mutations in *APP*. Although very rare, these families were the first examples of single-gene autosomal dominant transmission of AD.

Investigation of large families with multigenerational FAD led to the discovery of two additional AD-causing genes, the *presenilins*. Presenilin-1 (*PS-1*) is on chromosome 14 and encodes a protein called S182. Mutations in this gene cause an early-age-of-onset AD, with onset before the age of 60 and often before age 50, transmitted in an autosomal dominant, highly penetrant fashion. More than 100 different mutations have been found in the *PS-1* gene in families from a wide range of ethnic backgrounds. Presenilin-2 (*PS-2*) is on chromosome 1 and encodes a protein called STM2. A mutation in the *PS-2* gene was first found in a group of American families with Volga German ethnic background. Mutations in *PS-1* are much more common than those in *PS-2*. The presenilins are highly homologous and encode similar proteins that at first appeared to have seven transmembrane domains (hence the designation *STM*), but subsequent studies have suggested eight such domains, with a ninth submembrane region. Both S182 and STM2 are cytoplasmic neuronal proteins that are widely expressed throughout the nervous system. They are homologous to a cell-trafficking protein, sel 12, found in the nematode *Caenorhabditis elegans*. Patients with mutations in the presenilin genes have elevated plasma levels of $A\beta_{42}$, and *PS-1* mutations produce increased $A\beta_{42}$ in the media in cell culture. There is evidence that *PS-1* is involved in the cleavage of APP at the γ secretase site and mutations in either gene (*PS-1* or *APP*) may disturb γ secretase cleavage. Mutations in *PS-1* are the most common cause of early-age-of-onset FAD, representing perhaps 40–70% of all cases. Mutations in *PS-1* tend to produce AD with an earlier age of onset (mean onset 45 years) and a shorter, more rapidly progressive course (mean duration 6–7 years) than the disease caused by mutations in *PS-2* (mean onset 53 years; duration 11 years). Although some carriers of *PS-2* mutations have had onset of dementia after the age of 70, mutations in the presenilins rarely lead to late-age-of-onset AD. Clinical genetic testing for these uncommon mutations is available but likely to be revealing only in early-age-of-onset FAD and should be performed in association with formal genetic counseling.

The *Apo* ε gene on chromosome 19 is involved in the pathogenesis of AD. The protein, apolipoprotein E, participates in cholesterol transport (Chap. 421), and the gene has three alleles: ε2, ε3, and ε4. The Apo ε4 allele confers increased risk of AD in the general population, including sporadic and late-age-of-onset familial forms. Approximately 24–30% of the nondemented white population has at least one ε4 allele (12–15% allele frequency), and about 2% are ε4/ε4 homozygotes. Among patients with AD, 40–65% have at least one ε4 allele, a highly significant elevation compared with controls. Conversely, many AD patients have no ε4 allele, and ε4 carriers may never develop AD. Therefore, ε4 is neither necessary nor sufficient to cause AD. Nevertheless, the Apo ε4 allele represents the most important genetic risk factor for sporadic AD and acts as a dose-dependent disease modifier, with the earliest age of onset associated with the ε4 homozygosity. Precise mechanisms through which Apo ε4 confers AD risk or hastens onset remain unclear, but ε4 leads to less efficient amyloid clearance and to the production of toxic fragments from cleavage of the molecule. Apo ε can be identified in neuritic plaques and may also be involved in neurofibrillary tangle formation, because it binds to tau protein. Apo ε4 decreases neurite outgrowth in dorsal root ganglion neuronal cultures, perhaps indicating a deleterious role in the brain's response to injury. Some evidence suggests that the ε2 allele may reduce AD risk. Use of Apo ε testing in AD diagnosis remains controversial. It is not indicated as a predictive test in normal persons because its precise predictive value is unclear, and many individuals with the ε4 allele never develop dementia. Many cognitively normal ε4 heterozygotes and homozygotes show decreased cerebral cortical metabolic function with PET, suggesting presymptomatic abnormalities due to AD or an inherited vulnerability of the AD-targeted network. In demented persons who meet clinical criteria for AD, finding an ε4 allele increases the reliability of diagnosis; however, the absence of an ε4 allele cannot be considered evidence against AD. Furthermore, all patients with dementia, including those with an ε4 allele, require a search for reversible causes of their cognitive impairment. Nevertheless, Apo ε4 remains the single most important biologic marker associated with AD risk, and studies of ε4's functional role and diagnostic utility are progressing rapidly. The ε4 allele is not associated with risk for FTD, DLB, or CJD, although some evidence suggests that ε4 may exacerbate the phenotype of non-AD degenerative disorders, head trauma, and other brain injuries. Additional genes are also likely to be involved in AD, especially as minor risk alleles for sporadic forms of the disease. Genome-wide association studies have implicated the clusterin (*CLU*), phosphatidylinositol-binding clathrin assembly protein (*PICALM*), and complement component (3b/4b) receptor 1 (*CR1*) genes. *CLU* may play a role in synapse turnover, *PICALM* participates in clathrin-mediated endocytosis, and *CR1* may be involved in amyloid clearance through the complement pathway. *TREM2* is a gene involved with inflammation that increases the likelihood of dementia. Homozygous mutation carriers develop a frontal dementia with bone cysts (Nasu-Hakola disease), whereas heterozygotes are predisposed to the development of AD.

TREATMENT ALZHEIMER'S DISEASE

The management of AD is challenging and gratifying despite the absence of a cure or a robust pharmacologic treatment. The primary focus is on long-term amelioration of associated behavioral and neurologic problems, as well as providing caregiver support.

Building rapport with the patient, family members, and other caregivers is essential to successful management. In the early stages of AD, memory aids such as notebooks and posted daily reminders can be helpful. Family members should emphasize activities that are pleasant while curtailing those that increase stress on the patient. Kitchens, bathrooms, stairways, and bedrooms need to be made safe, and eventually patients will need to stop driving. Loss of independence and change of environment may worsen confusion, agitation, and anger. Communication and repeated calm reassurance are necessary. Caregiver "burnout" is common, often resulting in nursing home placement of the patient or new health problems for the caregiver. Respite breaks for the caregiver help to maintain a successful long-term therapeutic milieu. Use of adult day care centers can be helpful. Local and national support groups, such as the Alzheimer's Association and the Family Caregiver Alliance, are valuable resources. Internet access to these resources has become available to clinicians and families in recent years.

Donepezil (target dose, 10 mg daily), rivastigmine (target dose, 6 mg twice daily or 9.5-mg patch daily), galantamine (target dose 24 mg daily, extended-release), and memantine (target dose, 10 mg twice daily) are approved by the Food and Drug Administration (FDA) for the treatment of AD. Due to hepatotoxicity, tacrine is no longer used. Dose escalations for each of these medications must be carried out over 4–6 weeks to minimize side effects. The pharmacologic action of donepezil, rivastigmine, and galantamine is inhibition of the cholinesterases, primarily acetylcholinesterase, with a resulting increase in cerebral acetylcholine levels. Memantine appears to act by blocking overexcited *N*-methyl-D-aspartate (NMDA) glutamate receptors. Double-blind, placebo-controlled, crossover studies with cholinesterase inhibitors and memantine in moderate to severe AD have shown them to be associated with improved caregiver ratings of patients' functioning and with an apparent decreased rate of decline in cognitive test scores over periods of up to 3 years. The average patient on an anticholinesterase inhibitor maintains his or her mini-mental state examination (MMSE) score for close to a year, whereas a placebo-treated patient declines 2–3 points over the same time period. Memantine, used in conjunction with cholinesterase inhibitors or by itself, slows cognitive deterioration and decreases caregiver burden for patients with moderate to severe AD but is not approved for mild AD. Each of these compounds has only modest efficacy for AD. Cholinesterase inhibitors are relatively easy to administer, and their major side effects are gastrointestinal symptoms (nausea, diarrhea, cramps), altered sleep with unpleasant or vivid dreams, bradycardia (usually benign), and muscle cramps.