

# OREGON DUR BOARD NEWSLETTER<sup>©</sup>

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## Nonpharmacologic and Pharmacologic Interventions in Alzheimer's Disease

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Alzheimer's disease (AD) is the most common cause of dementia. Dementia itself is not a specific disease, but a clinical syndrome of declining intellectual function, and by definition, associated with impaired recent memory.<sup>1</sup> AD is usually the cause of dementia in seniors, either by itself, or as a co-morbid condition with stroke (e.g. vascular dementia) or parkinsonism (e.g. dementia with Lewy-bodies). Currently, an estimated 4 million Americans have AD. By the year 2050, it is projected that 14 million Americans will have AD.<sup>2</sup> The diagnosis of the disease can be reliably made using standardized diagnostic criteria and assessment tools.<sup>3,4</sup>

The progression of AD varies from person to person, but it is always progressive, usually starting with memory impairment, and leading to severe disability and death 5 to 15 years after diagnosis. At best, with current treatments, cognitive function can show modest improvement for up to one year. However, the progression of decline may be slowed and patients may benefit for longer periods with delays in functional decline, emergence of psychiatric symptoms and even nursing home placement.

In addition to cognitive decline, behavioral disturbances are also prevalent in AD. Problems such as depression, agitation, psychosis, aggression and sleep disturbances affect most, if not all, patients at some point during the course of the disease.<sup>5</sup> As these symptoms can result in decreased functioning and increased burden to caregivers, great attention has been focused on their treatment. This article will review the use and concerns that are often associated with various treatment alternatives used in the care of patients with AD.

Prior to the initiation of treatment of AD and its related symptoms, underlying medical and/or drug-induced causes of dementia-like symptoms should be evaluated. In up to 20% of cases, a dementia may be reversible.<sup>6,7</sup> For this reason, a thorough work-up and differential diagnosis is critical. Elderly patients with urinary tract or kidney infections display symptoms that are very similar to the symptoms of dementia (e.g. mental status changes, confusion). An accurate and thorough medication history is equally important. Overmedication and polypharmacy are common problems in elderly patients. This can cause additional adverse effects and drug interactions for a population of patients whose metabolism may already be impaired. Use of validated instruments such as the Mini-Mental State Exam (MMSE),<sup>8</sup> improves early detection of dementia, which in turn leads to earlier treatment and improved outcomes.<sup>9</sup>

An important first step to the introduction of any treatment modality for AD patients is to determine the goal of that particular therapy. Reasonable expectations should be given to either a pharmacologic or non-pharmacologic approach. Primary goals to include in the decision-making process include: how will this treatment improve the patient's quality of life and maximize their functional performance, what effect will it have on cognition, mood and behavior, do the side effects outweigh the benefits, when are results expected, and when should the treatment be stopped?

### Non-pharmacologic Alternatives

Although non-pharmacologic approaches to the treatment of dementia have no proven benefit for cognitive function, they can improve some

behavioral symptoms, as well as morale, comfort and quality of life.<sup>10</sup> Non-pharmacologic interventions that have been studied will be discussed.

Continued engagement in cognitively stimulating activities has been found to impact neural structure in older adults, and may delay the onset of dementia.<sup>11</sup> However, once dementia has developed, the story may be different. Non-pharmacologic methods attempted for the improvement of cognitive enhancement in patients with AD include reality training and memory enhancement. In the demented patient, these activities are associated with both benefit and risk.<sup>12</sup> The risks associated with these methods include increased patient frustration and depression and the benefit of restoring cognitive dysfunction is often transient. Guidelines established by the American Geriatric Society, the Alzheimer's Association and the American Association of Geriatric Psychiatry state the risks outweigh the benefit from these activities.<sup>7</sup> That is not to say that involvement in activities will not improve morale and quality of life, but these activities should be matched to individual capacity given the severity of their dementia.

Care must be taken to ensure that behavioral symptoms in dementia patients are not due to pain, discomfort (e.g. constipation, medication side effects, etc.), or occult illness (e.g. UTI, metabolic or endocrine disorders, etc.). The non-pharmacologic treatment of behavioral disturbances such as agitation and aggression associated with dementia is intuitively recommended and supported by clinical literature. Environmental factors (e.g. confusing, noisy surroundings) and interpersonal factors (e.g. arguing with a confused or delusional patient, rushing the patient, not using appropriately respectful or clear language) are considered primary triggers of behavior problems.<sup>12</sup> Identifying and eliminating triggers of problem behaviors is key. Evidence from controlled trials demonstrates that caregiver education and social support can significantly reduce general patient behavior problems, decrease depression and delay institutionalization.<sup>10,12</sup>

### Pharmacologic Approaches

Cholinesterase inhibitors (CI's) including tacrine (Cognex®), donepezil (Aricept®), rivastigmine (Exelon®), and galantamine (Reminyl®) are approved by the FDA for the treatment of mild to moderate dementia (defined by a score of  $\geq 10$  on the Mini-Mental State Examination). Tacrine is no longer recommended now that the other agents are available. As a class, CI's appear to have a positive effect, although modest, on cognitive symptoms compared to placebo. These medications may keep patients at or near baseline for up to one year.<sup>10, 13-15</sup> Recent data make it clear that AD patients do better over time on these medications, in terms of delayed decline in function and nursing home placement,<sup>16</sup> and many experts recommend their continued use even in the face of progressive decline. Use of these medications require careful titration in order to avoid the intolerance of adverse effects such as diarrhea, nausea, vomiting, weight loss and anorexia. To prevent an antagonistic effect, anticholinergic drugs (e.g. diphenhydramine, tolterodine, tricyclic antidepressants, etc.) should be avoided in patients who are receiving cholinesterase inhibitors. Documentation of improvement (or decline) with cholinesterase inhibitors is generally done with standardized instruments, such as the MMSE, which, on average,

generally shows a rate of decline of 3 points per year in AD patients. For a more thorough review of CI's and their efficacy data, the reader is referred to the following citations: 8, 9, and 10.

A new medication for the treatment of moderate or severe AD, memantine (Namenda®), will be introduced this winter. This drug belongs to a new class of medications, the NMDA antagonists.<sup>18,19</sup> A more thorough review will follow in a future issue of the newsletter.

Alternative therapies used for the treatment of cognitive symptoms or disease progression of AD include ginkgo biloba and vitamin E. The evidence for ginkgo biloba either for improved function or slowing progression remains unconvincing. A large, controlled clinical trial is underway. The use of high doses of vitamin E (2000 IU daily) to delay certain outcomes associated with disease progression, is supported by a multicenter controlled clinical trial.<sup>17</sup> Evidence does not support the use of either of these agents for the sole treatment of Alzheimer's dementia.<sup>10,18-19</sup> Other agents that may aid in the prevention or delayed onset of AD include the consumption of omega-3 fatty acids, reduced intake of saturated or trans-unsaturated fats, nonsteroidal anti-inflammatory agents and the use of lipid-lowering agents.<sup>10,18-22</sup>

The behavioral or neuropsychiatric symptoms of AD range from delusions and hallucinations to depression, apathy and agitation/aggression. While CI's have a limited ability to modify behavioral symptoms,<sup>10,23</sup> practitioners typically rely on medications that modify dopamine and serotonergic pathways.

Atypical antipsychotics are effective treatments for delusions, hallucinations, and agitation/aggression associated with AD. Guidelines established by the American Academy of Neurology, American Association for Geriatric Psychiatry, the Alzheimer's Association, and the American Geriatrics Society all recommend the use of antipsychotics (preferably atypical agents due to improved tolerance) for the treatment of agitation or psychosis in patients with dementia where environmental manipulation fails.<sup>6-7,10</sup> Research has focused primarily on the use of risperidone in this patient population with a limited number of studies alternatively using olanzapine, quetiapine and the anticonvulsant divalproex.<sup>10,23-24</sup>

Recently, a fear of increased rates of cerebrovascular adverse events (CAEs) has been associated with the use of risperidone in dementia patients. Such concern led the Food and Drug Administration (FDA) to request Janssen Pharmaceutica to change the Risperdal® package labeling from "Risperdal has not been shown to be safe and effective for the treatment of patients with dementia-related psychosis" to "Risperdal is not approved for the treatment of patients with dementia-related psychosis." A review of the available literature, however, suggests that the true incidence of CAEs needs to be further investigated. Findings that make the accessible studies inconclusive include: the majority of patients reporting a CAE had at least one or more risk factors for CAEs, many had a prior history of a stroke or TIA, and the largest and only study conducted in the United States noted a comparable rate of CAEs between risperidone and placebo.<sup>25-26</sup> While risperidone should be used with caution in patients with a known history of cardiovascular disease or other CAE risk factors, risperidone remains a first-line atypical antipsychotic for the treatment of psychosis associated with dementia.

## Conclusion

Pharmacotherapy is often the primary choice of treatment in patients with Alzheimer's dementia. Unfortunately, outcomes that are expected from dementia medications are frequently not achieved, and adverse effects that are not expected often occur. Nonpharmacologic alternatives are safe, moderately effective and free from drug interactions. With this in mind, nonpharmacologic therapies should be considered first when possible.

*Reviewed by Harleen Singh, Pharm.D., OSU College of Pharmacy*

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