Introduction

Alzheimer's Disease Management

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Alzheimer's disease is a neurodegenerative disorder with enormous personal, family, and public health consequences. Affecting primarily older individuals, the disease progressively eliminates the self and robs the family of the person they cherished. Affected individuals are not able to make a meaningful contribution to society and require increasingly intense health care and personal maintenance services as the disease progresses.

Alzheimer's disease is on the rise. It doubles in frequency every 5 years after the age of 60, increasing from a prevalence of approximately 1% among 60-year-olds to 35%–45% among those 85 years of age and older.[1] The size of the aged population is increasing and will continue to increase at least through the year 2020. As the number of aged individuals increases, the number of individuals with dementia, and specifically with Alzheimer's disease, will also increase. There are currently 4 million affected individuals, with that number rising to as many as 14 million if effective interventions are not identified.[2] This special supplement to *The Journal of Clinical Psychiatry* provides an update of information pertinent to the identification, diagnosis, and treatment of Alzheimer's disease.

All medical professionals who provide specialized services to the aged, including geriatric psychiatrists, neurologists, and geriatricians, will see an increased demand for services as more elderly patients with complex neuropsychiatric, neurologic, and medical diseases are seen and evaluated. Caring for the elderly requires specialized knowledge and expertise. In addition, caring for persons with dementia inevitably entails developing a close therapeutic alliance with their family members, which also requires skills and knowledge not commonly developed in practitioners not trained specifically to treat the elderly. In this special supplement, Peter V. Rabins, M.D., M.P.H., Chair of the American Psychiatric Association task force that developed the treatment guidelines for Alzheimer's disease, provides a succinct summary and commentary regarding the role of the psychiatrist in the treatment and management of Alzheimer's disease.

Alzheimer's disease is just one of many conditions that can adversely affect memory and cognition in the elderly and accounts for approximately 70% of all dementias in the elderly.[3] Truly reversible dementias are rare, but the identification of non–Alzheimer's disease and reversible disorders is important, particularly now that Alzheimer's disease–specific treatments and disease-specific interventions for non–Alzheimer's disease dementias are available. P. Murali Doraiswamy, M.D., and his colleagues address these important issues in their contribution on early recognition of Alzheimer's disease.

The etiologies and pathophysiology of Alzheimer's disease are increasingly well understood. There is a growing consensus that the increased production or aggregation of β-amyloid is a central feature of the pathogenesis of Alzheimer's disease. Neuritic plaques are formed in the brain with concomitant cell death, and the development of neurofibril-

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lary tangles further contributes to neuronal loss. Loss of cells in regions critical to neurotransmitter synthesis such as the nucleus basalis, locus ceruleus, and raphe leads to deficiencies in acetylcholine, norepinephrine, and serotonin, respectively. Involvement of the nucleus basalis of Meynert in Alzheimer's disease leads to a deficit in the production of choline acetyltransferase and a subsequent inability to synthesize acetylcholine at synaptic endings. The deficit in acetylcholine occurs early in the course of Alzheimer's disease and contributes importantly to the behavioral and cognitive changes characteristic of the disease. The deficit in cholinergic function underlies the principal current means of treating the symptoms of Alzheimer's disease. Peter J. Whitehouse, M.D., Ph.D., one of the pioneers in research regarding cholinergic dysfunction in Alzheimer's disease, reviews the pathology of the cholinergic system.

Neuropsychiatric symptoms are common in Alzheimer's disease. During the course of the illness, patients manifest apathy, agitation, depressive symptoms, delusions, irritability, disinhibition, and purposeless motor behavior. A subset of these symptoms may be linked to the cholinergic deficiency of Alzheimer's disease and may respond to treatment with cholinesterase inhibitors. Jeffrey L. Cummings, M.D., and Donna L. Masterman, M.D., review the challenges involved in measuring the behavioral changes in Alzheimer's disease, briefly review observations suggesting that cholinergic deficiency is an important contributor to neuropsychiatric symptoms in Alzheimer's disease, and review cholinergic therapies that reduce neuropsychiatric symptoms in the disorder.

Tacrine and donepezil are the only drugs that have been approved for the treatment of cognitive symptoms in Alzheimer's disease. Tacrine represented a breakthrough agent in the treatment of Alzheimer's disease. It was the first drug approved specifically for the treatment of cognitive symptoms in Alzheimer's disease, is among the first drugs to improve cognition in any degenerative disorder, and was an example of mechanism-based cognitive pharmacotherapy that evolved in concert with a modern understanding of the cholinergic deficiency of Alzheimer's disease. Side effects, particularly elevated liver enzymes, and the need to increase the dose of drug slowly and to monitor serum enzyme levels frequently limited the widespread use of this agent. Donepezil is as efficacious as tacrine. It produces modest cognitive improvement, can be administered once daily, reaches maximum doses of 10 mg/day after 4 weeks of administration of 5 mg/day, and produces no hepatotoxicity. Gastrointestinal side effects may occur at the higher dosage level. Larry E. Tune, M.D., and Trey Sunderland, M.D., review the pharmacology of cholinesterase inhibitors and provide an updated understanding of progress in cholinomimetic therapy.

The pace of discovery regarding the basic mechanisms of Alzheimer's disease and the treatment of this complex disorder is dramatic. Recent discovery of mutations that cause Alzheimer's disease as well as genetic risk factors for the disease has reformed our ideas of how the disease affects brain function. In addition, there have been breakthroughs regarding neuroprotective therapy in Alzheimer's disease with vitamin E and selegiline. The combination of neuroprotective therapy that delays the progress of Alzheimer's disease and cholinomimetic therapy that improves the symptoms of Alzheimer's disease is a regimen that promises to improve the quality of life of Alzheimer's disease victims and their caregivers. Further dramatic gains can be anticipated.

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