

Managing Alzheimer's Disease in Managed Care

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Summary

Alzheimer's disease affects a significant number of Americans and the numbers will only continue to grow as the population ages. The management of this disease includes cognitive enhancers and agents to manage behavior and other symptoms of the disease. Because knowledge of the neuropathology continues to expand, potential disease modifying agents are on the horizon.

Key Points

- Alzheimer's disease accounts for the majority of all cases of dementia.
- It is a costly and difficult disease to manage.
- The neuropathology of this disease includes amyloid plaques, neurofibrillary tangles, and brain atrophy.
- Current treatment is primarily targeted at the symptom clusters of depression, mania, psychosis, agitation, and neurovegetation rather than cognitive deficits.
- Medications can be used to modestly improve cognition, but outcomes have been disappointing.
- Many agents that have the potential to be disease modifiers are currently under study.

ALZHEIMER'S DISEASE (AD) ACCOUNTS FOR 70 percent of all cases of dementia in Americans age 71 and over.¹ Vascular dementia accounts for 17 percent of cases of dementia, and other diseases and conditions, including Parkinson's disease, Lewy body disease, frontotemporal dementia, and normal pressure hydrocephalus account for the remaining 13 percent.¹ The frequency of AD doubles every five years from 1 percent in the 60 to 65 year old group to 35 to 45 percent in the 85 and above group. It is estimated that 5.2 million Americans are affected by AD, and in 2040, more than 9 million will be.² The estimated cost of care is greater than 100 billion yearly.²

The National Institute of Neurological, Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) and American Psychiatric Association (Diagnostic and Statistical Manual of Mental Disorders [DSM]), have diagnostic criteria for AD. The diagnostic accuracy using these criteria is a sensitivity of 81 to 93 percent and specificity of 48 to 70 percent. Alzheimer's disease is a diagnosis of exclusion. Definitive diagnosis can only be made with a brain biopsy. The diagnosis is typically made clinically based on symptoms and cognitive assessment.

To meet the diagnostic criteria, the patient must have both cognitive and functional impairment, and other potential causes are excluded. The warning signs for AD include memory loss, difficulties with familiar tasks, language difficulty, disorientation, decreased judgment, decreased abstract thinking, misplacing objects, mood or behavior changes, personality changes, and loss of initiative.

The greatest risk factor for AD is advancing age.² A genetic factor in AD that develops after age 65 is APOE-e4. APOE-e4 is one of three common forms of the APOE gene, which provides the blueprint for a protein that carries cholesterol in the bloodstream. Some postulated risk factors for developing the disease include family history, hypercholesterolemia, hyper-homocystenemia, diabetes, closed head trauma, psychological stress, hypertension, low education level, and smoking. Non-genetic risk factors account for 50 percent of clinical variance.

Information about the neuropathology of AD is continually evolving. Chronic inflammation appears to be involved in the pathogenesis of many age-related diseases, including Alzheimer's disease (AD).³ Neuropathological hallmarks are neuritic plaques and neurofibrillary tangles that result in brain atrophy (Exhibit 1). Neuritic plaques result from the ac-

Exhibit 1: Neuropathology of AD

- Accumulation of abnormally phosphorylated tau proteins in neurons (tangles)
- Accumulation of 42 amino acid amyloid fragments (Aβ42) in the neuropil (plaques)
- Vascular changes of blood vessels, small strokes and neuronal death

cumulation of several proteins and an inflammatory reaction around deposits of amyloid. Neurofibrillary tangles result from intracellular deposition of hyperphosphorylated degenerate filaments, which result from aggregations of the microtubular protein tau. The plaques and tangles of AD are heavily infiltrated with activated glial cells and inflammatory factors, such as cytokines and chemokines. As cellular changes progress in the brain of the AD patient, neurons are lost in the hippocampus, entorhinal cortex, and associated areas of the neocortex.⁴

Diagnostic evaluation can include neuropsychological testing and neuroimaging. Neuropsychological testing is most useful in the evaluation of mildly impaired patients and patients with early onset dementia. Testing will characterize the extent of impairment, the type of dementia, and establish baseline cognitive function. Neuroimaging can be either magnetic resonance imaging (MRI) or positron emission tomography (PET) scan. An MRI is recommended as part of the initial evaluation. Scans specific for amyloid for use in early diagnosis are under development. PET scans contribute to diagnostic specificity and have been recently approved for reimbursement by Medicare to differentiate between AD and frontotemporal dementia. Imaging is most valuable in subacute onset (less than one year), early onset patients, and patients with vascular risk factors or focal lesion findings.

Numerous clinical scales are commonly used to identify cognitive decline. These include the Mini Mental Status Examination (MMSE), Neuropsychiatric Inventory (NPI), and Alzheimer's Disease Assessment Scale Cognitive Subscale (ADAS-Cog). The ADAS-Cog scale is the most reliable of these scales and gives a comprehensive view of a patient's cognitive deficits.

Treatments for cognitive and functional losses can be done with cholinesterase inhibitors (tacrine [Cognex[®]], donepezil [Aricept[®]], rivastigmine [Exelon[®]], galantamine [Razadyne[®]]) and glutamate-receptor antagonists (memantine [Namenda[®]]). The outcomes with the cholinesterase inhibitors are somewhat disappointing. The cognitive improvement is minimal with these agents. In a meta-analy-

sis of the cholinesterase inhibitors, the authors found that it is difficult to quantify benefits from the evidence available in the literature.⁵ Although the medications may result in statistically significant improvements in cognitive tests, these improvements may not translate into improved daily function of the patient within their current environment. Memantine is mostly useful for behavioral improvements in moderate to severe disease but gives little functional improvement.

Many other agents have been studied. There is no evidence that vitamin E improves function or cognition and it may in fact contribute to higher morbidity and mortality. Nonsteroidal anti-inflammatories, hormone replacement therapy, desferrioxamine, melatonin and ginkgo have little or no evidence of improvement on morbidity, and may be more harmful due to side effects.

AD unfortunately is not just memory impairment. The majority of the interventions with AD patients target the symptom clusters of agitation, psychosis, depression, mania, and neurovegetation (loss of appetite, sleep impairment) rather than the cognition issues. Ninety percent of AD patients develop behavior disturbances.

Although frequently used to treat agitation, none of the currently available antipsychotic medications are approved for the treatment of agitation or psychosis in AD. Because of a higher rate of adverse effects, conventional antipsychotics are no longer the first line choice. Second generation agents such as risperidone, olanzapine, and quetiapine are effective alternatives, but the adverse effects can be problematic in the AD patient. There is some evidence that other psychotropics such as the selective serotonin reuptake inhibitors, trazodone, and anticonvulsants are more appropriate and safer in the initial management of agitation than antipsychotics.

Many patients with AD will require treatment for depression. The selective serotonin reuptake inhibitors are equally effective as and better tolerated than tricyclic antidepressants and selective norepinephrine uptake inhibitors in head to head trials. Electroconvulsive therapy (ECT) is occasionally used and is supported by several larger, prospective studies and one small retrospective chart review.

Sleep disturbances are another common issue in AD patients. Available data does not suggest a specific course of action. Small studies have examined bright light therapy, sleep hygiene, and improving physical activity during day times with limited positive results. Few pharmacological agents have been studied in this population and none with positive results.

The future of the treatment of AD is the development of disease modifying agents based on the neuro-

pathology. Wide arrays of anti-amyloid and neuroprotective therapeutic approaches are under investigation. Interventions that reduce amyloid production, limit aggregation, or increase removal might block the cascade of events comprising AD pathogenesis. There are monoclonal antibodies under development to create a complex with the β -amyloid peptide of 42 amino acids in length (A₄₂), which is thought to play a role in the beginning of the AD process, so it can be cleared by the body. Agents targeted at reducing the consequences of amyloid production and deposition (tau hyperphosphorylation, oxidation, excitotoxicity, and inflammation) are other disease-modifying strategies under study.⁷ Potentially neuroprotective and restorative treatments such as neurotrophins, neurotrophic factor enhancers, and stem cell-related approaches also are under investigation.⁶

Conclusion

Alzheimer's disease is costly to manage both from an individual and a society point of view. Although medications are available to help improve cognition, the results have been disappointing. The majority of the therapeutic interventions in AD are currently tar-

geted at behavior disturbances. The future will hopefully bring new therapies that target the underlying neuropathology of this devastating disease. **JMCM**

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