent studies.

A reduced role for genetics may remain in late-onset AD,¹¹ but after age 85 years the risk of AD for relatives of AD individuals approaches that for relatives of nondemented persons.¹² Environmental factors that confer risk or protection appear to be increasingly important for very late-onset AD. The “critical window” hypothesis suggests that the ability of a factor to increase or reduce risk for AD may depend on the timing and duration of the exposure prior to onset of clinical symptoms.

Vascular factors

There is a strong link between AD and vascular risk factors.¹³ In nondemented elderly people with clinically evident cerebrovascular disease, cognitive decline was associated with a stroke risk score based on age, gender, systolic blood pressure, diabetes, electrocardiographic evidence of left ventricular hypertrophy, atrial fibrillation, and creatinine level.¹⁴ Cognitive decline can be documented 1 to 2 years post-stroke and is exacerbated by an interval stroke¹⁵ and by the presence of the *APOE* ϵ 4 allele.¹⁶ The presence of stroke risk factors in middle-aged individuals may herald later cognitive decline or development of dementia.¹⁴ Vascular risk factors that have been implicated in increasing dementia risk include blood pressure, diabetes mellitus,^{17–20} abnormal insulin metabolism,²¹ serum lipids,^{22,23} dietary fat intake,^{24,25} plasma homocysteine,²⁶ and smoking.²⁷ Thus, risk factors for cerebrovascular disease also are important for AD.

Many vascular risk factors are modifiable and can serve as targets for preventive strategies. Long-term use of antihypertension medications in African Americans was reported to reduce risk of cognitive impairment by 38%.²⁸ Initial case-control studies of individuals using 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, or statins, to inhibit cholesterol

synthesis reported that statin use was associated with a lower risk for AD.^{29,30} More recent prospective cohort studies, however, have not confirmed the association between use of statins or other lipid-lowering agents for reduced risk of dementia or AD.³¹ Two randomized treatment trials with simvastatin³² and pravastatin³³ showed no benefit for cognitive impairment or dementia. Statin use may be a surrogate marker of good health that itself is associated with lower risk of dementia, perhaps explaining the earlier positive case-control results.

Inflammation

Inflammation has been proposed as a contributing mechanism for the adverse effects of the metabolic syndrome, which represents a constellation of disorders conferring increased risk for vascular disease: abdominal obesity, hypertriglyceridemia, low levels of high-density lipoprotein, hypertension, and hyperglycemia. The increased risk for cognitive impairment and decline experienced by older adults with the metabolic syndrome may be mediated by inflammation; in a recent study, individuals with the metabolic syndrome who also had high serum levels of inflammatory markers had a relative risk of 1.66 (confidence interval [CI], 1.19–2.32) for cognitive impairment but those with low levels of inflammatory markers had no increased risk.³⁴ It is possible that inflammatory markers signal an active vasculopathic process that contributes to cognitive impairment, or that the inflammatory response itself may have adverse effects on cognition.

Activated microglia and inflammatory proteins are found in AD brains, consistent with a pathogenetic role. Elevated plasma levels of the inflammatory proteins α 1-antichymotrypsin, interleukin-6, and C-reactive protein have been associated with increased risk for dementia and AD.³⁵ Moreover, cell culture studies show that some nonsteroidal anti-inflammatory drugs (NSAIDs) shift the cleavage products of APP to less fibrillogenic forms of the amyloidogenic peptide $A\beta$,³⁶ consistent with earlier observational studies that use of anti-inflammatory medications is associated with reduced risk for AD.³⁷ Any protective effect associated with NSAIDs appears related to their use many years before dementia onset, as recent NSAID exposure provided no protection.³⁸ In keeping with this observation, almost all clinical trials of NSAIDs in AD have yielded null findings.^{39,40} The recent concern that Cox-2 (cyclo-oxygenase-2) inhibitors may be associated with increased risk for heart attacks and strokes resulted in the suspension of a prevention trial with NSAIDs that proposed to test directly the hypothesis that early NSAID use can reduce risk for AD.

Dietary factors

In a survey of middle-aged persons, fish consumption and intake of omega-3 polyunsaturated fatty acids were associated with reduced risk for cognitive impairment, whereas higher daily intake of cholesterol and saturated fat was associated with poor memory.⁴¹ The speculative mechanisms by which fish with high levels of omega-3 fatty acids (salmon, tuna, herring, sardines) may reduce risk for cognitive dysfunction include lowered risk for vascular disease and anti-inflammatory effects. Similar effects have been proposed for moderate alcohol intake. A report from the Nurses Health Study indicates that older women who consumed up to one drink a day had better mean

cognitive test scores and less risk of cognitive decline than nondrinkers.⁴² These associations were found for all types of alcoholic beverages.

Antioxidants from food and supplements have been postulated to reduce the risk of AD by lowering oxidative stress. A population-based study assessed the dietary intake of nondemented individuals age 55 years or older and found that high intake of vitamin C from food was associated with reduced risk of AD (relative risk 0.82, CI 0.68–0.99).⁴³ There was marginally reduced risk associated with dietary vitamin E. The combined use of vitamin C and vitamin E supplements in persons 65 years or older in another population-based study was associated with reduced occurrence of AD⁴⁴ but there was no notable risk reduction with either vitamin alone. Multivitamins, which contain approximately 22 IU of vitamin E and 75 to 90 mg of vitamin C, did not reduce AD risk in this study, suggesting that protection is associated only with the higher doses found with supplements (up to 1000 IU of vitamin E and 500 to 1000 mg of vitamin C).⁴⁴ Another study of both dietary and supplemental vitamin C and vitamin E, however, found that neither vitamin decreased risk for AD.⁴⁵ Adding to the controversy as to whether these vitamins have health benefits, a recent meta-analysis suggests a small but significant risk for all-cause mortality with high-dose supplemental vitamin E⁴⁶ (see treatment section below).

Estrogen

Estrogen has purported neurotropic, antioxidant, and anti-inflammatory effects. The declining levels of sex hormones in postmenopausal women have been proposed to account, at least in part, for a higher incidence of AD in women than men. The Women's Health Initiative Memory Study, however, found that estrogen plus progestin therapy afforded no protection against cognitive decline in women aged 65 years and older,^{47,48} and the combination-treated women were at increased risk for heart attacks, strokes, breast cancer, and thrombophlebitis. A trial of conjugated equine estrogen (CEE) alone recently was terminated because of increased risk of stroke and lack of benefit on cardiovascular outcomes. Analyses of longitudinal performance on a single global cognitive measure showed poorer scores for women assigned to CEE (0.625 mg per day) compared with placebo-treated women after mean follow-up of 5.4 years.⁴⁹ Moreover, the risk for development of mild cognitive impairment (MCI) or dementia was increased with a hazard ratio of 1.38 (CI, 1.01–1.89).⁵⁰ Similar adverse effects on cognitive performance with postmenopausal hormone therapy was found in the Nurses Health Study.⁵¹ The higher risk for cognitive impairment or dementia for women using estrogen, either alone or in combination with progestin, may relate in part to a higher frequency of cerebrovascular disease, although this remains unproven. At least for women age 65 years or older and for doses of 0.625 mg a day or higher, estrogen therapy to prevent MCI or dementia clearly is not indicated.

Women progressing through menopause often have more self-reported memory problems than premenopausal women. A study of the natural history of the menopausal transition found no significant decline in working memory or perceptual speed as women progressed through menopause.⁵² Self-perceived

cognitive problems in this period are not reflected by objective changes, at least on these measures.

Lifestyle

The self-reported frequency of cognitive engagement (eg, reading [newspapers, magazines, books], watching television, listening to radio, playing games [cards, crossword puzzles]) in community-living older adults was associated 4 years later with a 64% reduction in risk for AD.⁵³ A separate study found that individuals with AD had less demanding occupations than did controls.⁵⁴ A possible explanation for these observations is that increased neuronal activation associated with cognitive activity contributes to a cognitive reserve that mitigates AD neuropathology. Alternatively, AD lesions may develop many years before dementia is expressed and reduce the capacity to be involved in cognitively demanding tasks. Higher levels of long-term physical activity in older women⁵⁵ and men⁵⁶ were associated with better cognitive function. These effects may be mediated through improved cardiovascular fitness, better cerebral perfusion, beneficial effects on insulin resistance, or other mechanisms. Social interaction is also associated with less cognitive decline in older adults.^{57,58} Although effect sizes are relatively small, participation in intellectually and physically stimulating activities and involvement in social networks may be beneficial for cognitive health in older adults.⁵⁹

Table 1 summarizes known and candidate risk and protective factors for AD.

Diagnosis and Clinical Course

The conclusive diagnosis of AD rests on the clinicopathological correlation of cerebral senile plaques (SPs) and neurofibrillary tangles (NFTs) with the features of dementia. Enough now is known about the clinical and behavioral symptoms of AD so that the current clinical diagnostic process can identify AD with high accuracy (90% or higher in autopsy-confirmed series from dementia research centers).⁶⁰ Clinical diagnostic tools include a careful history of the presentation and course of dementia and of potentially contributing conditions (eg, stroke, depression, medications), objective tests of cognitive function, physical and neurologic examinations, and a limited number of laboratory procedures (thyroid function tests, vitamin B12 levels, and neuroimaging).

Standard diagnostic criteria and assessment procedures for AD have been published in a Practice Parameter by the American Academy of Neurology (AAN)⁶¹ and by the Clinical Practice Committee of the American Geriatrics Society.⁶² In spite of the availability of these clinical diagnostic criteria, the growing number of prevalent cases, and the availability of Food and Drug Administration (FDA)-approved medications, dementia remains notably under-recognized in the community. Forty-five percent of demented inpatients were not identified in one study,⁶³ and memory loss was documented in only 23% of cognitively impaired patients in a primary care setting in another.⁶⁴ There are continued efforts to develop brief diagnostic tools for dementia but as yet none have sufficient sensitivity, specificity, and "ease-of-use" to warrant widespread adoption by practitioners.

TABLE 1. Risk and Protective Factors for Alzheimer Disease (Partial List)

Domain	Candidate		Confirmed	
	Protective	Risk	Risk	Deterministic
Demographics		Female sex Low educational attainment	Age Family history	
Genetics	<i>APOE</i> ε2 polymorphism	Many, including polymorphisms for: Insulin-degrading enzyme Glyceraldehyde-3-phosphate dehydrogenase	<i>APOE</i> ε4 polymorphism	Mutations in genes encoding: APP PS1 PS2
Cardiovascular	Statin use	Cerebral infarcts Hypertension Diabetes mellitus Serum cholesterol Plasma homocysteine		
Inflammation	Nonsteroidal anti-inflammatory drug use	Plasma inflammatory markers (eg, C-reactive protein)		
Dietary	Omega-3-polyunsaturated fatty acid (fish consumption) Moderate alcohol intake Antioxidants (eg, vitamin C, vitamin E)	Fat intake		
Lifestyle	Engagement in cognitive, physical, and social activities			
Other		Estrogen replacement therapy Head trauma Personality (eg, distress proneness)		

APOE, apolipoprotein E; APP, amyloid precursor protein; PS1 and 2, presenilin 1 and 2.

Early and accurate diagnosis of AD is important so that patients and their families can plan for the future when the patient is still able to contribute to the decision-making and to initiate therapy when overall function may be relatively good. Neuropsychological measures that usually show deficits in dementia include delayed recall tasks that assess episodic memory and category fluency tasks (eg, naming animals) that tap semantic memory and perhaps executive function.^{65,66} Cognitive tests, however, may be insensitive to early-stage dementia. In a study of carriers of deterministic mutations for AD, 50% of individuals still scored higher than a proposed cutoff score for dementia on a common cognitive test 4 years after symptom onset.⁶⁷ Dementia remains a clinical diagnosis, and no test replaces an assessment by an experienced clinician.

Informant questionnaires may perform as well as neuropsychological batteries in the diagnosis of AD. The essential feature of dementia is a decline from a previously established level of intellectual function that is sufficient to interfere with the everyday performance of the individual.⁶⁸ Informant-based assessments can detect change from the patient’s prior level of cognitive and functional ability (longitudinal perspective) and have the advantage of assessing performance in that patient’s everyday activities (“face validity”). Another advantage of informant scales is cross-cultural fairness, whereas cognitive

tests are influenced by educational attainment and linguistic and cultural background.⁶⁹ Disadvantages include the fact that informants may not always be available or may not provide insightful observations. To examine this latter concern, a study found that all types of informants (eg, spouses, adult children, friends) were generally accurate in rating the participant’s cognitive functioning; accuracy was best for younger, better educated informants who lived with the patient and/or saw them frequently.⁷⁰ Information from an informant collateral source should be integrated whenever possible into clinical evaluations for dementia. Combining informant reports with brief cognitive tests of the individual may improve the prediction of AD over either method alone.⁷¹

In contrast to informant reports of cognitive decline, an individual’s self-reported memory difficulty often does not predict the presence or future development of dementia.⁷² On the other hand, cognitively normal individuals who present to dementia research clinics for evaluation frequently have a family history of dementia. Many of these people later develop cognitive impairment, suggesting that they initially sought evaluation because of their familial risk for dementia and related concerns about their own cognitive function.⁷³

The diagnosis of AD by itself does not necessarily imply incompetence, but as the disease progresses decisional capacity

inevitably is impaired. Nonetheless, 60% of dementia outpatients in one clinic voted in the 2000 national election, including 37% of moderately demented and 18% of severely demented individuals, although many required assistance.⁷⁴ Some demented individuals also continue to drive. Evaluating driving performance with an on-the-road driving test in persons with AD found that 67% of very mildly demented and 41% of mildly demented individuals were “safe” at baseline but performance decreased with time as a function of dementia severity.⁷⁵ Almost all of the mildly demented and the majority of the very mildly demented AD individuals who had been “safe” initially were unsafe after 2 years. A standardized, individualized assessment of driving skills early in the AD course with periodic re-evaluation may be useful in determining when driving no longer is safe.

Depression is associated with cognitive impairment in nondemented older adults. Although depression is considered to be a risk factor for AD, its effect on cognition for individuals with AD has been less studied. Depression was present in 15% of 167 very mildly demented and 24% of 155 mildly demented persons with AD in one series but had little influence on cognitive test performance in these groups, suggesting that the negative effect of depression for cognition observed in nondemented individuals is superseded by the dementia of AD.⁷⁶ In another study, symptoms of depression were unrelated to the neuropathological burden of AD and did not modify the relationship of plaques and tangles to dementia symptoms, indicating that depression likely is a comorbid disorder rather than an early manifestation of AD pathology.⁷⁷ Polymorphisms in the serotonin neurotransmitter genes are reported to be associated with the neuropsychiatric symptoms of AD. Genetic analysis of AD patients found that a polymorphism in the gene for the *5-HT2AR* receptor (a target of atypical antipsychotic agents) was associated with agitation, aggression, and delusions but not with affective symptoms or depression.⁷⁸ These findings point to the potential of combining neurogenetics and pharmacogenomics to optimize management of AD symptoms.

Predicting the rate of progression for individuals with AD may provide information about disease mechanisms. The average annual rate of decline on the 30-point Mini Mental State Examination (MMSE),⁷⁹ a surrogate measure of cognitive function, was -0.5 points for 166 nondemented elderly, -1.5 points for 20 very mildly impaired individuals, and -3.4 points for 39 individuals with mild AD.⁸⁰ In this study, predictors of decline included a positive family history, lower educational attainment, and larger ventricular volume as assessed by magnetic resonance imaging (MRI). Another study of potential predictors of rate of progression in AD examined demographic variables (age, sex, years of education, widowhood), genetic factors (*APOE* status, family history of dementia), presenting features (dementia severity, prominent language or visuospatial dysfunction), and comorbid disorders (depressive features, cerebrovascular disease). Dementia severity at entry was by far the strongest predictor of rate of decline, such that AD progresses more slowly in the early stages of dementia but accelerates with increasing dementia severity.⁸¹ Rate of decline was somewhat associated with age and prominent language and visuospatial deficits but was not associated with sex, education, number of $\epsilon 4$

alleles, family history of dementia, cerebrovascular disease, or depression.

In a study of AD patients followed for up to 13 years, motor signs were rare at initial assessment but prevalence increased with disease progression.⁸² Bradykinesia, rigidity, altered speech and facial expression, and impaired gait and posture were the most frequent abnormalities; rest tremor was rare. Abnormal motor signs were not associated with the presence of Lewy bodies in the 99 individuals who were autopsied, suggesting that lesions outside the extrapyramidal system may contribute to motor dysfunction in many AD patients.

Treatment

The AAN's Practice Parameter for the management of dementia recommended cholinesterase inhibitors (ChEIs) as standard treatment of “patients with mild to moderate AD, although studies suggest a small degree of benefit.”⁸³ The Practice Parameter also provided a guideline for vitamin E (1000 IU twice daily) to attempt to slow progression of AD. Both recommendations recently have been challenged.

The challenge for ChEI therapy rests on whether it is cost effective. Clinical trials of donepezil, rivastigmine, and galantamine, the three currently used ChEIs, consistently demonstrate efficacy with small improvements on cognitive and global function in patients with mild-to-moderate AD.⁸⁴ The duration of benefit may persist as long as 3 years for some patients.⁸⁵ A recent randomized, double-blind, 24-week placebo-controlled trial of donepezil 10 mg a day suggests that efficacy also can be demonstrated in early-stage AD.⁸⁶ An industry-supported study of donepezil versus placebo for 24 weeks in patients with moderate to severe AD found modest cost savings (US \$224, including drug costs) in favor of donepezil, primarily associated with less use of residential care.⁸⁷ An opposite finding came from a study of unselected AD patients who were naive to ChEIs and assigned randomly to donepezil or placebo in the AD2000 trial (free of industry support) in the United Kingdom.⁸⁸ Donepezil-treated patients were slightly more likely than placebo-treated patients to withdraw because of side effects (7% versus 3%) but there was no difference in the number of serious adverse events. Donepezil-treated patients were reasonably evenly divided between doses of 5 mg and 10 mg a day. Donepezil-treated patients performed slightly better on the MMSE (average benefit of 0.8 points) than placebo-treated patients with no attrition of benefit over 2 years. A parallel improvement in function (activities of daily living) also was seen for donepezil. However, there were no benefits for donepezil for institutionalization, progression of disability, costs for health and social services (despite the cost of donepezil not being included in the analysis), or caregiver measures of distress. Although the study confirmed that donepezil generally is well tolerated and is associated with persistent small improvements in cognition and activities of daily living, these benefits did not reduce costs for caring for study patients with AD. The authors concluded that treatment did not reach the minimum threshold for “clinically important difference.”⁸⁸ The cost-benefit ratio for ChEI therapy in AD remains controversial, and until definitive findings are available practitioners should continue to individualize treatment decisions for each patient.

The challenge for vitamin E concerns the possibility of an unanticipated serious adverse event. A meta-analysis of the Cochrane Clinical Trials Database examined vitamin E supplementation (alone and in combination with other vitamins and minerals) in doses up to 2000 IU a day and found a slight but significant increased risk of all-cause mortality, especially with doses of 1000 IU or greater a day (risk ratio 1.06, CI 1.00 to 1.11).⁴⁶ Interpretation of this finding is limited by methodologic problems, including a possible type I error as the meta-analysis excluded vitamin E trials that reported fewer than 10 deaths and did not adjust for mortality over different follow-up periods. However, the reported (and as yet unreplicated) benefit of vitamin E in AD is at best a modest slowing of clinical progression in moderately to severely demented individuals.⁸⁹ It may be prudent to avoid very high-dose vitamin E (eg, >400 IU a day) in the management of AD until further randomized, controlled clinical trials can evaluate its efficacy and safety.

Memantine was approved by the FDA in 2003 for the symptomatic treatment of moderate-to-severe AD. It is postulated to inhibit cytotoxic overstimulation of glutamatergic neurons, thus differing in mechanism of action from the ChEIs. In an industry-sponsored study in moderately severe AD patients on stable doses of donepezil, the addition of memantine 20 mg a day slightly improved cognitive, functional, and global scores in comparison with patients adding placebo.⁹⁰ For moderately advanced AD, memantine appears to be beneficial alone or in combination with donepezil. Its efficacy in mild-to-moderate AD has yet to be established. It is unknown whether memantine therapy is cost effective.

Treatment of the non-cognitive symptoms of AD (also referred to as neuropsychiatric symptoms or the behavioral and psychologic symptoms of dementia) can be problematic. These manifestations include apathy, aggression, agitation, hallucinations, delusions, sleep disturbances, and affective disorders. They can be seriously disruptive and often result in decreased quality-of-life for patients and caregivers. Atypical antipsychotic drugs, believed to have superior efficacy and safety compared with older neuroleptic agents, have not been widely studied in older adults.

Moreover, recent evidence suggests that atypical antipsychotic drug use may be linked to elements of the metabolic syndrome, risk of stroke, and increased mortality. A recent study of non-obese individuals (age 18–65 years) with schizophrenia or schizoaffective disorder found that clozapine and olanzapine were associated with insulin resistance and weight gain.⁹¹ A public health advisory was issued by the FDA on April 11, 2005, for more deaths associated with use of atypical antipsychotic drugs in older individuals with dementia (<http://www.fda.gov/bbs/topics/ANSWERS/2005/ANSO1350.html>). In spite of these potentially very serious side effects, many clinicians find that judicious use of the atypical antipsychotics is beneficial in treating agitation or psychosis in patients with dementia when nonpharmacological manipulations prove to be ineffective.⁸³

Systematic reviews of the few randomized trials of atypical antipsychotic drugs for the neuropsychiatric symptoms of dementia find modest efficacy at best (perhaps most convincing for olanzapine and risperidone) and frequent adverse

effects, including somnolence, parkinsonism, and gait disturbances.^{92,93} Current recommendations for the management of the behavioral and psychologic symptoms of AD begin with a careful assessment of the patient to identify potentially correctable medical problems (eg, infection or pain) that may precipitate or exacerbate the behavior, followed by nonpharmacological interventions (eg, simplify the environment to avoid overstimulation or direct agitation into physical activity). If these measures are insufficient, an atypical antipsychotic (for psychotic behavior) or an antidepressant (for anxiety) might be initiated in the lowest effective dose. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) was designed to assess the effectiveness of three atypical antipsychotics (risperidone, olanzapine, and quetiapine) and a selective serotonin reuptake inhibitor (citalopram) in treating agitation and psychosis in individuals with AD.⁹⁴ The CATIE results (expected in 2006) may clarify the role of atypical antipsychotic agents in the management of the neuropsychiatric symptoms of AD.

Emerging Detection Methods: Biomarkers and Neuroimaging

Biochemical biomarkers

An ideal biomarker for AD should: (1) reflect a fundamental feature of AD neuropathology; (2) be validated in autopsy-confirmed AD cases; (3) have high sensitivity and specificity for distinguishing AD from healthy aging and from other dementing conditions; and (4) be evaluated by assays that are reliable, reproducible, noninvasive, inexpensive, and simple to perform. No such biomarker or panel of biomarkers yet exists. Moreover, it is likely that no single marker will provide all information necessary to evaluate the risk, onset, and progression of AD. Nonetheless, several promising candidate biomarkers are under investigation.⁹⁵

The neuropathological hallmarks of AD, SPs and NFTs, are comprised mainly of aggregates of the proteins, A β and tau. These peptides have been extensively studied in the cerebrospinal fluid (CSF) of individuals with AD in comparison with nondemented controls and with people with non-AD dementing disorders. In addition to total tau, some assays quantify p-tau (tau phosphorylated at different epitopes, including threonine 181 or 231) as NFTs contain hyperphosphorylated tau. Numerous studies have found decreased levels of CSF A β (particularly A β ₄₂, the variant that aggregates rapidly and is deposited initially in SPs) and elevated levels of CSF tau and p-tau in AD patients compared with normal or disease controls.^{96–99} Some individuals meeting clinical and pathologic criteria for AD, however, fall outside the derived cutoff values for these analytes and some control values overlap those for AD. Static levels of A β and tau primarily have been studied, but longitudinal investigations are needed as changes in the levels of these proteins over time may correlate better with AD presence and course.

Other CSF constituents that are altered in AD include isoprostanes, putative markers of lipid peroxidation and oxidative damage in the brain, and sulfate, a prominent component of cerebral white matter. A preliminary longitudinal study of CSF F₂-isoprostanes in 40 mildly demented individuals with

AD found that, following volume correction, isoprostane mass correlated with clinical measures of AD severity.¹⁰⁰ Moreover, those individuals using supplemental vitamin E and vitamin C had reduced isoprostane levels, suggesting that antioxidant vitamins may suppress oxidative stress. In another preliminary study of 20 very mildly demented individuals with AD, there was a significant decrease in CSF sulfatide and in the ratio of sulfatide to phosphatidylinositol in comparison with nondemented controls.¹⁰¹ The role of sulfatide in AD is unknown.

The enzyme, glycogen synthase kinase-3 (GSK-3) has been linked to tau phosphorylation and to the metabolism of APP;¹⁰² GSK-3 is regulated in part by insulin. This enzyme thus appears related to both major pathologic hallmarks of AD (NFTs and SPs) and to a major risk factor for the illness (insulin resistance). Isoforms of GSK-3 are expressed in circulating lymphocytes. Total GSK-3 as measured in blood samples from individuals with AD and with MCI was increased relative to levels from nondemented controls, suggesting that it might serve as a peripheral marker for AD, even its prodromal stage.¹⁰³

Neuroimaging

The AAN's Practice Parameter for the diagnosis of dementia recommends noncontrast structural imaging with computed tomography or MRI in the routine initial evaluation of patients with dementia to exclude rare but potentially correctable causes of dementia (eg, subdural hematoma, hydrocephalus).⁶¹ In addition, quantitative neuroimaging techniques can provide indirect measures of AD that may serve as surrogate markers for diagnosis and disease progression. Marked variability in scanners, upgrades, and methods of image acquisition and analysis has limited comparison of results from different studies. A large, multi-site study now is underway to evaluate several neuroimaging modalities for the diagnosis of AD and in monitoring progression of MCI. This Alzheimer's Disease Neuroimaging Initiative will aim to: (1) develop standard neuroimaging methods for clinical trials; (2) improve neuroimaging methods; (3) determine the optimum methods for acquiring and processing brain images; and (4) validate the neuroimaging findings.

The hierarchical topography of neuronal involvement and loss in AD initially involves the entorhinal cortex and the hippocampus, then progressively extends to the neocortex with preferential involvement of higher order association cortex.¹⁰⁴ Atrophy is a surrogate for neuronal loss. Volumetric measures of entorhinal cortex and hippocampus show that rates of atrophy in these medial temporal lobe structures distinguish AD from nondemented aging although ventricular enlargement and whole brain atrophy rates also were significantly different in AD versus aging.¹⁰⁵ Medial temporal lobe atrophy rate also predicts rate of progression of AD.¹⁰⁶ Greater difficulty with boundary definition of the entorhinal cortex compared with the hippocampus results in better reproducibility of hippocampal measures,¹⁰⁷ but the entorhinal cortex may be the initial site of AD involvement. For example, atrophy of the entorhinal cortex is associated with poorer memory performance in nondemented older adults.¹⁰⁸ Comparing rates of atrophy as assessed by MRI scans approximately 2 years apart, the entorhinal cortex atrophied at a greater rate than the hippocampus in AD patients, implying that the entorhinal cortex is affected earlier in the

disease process (assuming degeneration proceeds at similar rates across regions).¹⁰⁹

High resolution MRI can track regional AD involvement of the cerebral cortex, where gray matter loss in the cingulate gyrus and in posterior cortical areas appears to distinguish mild AD from nondemented aging.¹¹⁰ Proton MR spectroscopy evaluates brain changes at the cellular level by measuring proton-containing metabolites, including N-acetyl-aspartate (NAA), which is postulated to be a marker of neuronal integrity. A decrease in NAA in the posterior cingulate gyrus has been reported for mild-moderate AD.¹⁰⁷ Different patterns of metabolite ratio changes may distinguish various dementias.¹¹¹ Other MR methods that are being explored for usefulness in early diagnosis and for measuring AD progression are diffusion tensor imaging or diffusion-weighted imaging, where the diffusivity of water molecules appears increased in the cerebral white matter of AD patients compared with controls, and functional MR (fMRI), which measures brain activation patterns (using paradigms involving memory, semantic processing, or visual responses).

Metabolic activity in the brain as measured by positron emission tomography (PET) has been inferred from uptake of the radioactive tracer, [¹⁸F] 2-deoxy-2-fluoro-D-glucose (FDG), which reflects glucose metabolism. Theoretically, metabolic changes may be present in specific brain regions before substantial neuronal loss occurs, suggesting that functional imaging (PET, fMRI), may detect abnormalities associated with AD prior to structural imaging (MRI), which measures atrophy. Some PET studies suggest that characteristic patterns of cerebral hypometabolism in the temporoparietal lobes in AD and in the frontal lobes in FTLT may be useful in the evaluation of demented patients.¹¹² The Centers for Medicare and Medicaid Services (CMS) recently approved reimbursement for FDG-PET as an adjunctive diagnostic tool for dementia when the differential diagnosis is uncertain and is reasonably expected to be clarified by PET (eg, AD versus frontotemporal lobar degeneration). Although in these limited circumstances FDG-PET may provide additional evidence to help the clinician establish the cause of dementia, it is not in itself diagnostic and Medicare coverage is not extended to PET for routine dementia diagnosis. There is no evidence to date that the limited increment of diagnostic precision provided by PET will meaningfully improve patient outcomes or be cost effective.

A major recent advance in AD neuroimaging has been the development of amyloid imaging tracers. Although efforts are ongoing to image amyloid plaques with MRI, several groups already have developed compounds with high binding affinity for amyloid for the *in vivo* PET detection of cerebral amyloid deposits.^{113–115} A benzothiazole amyloid imaging agent known as "Pittsburgh Compound-B," or PIB, enters and clears normal brain rapidly in experimental animals and shows good binding to A β amyloid deposition in postmortem human brain, but does not detect neurofibrillary tangles at the concentrations used for imaging studies.¹¹⁴ A proof-of-concept study by investigators at Uppsala University (Sweden) and the University of Pittsburgh reported that PIB retention in frontal cortex as determined by positron emission tomography was 90% higher in mild AD patients compared with older control individuals.¹¹⁴ Although many more AD and control individuals must be studied to validate this technique and to

define its sensitivity and specificity, amyloid imaging holds great promise as a clinical diagnostic tool and as a surrogate marker for anti-amyloid therapies. Assuming that PIB or other amyloid agents are valid indicators of cerebral amyloid deposition in vivo, amyloid imaging also can permit studies of the natural history of Aβ amyloidosis and help to determine its relation to the onset of the clinical symptoms of AD.¹¹⁶

Preclinical Stages and Potential Disease-Modifying Therapies

The brains of some nondemented elderly people have large numbers of SPs and NFTs.^{117–120} It is likely that these lesions indicate a preclinical stage of AD, because: (1) they are absent from the neocortex in at least some individuals in the tenth decade of life and thus are not inevitable with age; (2) identical mechanisms appear responsible for the appearance of SPs and NFTs in individuals without dementia and those with clinically expressed AD; and (3) the distribution of the lesions follows the characteristic hierarchical topographical pattern of AD.¹²¹ These lesions may be present for years or even decades without causing appreciable synaptic damage or neuronal loss.¹²² The absence of synaptic and neuronal damage presumably correlates with the absence of cognitive deficits as determined by standard measures.¹²³ Factors known to be associated with overt AD, if present in nondemented people, may predict development of AD. For example, the *APOE* ε4 allele was a risk factor for dementia in a population-based study of nondemented elders (27% of ε4 carriers were demented in 3 years versus 17% of non-ε4 carriers) but did not modify rate of cognitive decline.¹²⁴ In another study of individuals aged 85 years who came to autopsy, the 31% who had a neuropathological diagnosis of AD were significantly more likely to have an *APOE* ε4 allele.¹²⁵ Cognitive decline in 166 nondemented elderly persons in yet another study was associated with increased age, the *APOE* ε4 allele, small

hippocampal and total brain volumes on MRI, and the presence of cerebral white matter lesions (considered to be a marker of cerebrovascular disease and postulated to contribute to faster rates of decline by reducing cerebral reserve).⁸⁰ Longitudinal cognitive studies suggest that poorer baseline performance¹²⁶ or errors on a visual memory measure¹²⁷ significantly increase the risk of developing overt AD many years later and thus may represent an early expression of AD prior to diagnosis. These observations lend support to the hypothesis that a subset of normal elderly individuals has neuropathological AD.

The clinical syndrome of AD may be the end stage of a long process, perhaps occurring over a lifetime, in which many risk factors and modifying influences operate at different periods to eventually produce the neuropathological and clinical phenotypes of AD (Fig. 1). Preventive treatment of AD may need to be initiated during the preclinical stage because substantial neuronal damage already has occurred by the time of clinical diagnosis.¹²⁸ To realize the possibility of preventive therapy for AD, antecedent biomarkers of AD (eg, amyloid imaging) to detect the preclinical stage of the illness prior to the occurrence of dementia and disease-modifying therapies both must be developed. Ideally, these developments will proceed simultaneously so that individuals who are identified as being at high risk for later occurrence of dementia can be offered mechanism-based interventions, which in turn will have optimal effect when initiated prior to the occurrence of well-established AD neuropathology.

Alzheimer disease is a complex disorder; it is unlikely that a single pathogenetic mechanism is responsible for all cases. Many causative factors have been proposed for AD, including viral infection, oxidative stress, and apoptosis, but most current hypotheses involve Aβ and tau. Although debate continues as to the relative importance of each protein to the disease process, a recent report provides evidence that blocking Aβ in transgenic mice can prevent the development of

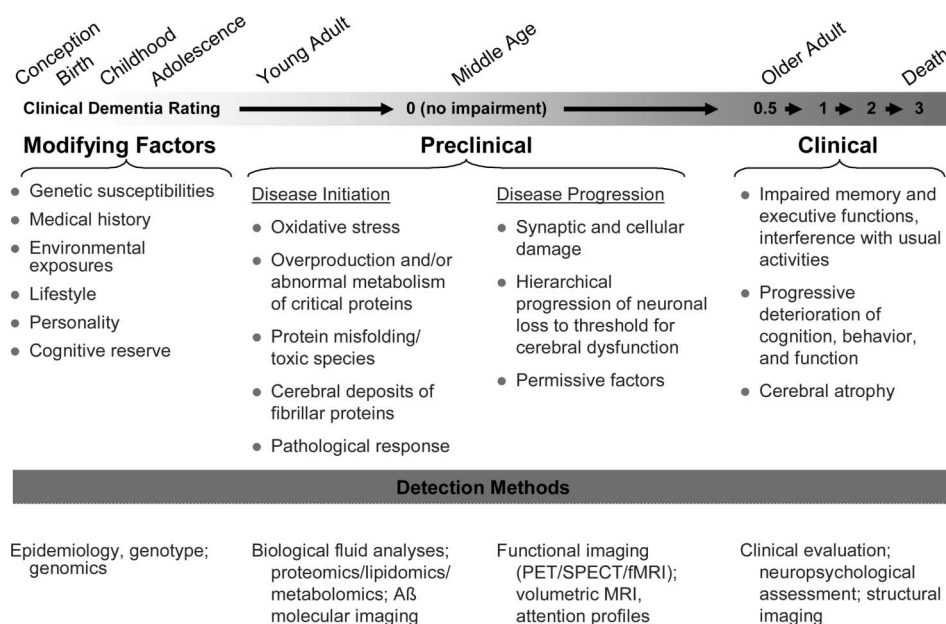


FIGURE 1. Hypothetical timeline of Alzheimer disease.

NFTs.¹²⁹ Postmortem studies of human brains also indicate that A β deposition precedes the appearance of NFTs in the neocortex.¹³⁰

There is growing evidence that overproduction or abnormal clearance of A β plays a central role in precipitating AD. The amyloid hypothesis (Table 2) proposes that cerebral deposits of insoluble fibrillar amyloid in the form of SPs induce a neurotoxic cascade resulting in nerve cell death that is marked by formation of NFTs. Refinement of the hypothesis implicates soluble A β oligomers that disrupt synaptic function^{131–133} and are prone to fibrillogenesis, which in turn is associated with dendritic and axonal abnormalities.¹³⁴ Therapeutic interventions that prevent accumulation of A β oligomers, reduce A β deposition, or promote A β clearance thus may be rational strategies for AD treatment and/or prevention.

Immunotherapy is a promising approach to removing or reducing the pathologic amyloid burden in AD.¹³⁵ Anti-A β antibodies clear existing amyloid deposits in older transgenic mice and may reverse neuritic alterations,^{136,137} providing hope that immunotherapy potentially could normalize dystrophic neurites and benefit cognition in individuals with established AD. A phase 1 vaccination trial of human aggregated A β ₄₂ in individuals with mild-to-moderate AD produced a positive antibody response in 58% of the participants (positive response associated with higher vaccine dose and longer duration of vaccination);¹³⁸ one of the 64 actively vaccinated participants developed meningoencephalitis 36 days after the fifth injection and died 1 year later.¹³⁹ The phase IIa trial of this synthetic full-length A β vaccine (with an adjuvant) in patients with mild-moderate AD, age 50 to 85 years (300 randomized to active vaccination and 75 to saline vaccination) began in 2001 but was suspended in January 2002 after meningoencephalitis developed in 18 of the 300 (6%) active patients.¹⁴⁰ Postmortem examination in 2 cases with meningoencephalitis (one each from the phase 1 and the phase IIa studies) revealed overall reduced amyloid burden with focal depletion of cerebral cortical SPs,^{139,141} consistent with evidence from transgenic mice that A β antibodies promote clearance of amyloid plaques. An additional autopsy case from a phase IIa study individual without encephalitis but with a positive antibody response found a virtual absence of amyloid plaques in frontal cortex and abundant A β -immunoreactive macrophages; there was no apparent effect on NFTs or on amyloid angiopathy.¹⁴² These data suggest that, although potential complications clearly are important, immunization strategies may be effective in reducing brain A β pathology.

TABLE 2. Basis for the Amyloid Hypothesis of Alzheimer Disease

1. Dominantly inherited AD is associated with overproduction, abnormal clearance, or increased deposition of amyloid (A β ₄₂)
2. Amyloid plaques are a neuropathologic hallmark of AD
3. Amyloid plaque deposition precedes development of:
 - a. Neocortical neurofibrillary tangles
 - b. Clinically expressed AD
4. Improved cognition in transgenic mice accompanies plaque clearance by immunotherapy

The encephalitis observed in the full-length A β vaccine trial has been attributed to a T-cell response rather than to anti-A β antibodies, suggesting that passive peripheral administration of humanized anti-A β antibodies may reduce A β deposits without producing encephalitis.¹⁴³ Passive immunotherapy is effective in clearing A β in animal models¹⁴⁴ and a clinical trial of passively administered humanized monoclonal anti-A β antibodies recently has been initiated. A novel active immunization model also has been demonstrated in mice using “gene-gun delivery” of plasmids coding for A β that elicit antibody responses to the A β peptide.¹⁴⁵

Additional mechanism-based treatments for AD are in various stages of development.¹⁴⁶ These include attempts to reduce A β production through inhibition of the secretases that cleave the peptide from its precursor protein, APP. Other strategies aim to prevent A β accumulation, either by attenuating metal ion interactions with A β through chelation of copper and zinc, as with clioquinol,¹⁴⁷ or by inhibiting A β oligomerization with agents such as curcumin.¹⁴⁸ Anti-tau approaches also are under investigation. A drug reported to have microtubule stabilizing properties, paclitaxel, may functionally compensate for the loss of normal tau function in maintaining microtubule networks and thus restore axonal transport in tau transgenic mice.¹⁴⁹ Much work remains, of course, to determine whether any potentially disease-modifying therapy is safe, tolerable, and efficacious. Rapidly accumulating knowledge about the neurobiology of AD, however, is yielding dividends as the field increasingly moves to clinical trials of therapies that have the potential to modify, arrest, or even prevent AD.

MILD COGNITIVE IMPAIRMENT (MCI)

There is intense interest in MCI as a possible prodromal stage of dementia. The MCI construct was developed to characterize older adults who were neither cognitively normal nor overtly demented. The AAN's Practice Parameter on early detection of dementia and MCI¹⁵⁰ recommended clinical monitoring for MCI individuals because of their increased risk of progressing to dementia (annual “conversion rate” of approximately 10% to 15%, compared with 1% to 2% for nondemented elderly aged 80 years or less). However, estimates of the prevalence of MCI and related constructs, including “age-associated cognitive decline” (AACD)¹⁵¹ and “cognitive impairment no dementia” (CIND),¹⁵² have varied greatly as have rates of “conversion” to dementia.^{153,154} Sources of variability include different criteria used to define MCI, differing methods to implement the criteria, and differences in the ascertainment and characteristics of individuals in the study samples. Resulting controversies about the boundaries of the condition in relation to normal cognitive aging and early-stage dementia have prompted refinement of MCI criteria that broaden the concept and include prodromal forms of non-AD dementias.¹⁵⁵

Basic criteria for MCI include cognitive complaints that are documented by objective cognitive testing in the presence of generally preserved activities of daily living (thus falling short of criteria for dementia).¹⁵⁵ MCI potentially can result from multiple etiologies, including some that may be stable (eg, post-traumatic encephalopathy) or reversible (eg, depression; medication-induced cognitive dysfunction; substance abuse).

Several subtypes of MCI have been proposed.¹⁵⁶ The most frequently studied subtype is amnesic MCI in which memory deficits predominate. When the memory deficit is relatively isolated, the subtype is “amnesic MCI, single domain”; when other cognitive domains (eg, attention, executive function, visuospatial skills, language) also are impaired, the subtype is “amnesic MCI, multiple domain.” When the presentation involves a non-memory cognitive domain, the subtypes are “non-amnesic MCI, single domain” and “non-amnesic MCI, multiple domain,” depending on the number of impaired domains. The reliability and validity of this classification scheme, the prevalence and incidence of MCI subtypes, and their underlying etiologies all remain to be determined.

There are conceptual and practical difficulties in applying criteria for MCI in the clinic. The diagnosis of amnesic MCI, for example, can be based on the subjective memory complaint of the individual, even if lacking corroboration by an informant. Self-reported memory problems, however, correlate better with depressive features than with future development of dementia whereas informant-reported cognitive difficulties are predictive of dementia.⁷² Informants are needed also to determine whether activities of daily living are preserved or impaired. Recent studies indicate that MCI patients experience changes in everyday function. For example, individuals with amnesic MCI (mean MMSE score = 28.4) demonstrated impaired ability to manage cash transactions, bank statements, and bill payments and had reduced overall financial capacity.¹⁵⁷ Determining that activities of daily living are “generally preserved” may depend on how carefully changes are sought by the clinician and whether informant observations are solicited. Furthermore, the cognitive deficits in MCI may be more widespread than initially was appreciated. An Alzheimer’s Disease Cooperative Study (ADCS) trial evaluating potential treatment effects of donepezil or vitamin E enrolled 769 participants with amnesic MCI from 69 centers in the United States and Canada; as expected, the greatest objective impairments were demonstrated in measures of episodic memory but impairments, albeit very mild, also were observed in multiple other cognitive domains.¹⁵⁸

It can be argued that MCI individuals who experience memory deficits, have compromised function in activities of daily living, and are impaired in additional cognitive domains already fulfill criteria for dementia, although at a very mild stage that may be below the current diagnostic threshold of most clinicians. Informant-based methods have been shown to reliably detect early-stage AD in individuals who meet MCI criteria; autopsy confirmation of AD in one series was 84%.¹⁵⁹ Longitudinal studies of individuals meeting criteria for amnesic MCI demonstrate progressive cognitive decline at rates that are influenced by the severity of impairment at baseline.⁸¹ Moreover, the neurobiological phenotype of amnesic MCI closely resembles that of clinically diagnosed AD, although at a milder stage. Common features include neuropsychiatric symptoms,^{160,161} over-representation of the *APOE* ϵ 4 allele,^{162,163} volumetric loss in the entorhinal cortex and hippocampus as measured by MRI,^{164,165} hypometabolism in AD-typical regions as measured by FDG-PET,¹⁶⁶ neuronal loss in vulnerable brain regions,¹⁶⁷ increased brain markers of oxidative stress,¹⁶⁸ cell cycle changes,¹⁶⁹ and abnormalities of the cholinergic system.¹⁷⁰

The views of the author of this Update regarding MCI in relation to AD can be summarized as follows:

1. MCI is heterogeneous; not all individuals with MCI develop clinically diagnosed AD.
2. Clinical methods incorporating informant interviews can accurately identify the subset of MCI with prodromal AD (this subset largely corresponds to amnesic MCI).
3. Clinically expressed AD begins with the MCI phase and, in these individuals, the etiology of MCI is underlying AD.
4. The MCI phenotype for the subset described in #3 is that of AD, only milder.
5. In the clinically defined subset of #3, MCI is not a risk factor for AD; it already is AD at its earliest symptomatic stage.

If some cases of MCI can be identified by their physicians as highly likely to represent early-stage AD, counseling and treatment become important issues. Attention to possible safety and security issues (eg, driving), financial and insurance planning, advance directives, and related topics may be appropriate at this stage when the individual still is able to engage in decision-making. No drug treatments have been approved by the FDA for the indication of MCI. An industry-sponsored randomized placebo-controlled trial of donepezil 10 mg a day for 24 weeks found no treatment effect for MCI individuals (mean MMSE score = 27.5) on the primary efficacy measures, although some secondary cognitive measures showed effects favoring donepezil.¹⁷¹ The results from the ADCS trial noted above in which donepezil and vitamin E were compared with placebo for rate of progression of MCI to clinically probable AD recently were reported.¹⁷² Vitamin E had no benefit for MCI. Over 3 years, the rates of progression to AD were not different between the donepezil and placebo groups, but donepezil-treated individuals had a slower rate of progression during the first 12 months of the trial. For MCI individuals with at least one *APOE* ϵ 4 allele, a lower rate of progression to AD was evident throughout the entire 3-year follow-up.¹⁷²

In the absence of published data clearly demonstrating a pharmacotherapeutic benefit for MCI but with increasing recognition that at least some MCI individuals have underlying AD, treatment issues are evolving. Although uniform recommendations cannot be provided, for individual cases when the clinician believes on clinical grounds that MCI is caused by AD, there may be a rationale for ChEI therapy based on the likelihood of early-stage AD.⁸⁶

NON-ALZHEIMER DISEASE DEMENTIAS

Vascular Dementia

Cerebrovascular damage can disrupt neural systems important for cognition, and the increased frequency of stroke with age has led to the common assertion that vascular dementia may be the second most common dementing illness, accounting for 15% to 20% of cases.¹⁷³ Neuropathological examination, however, reveals that vascular dementia as a discrete entity is rare; in the Florida Brain Bank series, only 3% of 382 autopsied demented patients with dementia had pure vascular

dementia.¹⁷⁴ Vascular lesions often coexist with other dementia etiologies, usually AD (found in 77% of cases of presumed vascular dementia).¹⁷⁴ In an autopsy series of Japanese-American men, the effect of concomitant cerebrovascular disease was strongest in cases with relatively sparse densities of AD lesions, suggesting that cerebrovascular lesions contribute dramatically to expression of dementia in men with subclinical AD and that prevention of cerebrovascular disease might sharply reduce dementia occurrence in these individuals.¹⁷⁵ The co-existence of AD and cerebrovascular disease, known as “mixed dementia,” will increase as the population ages.¹⁷⁶

The neuropathological basis of vascular dementia has been considered a matter of strokes, large and small. New evidence, however, has prompted revisions of traditional concepts of “multi-infarct dementia.” For example, in longitudinally studied Japanese-American men who came to autopsy, microinfarcts in the cerebral cortex, basal ganglia, and thalamus correlated as strongly to dementia as did senile plaques and more strongly than large or small (lacunar) infarcts.¹⁷⁷ Another study found that frontal white matter lesions, rather than the volume or number of cerebral infarcts, were the best correlate of cognitive dysfunction in stroke patients.¹⁷⁸ Vascular cognitive dysfunction in this study was characterized by executive (frontal) deficits and psychomotor slowing with preserved verbal memory. The relative contributions of microvascular pathology, white matter lesions, and infarcts to vascular cognitive impairment remain to be fully elucidated, as does the nature of their interactions (permissive, additive, or synergistic) with AD in cases of mixed dementia. Although the presence of at least one infarct increased the odds of dementia by 2.8 fold in 153 autopsied individuals in one study, it did not enhance the primary effect of AD pathology on cognitive dysfunction beyond an additive contribution.¹⁷⁹

Treatment trials of individuals clinically diagnosed with vascular dementia, alone or co-existent with AD, have reported efficacy for galantamine¹⁸⁰ and donepezil.¹⁸¹ A review by the Cochrane Dementia and Cognitive Improvement Group of published and unpublished data from placebo-controlled trials of donepezil in patients with vascular cognitive impairment found that the 5 mg and 10 mg daily doses over 24 weeks each were superior to placebo for cognitive and functional performance.¹⁸² ChEI therapy thus may be considered for demented individuals with vascular features, with or without associated AD.

Dementia with Lewy Bodies

Dementia with Lewy Bodies (DLB) now is recognized as the second most common dementing disorder in late life after AD, although concomitant AD is frequent (66% of DLB cases).¹⁷⁴ Immunocytochemical staining for ubiquitin and α -synuclein have greatly aided the detection of cortical Lewy bodies, the hallmark pathologic feature of DLB. Mutations in the α -synuclein gene can cause familial Parkinson's disease and synuclein is a major component of Lewy bodies. Rare mutations in the β -synuclein gene now have been associated with DLB; β -synuclein may modulate α -synuclein aggregation and toxicity.¹⁸³

Difficulties remain in clinical diagnosis. The core clinical features of DLB include recurrent visual hallucinations,

fluctuating cognition, and spontaneous features of parkinsonism¹⁸⁴ and are important to identify, as individuals with DLB not only may benefit from levodopa therapy in regard to motoric symptoms but also may have neuroleptic sensitivity.¹⁸⁵ Only 45% of autopsy-confirmed DLB cases, however, were correctly diagnosed during life in one series, perhaps because of low frequencies of the core features: visual hallucinations were present in only 42% and parkinsonism in only 55% of cases, and 30% lacked both features.¹⁸⁶ Patients with pure DLB were more likely to demonstrate core symptoms, but those with DLB associated with AD neuropathology had clinical features that masked the DLB syndrome. A similar overriding effect of AD has been noted with other dementing disorders.^{76,187} Rapid eye movement (REM) sleep behavior disorder has been proposed recently to characterize demented individuals with an underlying synucleinopathy,¹⁸⁸ and informant-reported cognitive fluctuations (including hypersomnolence and variations in attention and alertness) may help to distinguish DLB from AD.¹⁸⁹

The prevalence of mild parkinsonian signs (bradykinesia, rigidity, rest tremor, gait disturbances) increases with age in community-dwelling older adults and the risk of incident dementia increased with the number and severity of parkinsonian signs at baseline,¹⁹⁰ indicating that these signs are prognostically important. Another study of patients with Parkinson's disease (PD) found that demented individuals had annual rates of cognitive decline as measured by the MMSE comparable to those of patients with AD, whereas nondemented PD patients had minimal decline comparable to nondemented controls.¹⁹¹ Older age, greater PD severity, and the presence of hallucinations were associated with greater rates of cognitive decline.

Parkinson's disease and DLB may represent a clinicopathologic continuum. Patients with PD (with and without dementia) and with DLB both had similar responses to an acute challenge with levodopa, and 75% of DLB patients had improved motor response to chronic levodopa therapy.¹⁹² Visual perception is impaired in PD with dementia and in DLB compared with AD.¹⁹³ Striatal dopaminergic transport, as measured with a radiolabelled ligand using single photon emission computed tomography, is reduced in DLB to a similar degree as in PD but not in AD.¹⁹⁴ If validated in a larger series, this imaging measure may aid in the distinction of DLB from AD and other non-Lewy body dementias.

Frontotemporal Lobar Degeneration

Neurodegenerative diseases characterized by frontotemporal lobar degeneration (FTLD) are associated with the clinical syndrome of frontotemporal dementia. In individuals below age 65 years, FTLD is the second most common neurodegenerative dementia, after AD.¹⁹⁵ FTLD cases are clinically and neuropathologically heterogeneous, but molecular classification is progressing. Neuropathologic phenotypes of FTLD encompass the tauopathies, including classic Pick's disease (intraneuronal Pick bodies), corticobasal degeneration (CBD; tau-positive astrocytic plaques and ballooned neurons), progressive supranuclear palsy (NFTs), frontotemporal dementia with parkinsonism linked to chromosome

17 (FTDP-17; neuronal and glial tau-positive inclusions), and tau-positive argyrophilic grain disease. Other FTLN cases have tau-negative but ubiquitin-positive inclusions in brainstem motor nuclei and dentate gyrus. These cases are designated frontotemporal dementia-motor neuron inclusion dementia (FTD-MNID) to indicate that motor neuron pathology may be present without clinical manifestations of motor neuron disease. The FTD-MNID subtype is the most common pathologic diagnosis in FTLN.¹⁹⁶ Finally, some FTLN cases have no distinctive histopathology.

Several clinical subtypes of FTLN have been defined:¹⁹⁷ behavioral (frontotemporal dementia, or FTD), language (primary progressive nonfluent aphasia and semantic dementia), and motor (CBD, motor neuron disease). The behavioral subtype is most common but frequently is combined with language problems (Table 3). A clinicopathologic study of 61 cases of FTLN found a mean age at onset of 58.5 years and a positive family history in 33%.¹⁹⁸ Changes in personality or social conduct (90%), memory impairment (57%), language problems (56%), and dysexecutive symptoms (54%) were the most frequent presenting features. Many cases had combined features, suggesting a continuum of symptoms rather than discrete subtypes.

Motor neuron disease and FTLN co-occur more commonly than generally is appreciated.¹⁹⁹ The clinical syndrome (FTD-MND) includes cognitive impairment and amyotrophic features. The disease course is rapid (average of 2–3 years). Men are affected more than women. Both sporadic and familial cases occur and have similar clinical and neuropathological changes.²⁰⁰

Neuronal intermediate filament inclusion disorder

A novel disorder has been reported with neuronal inclusions composed of abnormal aggregates of α -internexin, a type IV intermediate filament protein.²⁰¹ Although neuronal intermediate filament inclusion disorder (NIFID) is immunohistochemically distinct from other subtypes of FTLN, its clinical features resemble those of frontotemporal dementia of early onset (mean age at onset = 41 years) combined with features of MND and CBD. Because clinical phenotypes of neurodegenerative dementing disorders may relate to selective vulnerability of cell populations with specific attributes (eg, type of neurotransmitter, neuronal connections, or gene expression patterns), understanding the pathophysiology of disorders such as NIFID may shed light on the mechanisms of neuronal dysfunction and death in other disorders characterized by protein processing abnormalities.²⁰²

Hippocampal Sclerosis

Hippocampal sclerosis (HS) is defined pathologically by severe neuronal loss and gliosis in the CA1 region of the hippocampus and is present in approximately 13% of demented cases,¹⁷⁴ almost always in association with AD or other dementing disorders. A retrospective case-control study of pathologically confirmed HS, FTLN, and AD cases found a pattern of behavioral abnormalities in HS, including socially inappropriate and stereotyped behavior, that resembled FTLN and differed from AD.²⁰³ Neuropathological examination in 18 HS cases from this series revealed tau-negative, ubiquitin-positive neuronal inclusions in the dentate gyrus in 11 of 18 HS cases, consistent with the FTD-MNID variant of FTLN.²⁰⁴

TABLE 3. Clinical Features of the Major Syndromes of Frontotemporal Lobar Degeneration

For each syndrome, features are prominent and represent the presenting symptoms

Frontal lobe dementia

At least 6-month history of change in personality and behavior, sufficient to interfere with interpersonal relationships and social compartment and accompanied by at least 5 of the following features:

- | | |
|------------------------------------|----------------------------|
| Disinhibition | Hyperorality |
| Distractibility | Emotional lability |
| Impulsivity | Reduced concern for others |
| Social withdrawal | Apathy |
| Restlessness | Loss of insight |
| Compulsive or stereotypic behavior | |

Primary progressive nonfluent aphasia

At least 6-month history of impaired expressive language, as marked by:

- Dysfluency
- Agrammatism
- Speech hesitancy/effortful speech
- Word-finding difficulty

Semantic dementia

At least 6-month history of:

- Impaired comprehension of word meaning, or of object or face identity (prosopagnosia) with impaired naming
- Fluent but empty speech with semantic paraphasias

Based on clinical classifications proposed in Knopman, Petersen, Edland, Cha, Rocca 2004. Reference 195.

These findings support a degenerative etiology for at least some cases of HS, rather than a vascular or hypoxic injury as previously thought. A distinct clinical profile for HS remains elusive.

Creutzfeldt-Jakob Disease

Various brain proteins have been studied as CSF markers of Creutzfeldt-Jakob disease (CJD), including neuron-specific enolase and 14-3-3. Molecular and phenotype analysis now define 6 subtypes of CJD, based on homozygosity or heterozygosity for methionine (M) or valine (V) at codon 129 of the prion protein gene and on the pathologic protease-resistant isoform of the prion protein (type 1 or 2).²⁰⁵ The MM 1 and MV 1 subtypes share a similar phenotype of classic CJD: rapidly progressive dementia, early myoclonus, and periodic electroencephalographic (EEG) changes. The other subtypes, comprising about 30% of all CJD cases, have atypical presentations with longer durations and usually lack EEG abnormalities. The sensitivity of CSF 14-3-3 protein is high for the classic CJD subtypes but low for the nonclassical subtypes.²⁰⁶ However, CJD patients who are negative for 14-3-3 protein and lack EEG abnormalities have changes on diffusion-weighted MRI in cerebral cortex and/or striatum²⁰⁷ or have signal increase on T2-weighted MRI in basal ganglia.²⁰⁸ Only rarely are the CSF and MRI findings both normal in CJD, even in cases with a nonclassical phenotype. Brain imaging should be included to support the diagnosis of CJD.

Based on cell models of prion infection, quinacrine was proposed as an antiprion agent. A French trial in patients with either CJD or variant CJD (associated with bovine spongiform encephalopathy) authorized quinacrine treatment as part of a compassionate procedure. Side effects, including hepatitis, were not uncommon. Compared with untreated cases, no significant clinical benefit or change in neuropathological lesion profiles was observed.²⁰⁹

SUMMARY

As noted, this update necessarily reflects the views of the author and cannot be assumed to be either all encompassing or balanced. With these caveats, important current themes in dementia research include the following:

1. AD is highly prevalent in older adults yet remains underdiagnosed.
2. The strongest risk factors for sporadic AD are age, family history, and *APOE* genotype. Many other modulating factors may operate at distinct “windows” or timepoints during a long preclinical phase of AD to increase or decrease risk for the clinically expressed disorder. Examples include cardiovascular factors in midlife (increased risk for AD) and engagement in cognitive, physical, and social activities (decreased risk for AD).
3. There is no conclusive evidence of reduced risk for AD for statins, nonsteroidal anti-inflammatory drugs, or the antioxidant vitamins E and C.
4. Estrogen replacement therapy does not reduce risk for AD, at least in women 65 years and older, and may be harmful.

5. AD can be diagnosed with high accuracy using clinical methods that combine informant interviews and objective assessment of the patient.
6. The rate of cognitive decline in AD is determined largely by the severity of dementia.
7. The FDA-approved symptomatic therapies for AD are the cholinesterase inhibitor drugs for mild-moderate AD and memantine for moderate-severe AD.
8. The cost-effectiveness of cholinesterase inhibitor therapy in AD has been questioned.
9. The safety of high-dose vitamin E supplementation and the atypical antipsychotic drugs have been challenged.
10. Multiple candidate biomarkers for AD are being investigated, but to date none have been validated.
11. CMS has approved reimbursement of PET studies as an adjunct tool for dementia evaluation in limited circumstances that involve the distinction of frontotemporal lobar degeneration and AD.
12. Neuroimaging measures potentially can be used as surrogate markers for AD. In particular, the advent of amyloid tracers holds promise for molecular imaging as a diagnostic and prognostic tool in AD.
13. Agents with the potential to modify the AD process currently are in trial or soon will be, including immunotherapeutic strategies using passive administration of anti-A β monoclonal antibodies.
14. The preclinical stage of AD will require detection by antecedent biomarkers but may be the optimal period for intervention should safe, tolerable, and effective agents be developed to delay or prevent the onset of dementia.
15. MCI criteria have been expanded to include prodromal forms of non-AD dementing disorders. Not all individuals with MCI will progress to dementia. However, the subset of MCI individuals with prodromal AD can be identified by clinical methods and for these individuals MCI may represent the earliest symptomatic stage of AD.
16. There is no currently approved treatment of the indication of MCI.
17. Pure vascular dementia is rare (at least in the United States). Attention increasingly is focused on understanding how vascular insults, including microvascular pathology, contribute to cognitive impairment in “mixed dementia.”
18. Dementia with Lewy Bodies is the second most common dementing disorder after AD. However, its clinical diagnosis is problematic.
19. Frontotemporal lobar degeneration encompasses a group of heterogeneous clinical and neuropathological phenotypes. Motor neuron disease and frontotemporal lobar degeneration frequently co-occur.
20. Neuroimaging findings in combination with cerebrospinal assays are useful in the diagnostic assessment of cases of suspected Creutzfeldt-Jakob disease.

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Announcements

21st International Conference of Alzheimer's Disease International
Location: Istanbul Convention Center and Exhibition Centre, Istanbul, Turkey
Dates: September 28–October 1, 2005

For more information:
<http://www.icec.org>

Fourth International Congress on Vascular Dementia
Location: Porto, Portugal
Dates: October 20–23, 2005

For more information:
www.kenes.com/vascular

Genetics of Alzheimer's Disease and Related Disorders

Location: Irving, Texas (US)
Dates: October 21–21, 2005

For more information:
cmregistrations@utsouthwestern.edu

5th Leonard Berg Symposium: Antecedent Biomarkers for Early & Preclinical Detection of Alzheimer's Disease

Location: St. Louis, Missouri (US)
Dates: October 7–8, 2005

For more information:
<http://alzheimer.wustl.edu>