

Practical Management of Alzheimer’s Dementia

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ABSTRACT

Alzheimer’s disease (AD) is the most common cause of dementia in the elderly. There currently is no effective treatment that delays the onset or slows the progression of AD. Significant advances in neuroscience, genetics and molecular biology over the past 25 years have changed the way we think about AD. This article reviews the literature on diagnosis and treatment of AD so that primary care physicians can manage this complex disease.

KEYWORDS: Alzheimer’s disease, dementia, dementia medications

INTRODUCTION

Every 68 seconds, a person in the United States is diagnosed with Alzheimer’s dementia (AD). By 2050, this rate is expected to double. An estimated 5.2 million Americans currently have Alzheimer’s dementia, and it is predicted that by 2050 that number will approach 13.8 million. AD has emerged as a serious public health concern, placing an immense burden on patients, families, the community, and health care resources. AD accounts for approximately 60% of all cases of dementia in the developed world. The focus of this review will be on practical management of primary care patients with probable AD.

A common misperception is that AD is a normal or expected occurrence of aging, and that it is part of the typical trajectory of age-related cognitive decline. Healthy aging has been found to be associated with generally stable performance on measures of cognitive functioning, such as the Mini-Mental Status Examination (MMSE). However, as individuals live to advanced ages (over the age of 80), it is more challenging to differentiate between the subtle changes of aging and those caused by early dementia. Unfortunately, family members and caregivers may fail to recognize or be in denial about the significance of their loved one’s cognitive decline, leading to delayed diagnosis and late treatment of dementia when behavioral problems become problematic or unmanageable. Pathologic changes that underlie AD begin to accumulate decades before cognitive and behavioral changes emerge. Markers of brain health versus cognitive decline may be identifiable earlier in life. In the seminal Nun Study published in JAMA, approximately 80% of nuns whose early-life writing samples were measured as lacking in complexity went on to develop Alzheimer’s disease in old age as opposed to 10% of those whose writing was rated as more complex.

Nearly a hundred years ago, post-mortem analysis of human AD brains provided the first clues to the pathophysiology of AD and potential interventions. Senile plaques composed of extracellular deposits of amyloid-β (Aβ) and neurofibrillary tangles formed by intracellular aggregation of phosphorylated tau protein were found in regions of cortex that serve memory and other cognition functions. Based upon demonstrated deficiencies in choline acetyltransferase, the enzyme responsible for the synthesis of acetylcholine, the “cholinergic hypothesis” of AD was proposed. The more recent “amyloid cascade” hypothesis of AD proposes that Aβ, specifically the least soluble forms Aβ 40 and 42, have a central role in AD. Aβ 40 and Aβ 42 are cleaved from amyloid precursor protein (APP) by beta and gamma secretase enzymes known as presenilin 1 and 2. Innovative studies over the last decade have evaluated enzyme inhibitors and immunotherapies that interfere with Aβ production, inhibit Aβ aggregation, and enhance Aβ clearance. Evidence for the reduction of amyloid and related AD pathology by these agents in transgenic mouse models has been very encouraging. Unfortunately, phase III human trials have been disappointing, including a recent trial of bapineuzemab, a human anti-Aβ monoclonal antibody, that failed to show benefit. These and other basic science mechanisms operative in AD and novel treatment approaches are reviewed elsewhere. Therapies targeting amyloid-based pathology have dominated recent drug development. Trials of tau-based therapies are newly underway.

Mutations in three genes – APP, presenilin 1 and presenilin 2 – all predispose to early onset (autosomal dominant) AD. In Trisomy 21, where there is duplication of the APP gene on chromosome 21, symptoms of AD may begin in the third or fourth decade of life. The E4 allele of the apolipoprotein E (APOE) gene has been identified as a major risk factor for late-onset AD. No specific environmental toxin has been consistently associated with AD.

DIAGNOSIS

AD typically progresses along a continuum from normal aging to amnestic, mild cognitive impairment (a-MCI) and
finally frank AD. Patients with a-MCI present with memory deficits that are greater than would be expected based on age and education; however, functional abilities remain intact and behavioral problems are rare. Amnestic-MCI progresses to AD at a rate of 5-15% per year. There are no FDA-approved treatments for a-MCI. In a 3-year placebo controlled trial, Peterson et al evaluated vitamin E 2000IU and donepezil 10mg for the treatment of MCI. Donepezil reduced the rate of conversion to AD at 12 months, but neither agent separated from placebo at three years. Nonetheless, this stage presents an opportunity for closer follow-up, modification of pre-morbid risk factors such as smoking, diabetes, and depression, and education and empowerment of the patient and family. Early diagnosis provides the patient and family an opportunity to anticipate problems and plan for the future (e.g., advanced health care wishes, wills) while the patient is still capable of making medical decisions.

A thorough history should be taken, preferably with a knowledgeable spouse or other family member present, in order to determine the time of onset and the course of cognitive decline. Recommended diagnostic tools include the Mini-Mental Status Examination (MMSE), the Clinical Dementia Rating Scale (CDR), and formal neuropsychological testing. Although neuropsychological testing remains the gold-standard for diagnosis, it is expensive and not available to all patients. No laboratory or imaging tests are sufficient to diagnose AD, although they may rule out reversible causes of dementia such as Vitamin B-12 deficiency, thyroid disease, electrolyte abnormalities, and certain structural lesions.

CT and MR imaging of AD typically demonstrate cerebral volume loss, especially in the temporal lobe structures such as the hippocampus. Brain single-photon emission tomography (SPECT) and fluorodeoxyglucose positron emission tomography (FDG-PET) studies in AD typically demonstrate, respectively, reduced cerebral blood flow and hypometabolism in posterior temporo-parietal regions. New biomarkers, such as cerebrospinal fluid measures of amyloid-β and phosphorylated tau have demonstrated impressive sensitivity and specificity in diagnosis of AD, but neither is utilized in routine practice or universally supported by published guidelines. In 2012, a PET scan that selectively binds amyloid-β plaques was approved by the FDA for AD testing. Unfortunately, this test is still not covered by the Centers for Medicare or Medicaid Services or any private insurers. This test should be reserved for patients with early-onset cognitive dysfunction (usually defined as 65 years or less in age), atypical clinical presentations or course of illness, or other unexplained cognitive decline.

### PHARMACOLOGIC TREATMENT OF COGNITIVE SYMPTOMS

There are no available therapies that can stop or reverse the course of AD. The pharmacologic agents approved for the treatment of AD remain limited and include the three cholinesterase inhibitors (ChEI) donepezil (Aricept™), rivastigmine (Exelon™), and galantamine (Razadyne™) and a single N-methyl-d-aspartate receptor antagonist, memantine (Namenda™). The ChEI are approved for all three stages of AD, from mild to severe, and serve primarily to reduce the rate of cognitive decline. Memantine is approved for moderate to severe AD. Studies suggest no benefit from memantine in early disease. The American Psychiatric Association (APA) recommends that all patients with mild to moderate AD be offered treatment with a ChEI. Consistent with recent FDA approval of ChEIs for severe AD, the APA suggests

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Indication</th>
<th>Available Formulations</th>
<th>Start dose</th>
<th>Target dose</th>
<th>Renal dosing</th>
<th>Hepatic dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>Aricept™</td>
<td>Mild-mod AD: 5,10mg Mod-severe AD: 10mg, 23mg</td>
<td>5, 10mg tabs 5, 10mg ODT 23mg tabs</td>
<td>5mg QD</td>
<td>10mg QD</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Galantamine</td>
<td>Razadyne™</td>
<td>Mild to moderate AD</td>
<td>4, 8, 12mg tabs 4mg/ml sol’n 8,16,24 mg caps</td>
<td>4mg BID</td>
<td>8mg QD</td>
<td>16mg max</td>
<td>16mg max</td>
</tr>
<tr>
<td></td>
<td>Razadyne ER™</td>
<td>Mild to moderate AD</td>
<td>4,8,12mg tabs 4mg/ml sol’n</td>
<td>4mg BID</td>
<td>8mg QD</td>
<td>16mg max</td>
<td>16mg max</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>Exelon™</td>
<td>Mild to moderate AD</td>
<td>1.5,3,4.5, 6mg caps 2mg/ml sol’n</td>
<td>1.5mg BID</td>
<td>6mg BID</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td></td>
<td>Exelon Patch™</td>
<td>Mild to severe AD</td>
<td>4.6,9,13,3.3mg patch</td>
<td>1.5mg BID</td>
<td>6mg BID</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Memantine</td>
<td>Namenda™</td>
<td>Moderate to severe AD</td>
<td>5, 10mg tabs</td>
<td>5mg QD</td>
<td>10mg BID</td>
<td>5mg BID max</td>
<td>No change</td>
</tr>
<tr>
<td></td>
<td>Namenda XR™</td>
<td>Moderate to severe AD</td>
<td>7,14,21,28mg tabs</td>
<td>7mg QD</td>
<td>28mg QD</td>
<td>No change</td>
<td>No change</td>
</tr>
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</table>
Evidence suggests that ChEI treatment for at least six months delays the need for nursing home admission. There are reports of marked improvement in cognitive and neuropsychiatric status with initiation of cholinesterase inhibitors in cases of dementia with Lewy bodies (DLB), perhaps consistent with pathologic observations of more significant loss of cholinergic neurons in DLB. Rivastigmine is FDA-approved for PD dementia, though its clinical benefits are modest.

There are no specific recommendations regarding the discontinuation of ChEIs or memantine. Some reports suggest subacute cognitive deterioration when these agents are abruptly stopped. Typical practice in the US includes early treatment with a ChEI and addition of memantine when disease progresses to the moderate-to-severe stage. Howard et al compared continued treatment with donepezil alone to addition of memantine to donepezil and memantine alone (after donepezil discontinuation) in moderate-to-severe AD. Continued treatment with donepezil alone and memantine alone were associated with similar cognitive benefit compared to placebo. In contrast to earlier studies, the combination of donepezil and memantine provided no additional benefit compared to continued donepezil alone.

The most common adverse effects of ChEIs include nightmares, weight loss, gastrointestinal bleeding, symptomatic bradycardia, and syncope. Rivastigmine is available as a once-daily transdermal formulation, Exelon patch™, that may improve gastrointestinal tolerability. Memantine is typically dosed at 10 mg twice daily. Namenda™ is now available in a 20 mg XR formulation that is intended for once daily dosing. Adverse effects of memantine include fatigue, dizziness, constipation, headache and occasionally worsening of AD-related behavioral problems.

**Summary of SGAs used in dementia-related psychosis and agitation**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Available Formulations</th>
<th>Start dose</th>
<th>Typical dose</th>
<th>Common side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>Abilify™</td>
<td>2,5,10,15,20,30mg tablets, 10,15mg ODT, 1mg/ml oral sol’n, 9.75mg single dose injection</td>
<td>2mg</td>
<td>5-10mg</td>
<td>Somnolence, EPS, fatigue, nausea, akathisia. Least likely to cause QT prolongation</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Zyprexa™</td>
<td>2.5,5,10,15,20,30mg tablets, 10mg,15mg ODT, 10mg single dose injection</td>
<td>2.5mg</td>
<td>5-10mg</td>
<td>Postural hypotension, constipation, weight gain, dizziness. Doses &gt;10mg/day may cause anticholinergic side effects</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Seroquel™</td>
<td>25,50,100,200,300,400mg tablets</td>
<td>12.5mg</td>
<td>25-50mg</td>
<td>Somnolence, dizziness, nausea, fatigue. Least likely to cause parkinsonism</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Risperdal™</td>
<td>0.25,0.5,1,2,3,4mg tablets, 0.5,1,2,3,4mg ODT, 1mg/ml oral sol’n</td>
<td>0.5mg</td>
<td>1-2mg</td>
<td>Parkinsonism, akathisia, dystonia, tremor, sedation</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Geodon™</td>
<td>20,40,60,80mg tablets, 20mg/ml single dose injection</td>
<td>20mg</td>
<td>40-60mg</td>
<td>Somnolence, EPS, dizziness. May cause significant QT prolongation</td>
</tr>
</tbody>
</table>

**NEUROPSYCHIATRIC-BEHAVIORAL SYMPTOMS AND THEIR PHARMACOLOGIC TREATMENT**

Behavioral symptoms in dementia are common and include anxiety, apathy, depression, irritability, agitation, aggression, delusions, and hallucinations. The occurrence of these symptoms varies depending on the cause and stage of dementia. Apathy, irritability, and depression are common in early dementia while agitation, delusions, and hallucinations tend to occur in the later stages of the disease. Aggressive behaviors can be verbal and physical. It is often difficult to distinguish between psychotic and non-psychotic forms of aggression.

Depression is often a harbinger of dementia in patients with no prior psychiatric history of a mood disorder. Indeed, late-onset depression may represent a presenting behavioral syndrome of an overarching neurodegenerative disorder.
such as AD or vascular dementia. The evidence base for pharmacologic treatment of depression in dementia patients is limited. SSRIs are considered first line agents for treating depression in dementia patients. Sertraline and citalopram have minimal pharmacokinetic interactions and are particularly indicated in elderly patients who are often on multiple medications. SSRIs have a broad range of additional effects including attenuation of anxiety, irritability, hostility, and obsessions and compulsions. Compared to placebo, citalopram (Celexa™) at 30mg daily significantly reduced agitation and caregiver distress in patients with probable AD. Mild decline in cognitive performance and mild prolongation of the QTC interval (mean 18 msec) were noted in the citalopram-treated group.

Tricyclic antidepressants (TCAs) are associated with numerous adverse effects including cardiac arrhythmias, urinary retention, constipation, delirium, and overdose risk and should be used with caution in dementia patients. The anti-cholinergic effects of TCAs may be additive to the cholinergic loss of AD and exacerbate cognitive dysfunction. Mirtazapine (Remeron™) may be particularly effective in addressing complaints of poor appetite and insomnia that are common in depressed AD patients. There is some evidence that ChEIs can improve mood and other non-cognitive behavioral symptoms in AD. For this reason, a trial of a ChEI targeting both cognitive and neuropsychiatric symptoms in behaviorally dysregulated AD patients makes sense before the addition of a primary psychotropic agent. A trial of stimulants, such as methylphenidate, may be warranted in those patients with prominent apathy or those who partially respond to SSRIs.

Neuropsychiatric symptoms of agitation, aggression, and psychosis are associated with global decline in patient function and have a very negative effect upon caregiver and family quality of life. These symptoms typically evolve over months, but when they emerge abruptly, it is important to evaluate for a diagnosis of delirium. Delirium is particularly common in demented patients. Medications with anticholinergic properties, benzodiazepines, and narcotics are often implicated as causes of delirium atop a baseline dementia. Uncontrolled pain, constipation, malnutrition, dehydration, and infection, particularly urinary tract infections, may also precipitate delirium. It is imperative that these conditions are addressed before assuming that agitation is due primarily to underlying AD or disease progression.

Although there are currently no FDA-approved agents for the treatment of dementia-related agitation and psychosis, second-generation antipsychotics (SGA) have been utilized to treat these symptoms. A recent study of Medicare beneficiaries in nursing homes found that 27% were prescribed antipsychotics. The use of these medications in dementia management remains controversial, especially in light of the 2005 “black box” warning. Schneider et al found a significant increase in cerebrovascular events, especially with risperidone, when using SGAs for the treatment of agitation and psychosis in demented nursing home patients. Additional analysis of the data documented an increase in all-cause mortality in dementia patients treated with SGAs compared to placebo. Antipsychotic use in dementia has declined since the issuance of this warning, particularly in nursing homes.

There is a limited evidence base regarding the effectiveness of SGAs for the treatment of dementia-related agitation and psychosis. The CATIE-AD trial examined the effectiveness of the three most commonly used SGAs – quetiapine, risperidone, and olanzapine. All of these agents, but particularly olanzapine, were associated with significant weight gain. Sedation and confusion were common side effects of all three medications. Olanzapine and risperidone were associated with Parkinsonism and other extra-pyramidal symptoms (EPS). Quetiapine was relatively free of EPS side effects. The CATIE-AD trial concluded that the adverse effects of these medications may outweigh any benefit they provide for the treatment of behavioral symptoms in dementia patients. Given their “black box” warning, SGAs are likely best reserved for patients with prominent psychosis and/or agitation who have not improved with non-pharmacologic treatments, cholinesterase inhibitors, or SSRIs. If ineffective, these agents should be discontinued rather than adding a second drug. Even when clinically beneficial, noting the evolving course of the underlying dementia, SGAs should be periodically tapered or discontinued to reassess their indication. Typical suggested starting doses of these drugs include risperidone 0.5mg, quetiapine 25mg, or olanzapine 2.5mg, all dosed once daily at bedtime. Given the limited evidence base and the warning regarding the use of these agents in dementia, careful informed consent discussion with patient and family about the risks and benefits of treatment versus the risks of untreated agitation should precede the initiation of any antipsychotic medication.

Behaviors such as wandering, yelling, and stubbornness can be particularly difficult to manage, often precipitate nursing home placement, and frequently persist in the institutional care setting. It is important that medication not be used as a “chemical restraint” to control these relatively benign behaviors. A multidisciplinary approach with input from properly trained nursing staff, social workers, and family can be helpful in designing a non-pharmacologic plan to help manage these behaviors. Novel approaches such as aromatherapy are being increasingly utilized in long-term care with success.

Psychosocial interventions include cognitive and social stimulation such as adult day care participation, behavior-oriented therapies, and caregiver support. Since activities of daily living (ADLs) such as self-care, personal hygiene, and dressing tend to worsen with progression of AD, patients with advanced AD require a greater level of caretaker commitment. Management of medical decisions and financial affairs, and cessation of driving often emerge as problems for caregivers. It is important to provide adequate caregiver...
support, as “caregiver burden” is associated with high rates of AD patient nursing home placement. Caregivers often benefit from referral to Alzheimer’s Association support groups. When at-home care is no longer viable, families face the difficult decision of placing their loved one in an assisted-living facility or nursing home. The onset of behavioral problems such as aggression and delusions, rather than frank cognitive decline proper, often hastens this transition to long-term care.

References

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