Current and Future Directions in the Treatment of Alzheimer Disease

K. Farncik, MD, FRCP(C), Psychiatrist, Division of Geriatric Psychiatry, University of Toronto, Toronto, ON.

M. Perszyko, PsyD, CPsych, Division of Geriatric Psychiatry, University of Toronto, Toronto, ON.

Significant work has been done in the treatment of Alzheimer disease (AD) since cholinesterase inhibitors (CI) were approved in Canada five years ago. This has led to a better understanding of these drugs in terms of their different properties, therapeutic efficacy and indications for switching, and their use has since been extended to the treatment of AD with vascular pathology. Other treatments for AD, such as estrogens and non-steroidal anti-inflammatory drugs (NSAIDs), have also been evaluated further, while newer treatments, including a vaccine for AD, are currently in development. Although research outcomes have not always been positive, a significant effort is being made to achieve greater impact in a disease that is becoming ever more prevalent.

Cholinesterase Inhibitors

Currently, the CIs are the only class of drugs that have been proven efficacious in the symptomatic treatment of AD. There are two types of CIs: acetyl and butyryl. Butyrylcholinesterase levels in the brain increase with the progression of AD, whereas levels of the enzyme acetylcholinesterase decrease. The CIs approved in Canada that have demonstrated efficacy as well as a favourable safety profile are donepezil, rivastigmine and galantamine. Rivastigmine inhibits both enzymes while donepezil and galantamine are acetylcholinesterase inhibitors. Galantamine also has a second mechanism of action, the allosteric modulation of nicotinic receptors, the true clinical significance of which has yet to be resolved. These CIs have all been evaluated through randomized controlled trials of patients with mild to moderate, to moderately severe AD. Data from placebo-controlled trials indicates that these drugs have a positive impact on cognition, activities of daily living (ADLs), behavioural aspects, global functioning and caregiver burden for up to six months, with open label data confirming that benefits may be maintained for at least up to three years.

The treatment of vascular dementia and mixed dementia (a combination of AD and vascular dementia) with CIs is currently being examined, and so far studies indicate that these patients benefit from treatment with cholinesterase inhibitors. The rationale behind these findings is that vascular dementia is also associated with cholinergic deficits. Furthermore, it may be of significance that cholinesterase inhibitors have been shown to increase cerebral blood flow.

The decision of which CI to prescribe initially is influenced by a number of factors. Donepezil is given once daily and is the simplest to administer, while both rivastigmine and galantamine require twice daily dosing and titration. In terms of side effects during treatment initiation, rivastigmine has been associated with a greater degree of nausea and vomiting than donepezil and galantamine, although this has largely been attributed to excessively rapid titration used in clinical trials. A dose increase every four weeks is currently recommended for rivastigmine therapy. There are also differences between the CIs in maintenance side effects. For example, unlike galantamine, both donepezil and rivastigmine are associated with sleep problems. Donepezil and galantamine are both metabolized by cytochrome P450 liver enzymes, which can potentially lead to interactions in cases of polypharmacy. Whether there are significant differences in efficacy between the drugs is still unclear. Although limited comparison data are currently available, the completion of ongoing and unbiased studies is necessary before more accurate conclusions can be drawn.

CIs appear to have a positive symptomatic effect in 40–50% of AD patients, although the definition of response has been controversial. One definition was that of a four-point improvement on the Alzheimer’s Disease Assessment Scale-cognitive subscale (ADAS-Cog) over six months. However, many believe that maintenance of baseline levels, and therefore stabilization, signifies improvement.

Switching to another CI may be indicated if it is felt that the first drug is not efficacious or if side effects are an issue. A panel of experts have offered recommendations for switching between CIs, yet further research will likely modify these suggestions. A washout period between CIs is required only if persisting side effects are present, and one week typically is sufficient. Otherwise, a second CI can be started immediately upon discontinuation to minimize loss of existing therapeutic benefit. Abrupt cessation of treatment with acetylcholinesterase inhibitors can lead to cognitive decline.

The second CI should be titrated based on the standard protocol, with efficacy and tolerability monitored monthly for the first three months. In one study, it was noted that 30% of patients who were not able to tolerate donepezil tolerated rivastigmine after they were switched due to side effects, and 25% of patients for whom donepezil was ineffective improved with rivastigmine.

It is important to note that CIs, as well as other pharmacological treatments, are one component of an overall
Alzheimer Disease

treatment approach that includes patient and caregiver education, evaluation of competency, monitoring for caregiver burnout and ongoing assessment and treatment of associated symptomatology, such as depression and agitation.  

Antioxidants: Vitamin E

Oxidative mechanisms are considered a factor in the etiology of AD. The neuroprotective effect of vitamin E in AD has been documented in a study in which vitamin E as well as selegiline delayed the progression of AD, institutionalization and loss of ADLs. Observational studies also have shown that dietary vitamin E may help to reduce the risk of developing AD, although vitamin E supplements may not have the same effect. The significance of the source of vitamin E remains unclear, as another study found that vitamin E from food or supplements was associated with less cognitive decline with age.

The minimum dose of vitamin E required for therapeutic efficacy is still controversial, although 2000IU is generally well tolerated. Vitamin E supplementation may be associated with gastrointestinal side effects at higher doses and also is contraindicated in the presence of abnormal blood coagulation. Further clinical trials of vitamin E in AD patients are currently being sponsored by the National Institute of Aging.

Anti-inflammatory Agents

Inflammatory processes in the brain, which have been identified in AD patients, are thought to contribute to nerve degeneration and neuronal loss. Although some studies have found little or no association between NSAID use and AD, this may be due to inaccurate documentation of drug exposure. A recent study, for instance, demonstrated a beneficial effect of NSAID use in AD, in that the risk of developing the illness appeared lowered in a group of subjects who were older than 55 and not demented at baseline. The in’t Veld study examined the use of 16 NSAIDs (of which diclofenac, ibuprofen and naproxen were the most widely used) in nearly 7,000 patients using pharmacy records rather than patient reports. Pharmacy records were felt to be more accurate given that some patients interviewed in previous studies were cognitively impaired. Results of this study point to a reduced risk of AD in subjects who had taken an NSAID. With regard to specific treatment, a six-month double-blind, placebo-controlled study of mild to moderate AD patients found that 100 to 150mg/day of indomethacin had a neuroprotective effect in AD. A trial with prednisone, however, has been inconsistent with NSAID findings. In the multicentre trial of 138 individuals with mild to moderate AD, conducted by the Alzheimer’s Disease Cooperative Study, prednisone was not found to slow the rate of cognitive decline. This may be because the dose used was too low, or because other deleterious effects of prednisone nullified the anti-inflammatory effect.

Given the toxicity and limited tolerability of NSAIDs which were associated with a 40-50% dropout rate in clinical trials of AD, COX-2 inhibitors are being investigated as an alternative. COX-2 may have a very significant role in degenerative processes such as AD, with COX-2 expression correlated with disease stage and amyloid plaque pathology. Whether selective COX-2 inhibition is advantageous in neuroprotection is unclear. A 12-month trial involving 349 patients receiving either rofecoxib, naproxen or placebo is currently underway in order to address this issue.

Estrogens

Properties of estrogen, such as modulation of the cholinergic system and neuroprotection, have been thought to have potential significance in AD. A number of prospective and case-controlled studies have concluded that estrogen use in postmenopausal women appears to delay the onset, and decrease the risk, of developing AD, but randomized clinical trials are needed to confirm these findings. More recently, randomized, double-blind placebo-controlled trials of estrogen in women with mild to moderate AD have determined that estrogen replacement therapy for up to one year did not improve global, cognitive or functional outcomes, nor did it slow deterioration. Although some evidence supports a preventative role for estrogen, emerging evidence of associated side effects raises the issue of whether benefit outweighs the risks, such that estrogen is not recommended for the prevention or treatment of AD at this time.

Memantine

Memantine, an NMDA receptor antagonist, has been shown to be effective in the treatment of moderate to moderately severe AD. Memantine is a neuroprotective agent that reduces the influx of calcium caused by an increased sensitivity to glutamate or increased glutamate levels which occur in neurodegenerative disorders. The drug has been approved in the European Union for the treatment of AD, while trials are ongoing in North America with a submission made for regulatory approval. Of note is that calcium channel blockers are also being evaluated as neuroprotective agents in AD through their effect on intracellular calcium levels.

Treatments in Development

Statins

Statins are a class of drug that lowers low-density lipoprotein (LDL) cholesterol. Elevated cholesterol has been associated with an increased risk of developing AD and may affect amyloid-beta (Aβ) peptide production. Approved statins include atorvastatin, fluvastatin, pravastatin and lovastatin. While research has shown an association between statin use and a decreased prevalence of AD, these studies are not randomized clinical trials and further evaluation is necessary. In a study by Green involving over 900 patients with AD and over 1,600 non-demented relatives, statin use was found to reduce the risk of developing AD by 39%. Edland followed 722 individuals for up to 14 years and found that those who used statins did not develop AD while 3% of those who never used statins did. He concluded that his results were not statistically significant, citing an indication bias such that individuals who use statins may be healthier.
Alzheimer Disease

and/or better educated than non-users. In contrast, Rockwood et al.\textsuperscript{37} adjusted for education and health status and found no indication bias impacting on the results that lipid-lowering agents were associated with a lower risk of AD. However, although there is evidence that reduced serum cholesterol levels appear to slow the pathogenesis of AD, no recommendation can be made regarding the use of statins in the treatment AD. Randomized clinical trials are necessary to establish whether statin use can prove effective in AD, and the National Institute on Aging began such a study in the Autumn of 2002.

**Alzheimer Disease Vaccine**

Neuropathology and deterioration in AD are associated with an accumulation of Aβ peptide, either through an excess production of the peptide or an inability to clear it effectively. It has been hypothesized therefore that inhibiting Aβ peptide production or increasing clearance would decrease pathology.\textsuperscript{38} Immunization with the peptide is believed to cause antibodies to bind to and facilitate clearance of the peptide from the brain. Studies using transgenic mice showed a decrease in amyloid deposition and improvement in memory following immunization.\textsuperscript{39}

**Human trials** began in 2000 by Elan Pharmaceuticals, Inc. The treatment was found to be safe in Phase 1 testing, and some patients reportedly had an immune response to the peptide. However, early in 2002, the company reported that Phase 2A trials were being suspended following the occurrence of inflammation in the central nervous system in four patients. At that point, 360 mild to moderate AD patients had received the trial vaccine.\textsuperscript{40} The company has not released any current information of the status of the vaccine.

---

### Established and Developing Treatments for Alzheimer Disease (AD)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mechanism of Action</th>
<th>Comments</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>Acetylcholinesterase inhibitor</td>
<td>Indicated for Tx* of AD</td>
<td>Approved in Canada for Tx of mild to moderate AD</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>Acetylcholinesterase and butyrylcholinesterase inhibitor</td>
<td>Indicated for Tx of AD (dual mechanism)</td>
<td>Approved in Canada for Tx of mild to moderate AD</td>
</tr>
<tr>
<td>Galantamine</td>
<td>Acetylcholinesterase inhibitor with nicotinic receptor modulation</td>
<td>Indicated for Tx of AD (dual mechanism)</td>
<td>Approved in Canada for Tx of mild to moderate AD</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Antioxidant (neuroprotective)</td>
<td>Probably beneficial at higher doses</td>
<td>Available without prescription</td>
</tr>
<tr>
<td>Estrogens</td>
<td>Multiple potential mechanisms</td>
<td>Not beneficial in AD Possible role in prevention</td>
<td>Available for hormone replacement therapy</td>
</tr>
<tr>
<td>Memantine</td>
<td>NMDA antagonist</td>
<td>Indicated for Tx in more severe AD</td>
<td>Not approved in Canada</td>
</tr>
<tr>
<td>Statins</td>
<td>Reduce low-density lipoprotein cholesterol Association of cholesterol levels and AD</td>
<td>Insufficient data in AD</td>
<td>Approved for lowering cholesterol</td>
</tr>
<tr>
<td>Vaccine</td>
<td>Decrease production and increase clearance of amyloid beta</td>
<td>Problematic side effects</td>
<td>Research stage</td>
</tr>
<tr>
<td>Leteprinim potassium</td>
<td>Neurotrophic/ neuroprotective</td>
<td>Insufficient efficacy for Tx</td>
<td>Research stage</td>
</tr>
<tr>
<td>Calcium channel antagonists</td>
<td>Neuroprotective</td>
<td>Insufficient data in AD</td>
<td>Research stage</td>
</tr>
<tr>
<td>Alzhemed</td>
<td>Blocks amyloid deposition</td>
<td>Insufficient data</td>
<td>Research stage</td>
</tr>
</tbody>
</table>

*Tx: Treatment
Alzhemed

Neurochem Inc. is developing a disease-modifying drug for AD, called Alzhemed,31 that is a sulfonated molecule that interferes with the formation and deposition of amyloid in the AD brain. In studies using transgenic mice, a significant reduction of amyloid was noted. The drug was also noted to significantly decrease soluble Aβ in the brain and plasma. Alzhemed is expected to “inhibit the formation and the deposition of amyloid fibrils in the brains of AD patients”.41

In Phase 1 testing, Alzhemed was shown to be safe and well tolerated in 86 subjects: 74 healthy young adults and 12 elderly adults. The most frequent adverse events were nausea, vomiting, dizziness and headache. Phase 2 testing is being planned to assess the safety and efficacy of Alzhemed in 450 mild to moderate AD patients.

Neotrofin™

Neotrofin™ (leteprinim potassium) is a neurotrophic and neuroprotective agent that has been under development for a number of years. The active ingredient in letetprinim appears to cross the blood-brain barrier, and activates genes that produce nerve growth factors, proteins that regulate cell maintenance and repair. Recent Phase 2 data, however, have not demonstrated sufficient efficacy for potential approval as a treatment for AD. Future trials in which the dose is modified may still be considered.42

Summary

Efforts are continuing to improve treatment outcomes for individuals with AD. At this time, CIs are the only drugs that significantly impact on outcome. Ongoing research, in conjunction with clinical experience, has better defined the utilization of these drugs. In terms of other treatments, vitamin E has demonstrated a potential benefit, and may also have a role in prevention; however, the appropriate therapeutic dose has yet to be established. Estrogens are not an efficacious treatment but may still have a role in prevention, although given emerging safety data their use cannot be recommended at this time.

NSAIDs demonstrate treatment efficacy and potential in prevention, although they are associated with significant tolerability and safety issues. Results of studies with COX-2 inhibitors will therefore be important. Data from studies of some of the newer agents, including the AD vaccine and neurotrophic agents such as letetprinim potassium, have been disappointing. However, other drugs such as statins and Alzhemed are currently being evaluated in the hope that they can achieve a greater disease-modifying effect than that achieved with existing treatments. ◆

Dr. K. Farcnik has conducted clinical trials for Hoffmann LaRoche, Neurotherapeutics Inc., N ovaris, Janssen-O rtho, Pfizer and Sandoz. He has lectured for N ovaris and Janssen-O rtho and has done advisory work for Novartis and Pfizer.

M. Persky has declared no competing financial interests.

References


www.geriatricsandaging.ca


