Drug Treatment for Alzheimer's Disease

ALZHEIMER'S DISEASE (AD) can be diagnosed clinically and is a treatable disorder. Disease modifying and symptomatic therapies are available. Stage-specific treatment, control of behavioral disturbances, and care of the caregiver are all important aspects of therapy.

Treatment begins with the clinical diagnosis of AD and determination of its manifestations. In addition to an assessment of memory and other cognitive domains, a complete evaluation identifies associated behavioral disturbances, including delusions, dysphoria, apathy, irritability, anxiety, and disturbances in sleep or appetite. If the caregiver reports behavioral changes that urgently require treatment, the first arm of therapy consists of symptom-appropriate psychotropic medication.

The clinician must also determine the severity of AD. Therapies that slow its progression may be appropriate for earlier, but not later, phases of the disease. Similarly, symptomatic therapies are indicated for mild to moderate AD. In patients with advanced AD, cholinesterase inhibitors and neuroprotective agents prolong disability and caregiver burden instead of preserving function.

Recent studies have shown the benefits of neuroprotective agents such as vitamin E and selegiline. Vitamin E, 2000 IU once a day, and selegiline, 5 mg twice a day, each proved more effective than placebo therapy at both slowing the decline of cognition and functional ability and prolonging the time to death. Given together, the two drugs had neither an additive nor synergistic effect. Vitamin E has no side effects, which makes it a better choice for neuroprotective therapy.

Estrogen given to women as postmenopausal hormone replacement therapy may have a neuroprotective effect. Estrogen has already proven beneficial for depressed mood and mild memory impairment in patients, possibly through the preservation and promotion of dendritic synapses, antioxidant effects, cholinergic effects, and maintenance of vascular competency.

Donepezil is the current drug of choice for symptomatic treatment of AD. This cholinesterase inhibitor specifically targets the central nervous system and compensates for the cholinergic deficit present in the brain in AD. It offers a more benign side effect profile than its predecessor, tacrine. Donepezil is given once a day, can be increased to maximal dose (10 mg a day) after the first month at 5 mg a day, and spares patients frequent phlebotomy to assess liver functions. Donepezil and tacrine have equal efficacy. Some behavioral disturbances also may improve with donepezil treatment, and the clinician should track behavioral changes along with memory and ADL function at follow-up evaluations. Donepezil is coadministered with vitamin E and, in women, with estrogen replacement therapy. If behavior problems persist, psychotropic medication should be given as well.

There is no AD-specific treatment available or appropriate for the disease's late and end stages. In the absence of such treatment, the clinician bears the responsibility of giving stage-specific counsel to the patient and the caregiving family. Patients with advanced disease may still require psychotropic agents for the control of disturbing behavior, and these should be used as necessary. Attention to skin care, nutrition, and hydration are critical. The protocol for treatment will change drastically in the coming years, as muscarinic cholinergic agonists and new recommendations regarding neuroprotection with nonsteroidal anti-inflammatory agents, neurotrophins, and other agents become available.

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The Role of Apolipoprotein E Testing in the Diagnosis of Alzheimer's Disease

THE IMPORTANCE OF EARLY and accurate diagnosis of dementia has become increasingly recognized, particularly when associated with Alzheimer's disease (AD). A key reason for this is heightened public awareness of dementia: symptoms such as failing memory are likely to be brought to medical attention rather than dismissed as unimportant or due to aging.

Treatment strategies in AD that aim to slow clinical progression require early diagnosis supported by early treatment initiation. The standard method of diagnosing AD remains the clinical approach, in which the clinician obtains a history of cognitive decline, documents that recent memory and other areas of cognition are impaired, and rules out other causes of dementia. For early diagnosis, brief screening tests such as the Mini-Mental State Examination are insensitive. By expanding the tests of memory, abstraction, drawing, and language, the clinician can increase the diagnostic yield; for many patients, however, serial testing, over months and sometimes years, is necessary to document progressive cognitive decline. The clinical problems associated with the early detection and differential diagnosis of dementia have fueled studies of the role of biological markers (such as neuroimaging and the testing of cerebrospinal fluid and blood) and genetic (DNA) risk factors as diagnostic aids. The most consistent findings involve testing for variants of Apolipoprotein E (Apo-E).

Apo-E is a lipoprotein that is involved in cholesterol transport in the brain. Humans have three major genetic variants (alleles) of Apo-E—e2, e3, and e4. In the general population, e3 is the most common allele. According to numerous studies, the e4 allele carries an

increased risk for the development of AD. A recent study that pooled data from many centers has clarified the extent of risk: overall, the e4/e4 genotype increased the risk of AD by 15-fold, while the e3/e4 and e2/e4 genotypes increased the risk about 3-fold (compared to the e3/e3 genotype). The effect of e4 was particularly evident for patients with dementia onset in their 60s and 70s. The e4 allele is estimated to be associated with about 40% to 50% of cases of sporadic AD.

How could Apo-E e4 fit into a diagnostic approach to dementia? Presymptomatic screening is unlikely to be useful because of the widely varying and unpredictable age at onset of AD among e4 bearers, the lack of protection from AD in e3/e3 bearers, and the lack of proven preventive therapy for AD. Apo-E genotyping in someone without cognitive decline provides only a vague prediction of the magnitude and timing of the risk of AD.

A stronger case can be made for using Apo-E in the clinical diagnosis of AD. Several autopsy studies have shown that the e4 allele is increased specifically in patients who showed pathology of AD, not of other brain disorders. This implies that in a demented subject, the presence of one or two e4 alleles makes AD more likely, and the absence of an e4 makes AD slightly less likely. In patients with dementia who do not have clear clinical diagnoses, or when more than one potential cause of dementia is present, Apo-E genotyping may increase the confidence that AD is present if one or two e4 alleles are found.

By extension, ApoE genotyping may have some value in early diagnosis. In an older patient with mild memory dysfunction, the presence of the Apo-E e4 allele increases the likelihood that the symptoms are AD-related (rather than associated with normal aging or depression). The absence of an e4 allele, however, only marginally decreases the likelihood of AD. In studies of older people with mild memory difficulty or with risk factors for AD, Apo-E genotyping has been shown to be a predictor in those whose symptoms progress to clinically diagnosed AD. In short, the main value of Apo-E as an adjunct to diagnosis comes when AD cannot be confidently excluded and other conditions fall into the equation. Finding one or more e4 alleles can then alert clinicians to the probability of AD. As is the case with diagnostic tests in general, good clinical judgment is essential to maximize the value and interpretability of Apo-E genotyping in relation to dementia.

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Genetic Testing

RECENT ADVANCES IN molecular biology have resulted in a rapidly expanding number of diagnostic tests for neurogenetic disorders. Gene discovery has led to direct DNA tests for disease-causing mutations. Many of these tests are based on trinucleotide repeat expansions underlying at least 11 different disorders. Eight are autosomal dominant, including Huntington's disease, myotonic muscular dystrophy, and several types of spinocerebellar ataxias (SCA); two are X-linked including fragile X mental retardation and Kennedy's spinal bulbar muscular atrophy (SBMA); and one is autosomal recessive (Friedreich's ataxia). Other commercially available DNA tests for point mutations, duplications, or deletions include one type of familial amyotrophic lateral sclerosis (ALS) (superoxide dismutase 1); one form of early-onset familial Alzheimer's disease (presenilin 1); and three types of hereditary neuropathy (Charcot-Marie-Tooth Type 1A [CMT1A], X-linked Charcot-Marie-Tooth [CMTX], and hereditary neuropathy with liability to pressure palsies [HNPP]). Several tests are also available for the common mutations that occur in mitochondrial DNA including MELAS (mitochondrial encephalomyopathy with lactic acidosis and stroke), MERRF (myoclonic epilepsy with ragged red fibers), and LHON (Leber's hereditary optic neuropathy).

These DNA tests have advantages and disadvantages. The greatest advantage is that they are highly specific and are remarkably valuable diagnostic tools. They are often considered the gold standard of diagnosis. A positive test establishes an exact diagnosis, whereas a negative test encourages further evaluation for other causes of the clinical syndrome. The results are also important for accurate genetic counseling, because a positive result indicates the pattern of inheritance. (For example, CMT1A and familial ALS are clinically similar to CMTX and Kennedy's SBMA, respectively, but the first two disorders are autosomal dominant and the second two are X-linked.) There is sometimes an economic advantage; for instance, a single DNA test may be much less expensive than an extensive but less specific battery of clinical tests. Also, DNA tests may lead to an early identification of gene carriers that will make them available for early therapeutic intervention.

DNA testing also carries many potential disadvantages. A positive DNA test for a serious neurogenetic disorder such as Huntington's disease may lead to tremendous anxiety and depression in some patients. Therefore, DNA testing of asymptomatic family members at risk for the mutation should be done in the context of formal genetic counseling. There is concern that DNA testing may create persons who are "genetic outcasts," who will be unable to obtain insurance or employment. It is unclear how the results of DNA testing should be used in legal proceedings such as divorce, child custody, or criminal prosecution. Families may have exaggerated expectations from DNA testing, so it is important to note that most positive tests do not pro-