

2006 marked the 40th year of publication for *The Annals*. Throughout its history, *The Annals* has provided important contributions to the development of clinical pharmacy. In 2007, we are continuing to publish articles reflecting on the history of clinical pharmacy through the eyes of practitioners, including those pioneering clinical pharmacy, as well as those who have more recently entered the profession and a well-established specialty. In addition, we are presenting articles and editorials from the early history of *The Annals* that have given direction and shape to the practice of clinical pharmacy (see page 1499).

Alzheimer's Disease: Will Advances Made in the Past Turn the Tide?

Todd P Semla

Sixty years before the first issue of *Drug Intelligence & Clinical Pharmacy* was published, Alois Alzheimer published his account of the pathological findings of a 55-year-old woman who suffered from the disease that now bears his name. In the 60 years that transpired from Alzheimer's description of the high-density protein plaques and neurofibrillary tangles to *Drug Intelligence & Clinical Pharmacy's* first issue, Alzheimer's disease (AD) was a forgotten illness infrequently differentiated from other dementias and referred to as organic brain syndrome.

In the 1970s, some of the mystery of AD began to unravel when scientists determined that the neuropathology most often affected specific regions in the brain that regulate memory, attention, and other higher cognitive functions. Autopsy studies determined that neuronal and synaptic loss occurred early in the disease and correlated with severity as the disease progressed.

Making the diagnosis of AD was difficult and explains, in part, why AD was not originally differentiated from other causes of dementia. Attempts to improve diagnostic accuracy were approached from 3 fronts: assessment of memory and cognitive function, biomarkers, and structural and functional changes observed via neuroimaging. A

biomarker in the blood, cerebral spinal fluid (CSF), or genes would increase diagnostic accuracy and allow for the introduction of treatment options earlier in the illness. Biomarkers in the CSF that are relevant to AD include abnormal τ and amyloid peptide production. Unfortunately, those identified to date are not sensitive or specific enough to warrant routine testing.

The advances in neuroimaging have allowed researchers to go beyond correlating symptoms with pathological changes. Brain structure imaging became available in the 1970s with computed tomography (CT) and enhanced in the 1980s with the introduction of magnetic resonance imaging (MRI). CT and MRI allowed clinicians to rule out cognitive loss due to structural changes, vascular events, and tumors. While not confirming a diagnosis of AD, when combined with the results of neuropsychiatric tests, the CT and MRI increased the diagnostic accuracy to 90% or greater based on postmortem findings. Functional MRI and positron emission tomography were introduced in the 1990s; both allow the measurement of cerebral blood flow to be observed under stressed conditions.

A hypothesis formed in the 1980s focused on amyloid, the peptide deposits found in senile plaques characteristic of the AD brain. These peptides were found to be degradation products of amyloid precursor protein (APP). The gene for APP is located on chromosome 21. Individuals with Down's syndrome are known to have trisomy 21 and are prone to dementia later in life. This finding led to a se-

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ries of studies that confirmed the association of multiple mutations of *APP* with familial forms of AD.

Understanding of the genetic contribution to the development of AD continued in the 1990s with investigations of apolipoprotein E (ApoE). ApoE is found in senile plaques, vascular amyloid, and neurofibrillary tangles. There are 3 variants of the ApoE gene: *APOE2*, *APOE3*, and *APOE4*. Inheritance of the *APOE4* allele increases the risk and reduces the age of onset of late-onset AD. Individuals without an *APOE4* allele tend to have a mean age of onset of 84 years versus those with one *APOE4* allele (75 y) or 2 *APOE4* alleles (68 y). Individuals who inherit the *APOE2* variant appear to be protected from developing late-onset AD.¹

An increased accuracy in diagnosis and the ability to identify neurochemical changes that correlate with symptoms at different stages of the illness are important, but without a cure or a treatment to arrest progression of the illness, improved diagnostic accuracy is not very comforting to those afflicted or their caregivers.

Treatment

Early treatment for dementia and AD focused on the hypothesis that poor or insufficient cerebral blood flow was associated with AD, so cerebral vasodilators such as the ergot derivatives were widely prescribed. These drugs were found to be ineffective and are no longer recommended and rarely prescribed.

The “cholinergic hypothesis” arose in the 1980s, with the finding that acetylcholine was the most significantly affected neurotransmitter. Acetylcholine is critical to learning and memory function. Tacrine, an acetylcholinesterase inhibitor and the first drug indicated for the treatment of AD, became available in 1993. Tacrine’s therapeutic usefulness was short-lived due to hepatotoxicity and required monitoring of liver enzymes, a complicated dose titration schedule, and 4-times-a-day dosing. Additionally, tacrine is a substrate for the CYP3A4 and, consequently, is involved in numerous drug interactions. Prior to its approval, tacrine had a controversial course. Early clinical trials reported examples of phenomenal success (eg, patients returning to work as stockbrokers or playing golf) and resulted in great enthusiasm among AD activists and immense political pressure to approve such a promising agent despite the serious methodologic flaws in these early trials. Perhaps tacrine’s greatest contribution was in helping to raise AD’s profile in public and political forums and provide incentive for the Food and Drug Administration (FDA) to develop standards on how drugs for AD were to be evaluated.

The use of tacrine plummeted with the approval of donepezil in 1996. Donepezil, a cholinesterase inhibitor, does not have the hepatotoxicity of tacrine and does not require the same level of monitoring; it has the additional advantage of a once daily dosing schedule. Two additional

cholinesterase inhibitors were subsequently approved—rivastigmine in 2000 and galantamine in 2001—each with an additional mechanism of action besides inhibiting the enzyme acetylcholinesterase. Trials comparing donepezil, rivastigmine, and galantamine are lacking, so it is unknown whether there are differences in efficacy among them. Until recently, all of the cholinesterase inhibitors’ label indications were for mild-to-moderate AD.

Conclusions concerning the effectiveness of cholinesterase inhibitors vary. In 2006, the National Institute for Clinical Excellence in the United Kingdom updated its recommendations, concluding that the cholinesterase inhibitors are effective only for patients with moderate AD. About the same time, the FDA approved donepezil’s labeling indication to include treatment of severe AD.

Memantine, a specific noncompetitive *N*-methyl-D-aspartate receptor antagonist, received FDA approval and labeling for severe AD (Mini-Mental Status Exam score <10) in 2003. Memantine’s principal efficacy was demonstrated using instruments that measure clinician and caregiver impressions of change(s) in a patient’s activities of daily living.

The natural question about combining a cholinesterase inhibitor with memantine was addressed in one trial comparing the combination of memantine and donepezil with placebo plus donepezil in community-dwelling patients with moderate-to-severe AD.² The investigators concluded that there was a statistically significant benefit favoring the combination, although clinical significance was questionable.

The question remains as to how long a patient should continue using AD drugs when it is obvious that the disease has progressed (ie, when should they be stopped?). There is no single answer. The average time that a patient stays on a cholinesterase inhibitor is about 3 years. Whether this question will ever be answered scientifically is open to debate. It may eventually be addressed through policy, given the ever-shrinking resources and growing demand on the healthcare dollar.

Treatment of behavioral disorders or psychopathology that occurs in various stages of AD has been a long-standing problem. In the 1970s and 1980s, particularly in nursing homes and other institutionalized settings, antipsychotics, benzodiazepines, and other tranquilizing agents were widely used to treat a variety of symptoms. Publication of findings that these agents offered little in the way of effectiveness, were overprescribed, and were responsible for a number of serious adverse events led, in part, to the passage by Congress of the Omnibus Budget Reconciliation Act of 1987, commonly referred to as OBRA 87. This legislation allowed the Health Care Financing Administration (now the Centers for Medicare and Medicaid Services) to issue guidance on the appropriate indications, dose, and duration of use of psychotropic drugs in nursing homes. This guidance on unnecessary drugs (F329) was updated and expanded in 2006.

Atypical antipsychotics became the preferred agents for behavioral disorders, because their adverse effect profiles seemed to offer an advantage over conventional antipsychotics. Despite this perception, the CATIE-AD (Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease) concluded that any advantage in clinical effectiveness credited to atypical antipsychotics compared with placebo is offset by their adverse effects. Prior to the publication of the CATIE-AD, the FDA had already placed warnings in the labeling of the atypical antipsychotics regarding an increased risk for stroke and mortality in elderly patients with dementia. The increased mortality risk was later confirmed by an independent analysis. A second group of investigators reported that the mortality risk associated with conventional antipsychotics was greater than that with atypical antipsychotics in patients aged 65 years and older. These findings have limited the role of antipsychotics to treatment only for patients for whom other interventions have failed or are inappropriate given the clinical circumstances.

Future Treatment

At present, more than 70 compounds are under Phase 1, 2, or 3 investigation as treatment for AD. Several compounds are already marketed for different indications, such as the hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) and the nonsteroidal antiinflammatory drugs (NSAIDs), which have been shown in epidemiologic studies to reduce the risk of developing AD. The development of the transgenic mouse provided an animal model in which to test new compounds with mechanisms affecting amyloid degradation, production, deposition, or accumulation. Several of these agents are currently in Phase 3 trials (eg, flurbiprofen [an NSAID] and tramiprosate [an amyloid antagonist]).

Earlier this year it was reported that there are more than 5 million patients with AD living in the US. As the baby boomers quickly approach the age at which the incidence of AD increases and prevalence grows, new treatments that halt, slow, or even reverse the progression of AD, as well as better strategies that address the accompanying complications, will be welcome. The Alzheimer's Association estimates that, without advances in treatment, the prevalence of AD in the US could reach 7.7 million by the year 2030. By the time *The Annals* celebrates its 80th anniversary, as many as 16 million people could have AD. Pharmacists have an obligation to advise patients and their caregivers on the risks and benefits of treatments for AD and the accompanying complications. Given the approaching wave of patients, there are undoubtedly expanded roles and opportunities for pharmacists as researchers, educators, and clinicians to combat this devastating disease.

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References

1. Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 1993;261:921-3.
2. Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, Gergel I. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. *JAMA* 2004;291:317-24.