A Decade of Drug Therapies: A Review

Medications currently in use by clinicians to treat patients with Alzheimer’s disease (AD) do not alter the disease’s course, but rather provide symptomatic relief by stabilizing the patient’s function, cognition and behavior, and delaying their decline. Though pharmacologic treatments to treat AD have evolved over the past 10 years, physicians are still waiting for a new therapy that will treat the disease at its earliest stages.

By Marie-Pierre Thibodeau, MD; and Fadi Massoud, MD

Alzheimer’s disease (AD) is the most common form of dementia and neurodegenerative disease in aging adults. It is estimated that more than 35 million people will be affected by dementia worldwide in 2010, equaling more than one new case every seven seconds.1 The 2009 World Alzheimer Report estimated that the global prevalence of dementia will almost double every 20 years, with an estimated 65.7 million people diagnosed by 2030 and 115.4 million by 2050.1 Currently, more than 500,000 Canadians have been diagnosed with dementia, which represents one in 11 Canadians older than 65 years of age, and approximately four in 11 older than 85 years of age. As the population ages—the first wave of baby boomers will turn 65 in 2011—the proportion of people affected by dementia will increase dramatically.

Significant costs and burden on the Canadian healthcare system will also continue to rise. The yearly cost of dementia in Canada was estimated at $15 billion in 2008 and will reach $153 billion by 2038 if nothing changes.2 Moreover, for dementia alone, the number of family caregiving hours is expected to rise more than threefold, increasing from approximately 231 million hours in 2008 to 756 million hours in 2038. The physical and psychological toll on family caregivers is significant: 40% to 75% of caregivers are diagnosed with a psychological illness, and 15% to 32% are depressed.3

Researchers have tried to address the issues mentioned above by searching for ways to modify the progression of AD. The past ten years have led to the development of medications that alleviate AD symptoms, but physicians are still waiting for a molecule that will alter the disease’s course by tackling it at its earliest stages. In 2010, patients and physicians can realistically expect that the future will bring us such disease-modifying medications.

The following article reviews the current recommendations regarding the pharmacologic treatment of AD, and provides critical discussion of the efficacy and tolerability of ChEIs and N-methyl-D-aspartic acid (NMDA) antagonists. Recently developed drugs that have failed or are currently being studied are also discussed.

Disease Mechanisms
Before discussing the available treatments, it is important to understand the mechanisms of the disease, which are central to the currently available therapeutic approaches.

The most widely accepted pathophysiologic mechanism of AD is the amyloid cascade. The mismetabo-
lism of the amyloid precursor protein (APP) by ß- and gamma-secretases lead to the aggregation of Aß42, an insoluble fragment that deposits in plaques (Figure 1).

The formation of these amyloid plaques further instigates pathologic events, including:

- The formation of neurofibrillary tangles (NFTs) from hyperphosphorylation of the tau protein;
- an inflammatory response;
- death of tangle-bearing neurons;
- disruption of synaptic connections (leading to a reduction in neurotransmitters, especially acetylcholine);
- oxidation;
- death of neurons with neurofibrillary tangles; and
- clinical symptoms of dementia.

This hypothesis remains controversial, however, and emerging evidence shows that many other mechanisms may be involved, including the theory that the central mechanism is in fact hyperphosphorylation of the tau protein. More recent data has suggested the importance of vascular disease in the pathology of AD.

**Cholinesterase Inhibitors (ChEIs)**

The medications currently available (Table 1) do not affect the underlying pathophysiologic process of the disease, rather its consequence: loss of acetylcholine. Before the development of currently utilized ChEIs, researchers studied acetylcholine precursors and cholinergic agonists. Most trials failed due to the lack of benefits or intolerable side effects.

**Tacrine** was the first ChEI to be commercialized in 1993 and was only approved for use in Canada under a special access program. It was quickly taken off the market due to its poor bioavailability (four doses daily) and hepatotoxicity. Since then, three other medications have been approved for the treatment of AD, described below.

**Donepezil**, a reversible and selective acetylcholinesterase inhibitor (AChEI), is the first of the second generation of ChEIs and the most studied. It is widely bioavailable and metabolized by the P450 cytochromes 2D6 and 3A4, and is associated with a risk of drug interactions. Donepezil has a long plasma elimination half-life of 70 hours, allowing it to be given once daily (od). The recommended dose is 10 mg daily and the lowest effective dose is 5 mg daily. The U.S. Food and Drug Administration has recently approved its use up to 23 mg.

**Rivastigmine** pseudoirreversibly inhibits acetylcholine and butyrylcholine esterases, but the clinical significance of this dual action remains unclear. The drug has a lower interaction risk because it is metabolized by esterases and excreted in urine. With a short half-life, rivastigmine has to be given twice daily (bid) orally, but a daily patch has been available since 2007. The minimal effective dose is 3 mg bid orally (maximal dose: 6 mg bid), whereas the patch’s effective minimal and maximal doses are 10 cm².

**Galantamine** is a selective and reversible AChEI that also acts as an allosteric modulator on nicotinic receptors, but the added benefit of this mechanism remains unclear. The drug’s elimination half-life is six hours, but an extended-release formulation is available, permitting a daily dose. Galantamine’s minimal effective dose is 16 mg daily and the maximal dose, 24 mg daily. As for donepezil, it is metabolized by the P450 cytochromes 3A4 and 2D6 increasing the potential risk of drug interactions.

**NMDA Antagonist**

The rationale behind the use of memantine is the glutamatergic excitotoxicity theory, which stipulates that an abnormal and sustained increase in glutamate may lead to nerve-cell damage. Memantine, an NMDA receptor, is a low-to-moderate uncompetitive antagonist that blocks glutamate binding to its receptor, and can be given od or in two divided doses. This drug is metabolized by the kidney, thus caution must be taken when prescribed to patients with renal failure. The drug’s minimal therapeutic dose is 10 mg daily, and the maximal dose, 20 mg daily.

**Goals of Treatment**

When beginning ChEI or memantine therapy, the goals of treatment should be clearly established with the patient and their family. ChEIs and memantine are not miracle drugs, they do not alter the course of the disease. The treatment options available mainly stabilize the patient and delay his/her decline, though some patients may experience a transient symptomatic improvement. Clinicians must set realistic expectations that take into account the modest benefits that can be seen in various areas, discussed later in this article.
The Efficacy of ChEIs

ChEIs have been measured for their effects on cognition, function, global impact, behavior and caregiver burden. Most studies of this class of drug have been 24 weeks long. Few head-to-head trials have been performed and none have clearly shown a significant difference in terms of efficacy between the studied molecules (donepezil vs. rivastigmine was the only double-blind trial), although there were some differences regarding the side-effect profile (rivastigmine’s was larger than donepezil’s). Most of these studies suffered from significant methodological limitations, complicating their interpretation even further.

Cognitive benefits are usually evaluated in trials by measuring variations on the AD Assessment Scale-cognitive subscale (ADAS-Cog; a scale from 0 to 70 points) or the Mini-mental State Examination (MMSE). In a review of 13 studies, the global effect of ChEIs was -2.7 points on the ADAS-Cog, with a clinically meaningful change estimated at four points. Further, individual trials have had an effect that varied between -1.4 and -3.9 points. The maximal improvement is usually observed at three months with cognition returning to baseline (i.e., before treatment was initiated) at 12 months.

Functional effects are measured using scales, such as the AD Cooperative Study Activities of Daily Living Inventory (ADCS-ADL; 0 to 78 points) or the Disability Assessment for Dementia (DAD; 0% to 100%) scale. Unlike cognition, function is more likely to stabilize than to improve with ChEI treatment, but, typically, lost capacities are not regained. Studies examining donepezil, rivastigmine and galantamine over a period of 24 weeks showed significant benefits when compared to placebo according to the most recent individual meta-analyses.

Behavioral benefits using the Neuropsychiatric Inventory (NPI; up to 12 points for 10 domains [total 120 points]) were noted in patients taking galantamine and donepezil when compared to placebo during trials lasting six months (-2.44 points). In these studies, ChEIs usually prevented the emergence of new behaviors and helped attenuate already existing symptoms. A study by Holmes et al demonstrated that behavioral symptoms recurred in patients with AD when their ChEI treatment was suspended (i.e., decline in NPI). In addition, decreased caregiver burden has been associated with subjects taking donepezil and galantamine due to a reduction in time spent caring for these patients. Rivastigmine’s behavioral benefits have mainly been seen in patients with Lewy body dementia and Parkinson’s disease.

Global effect is measured using the Clinician Interview Based Impression of Change (CIBIC-plus; domain graded from 1 to 7, 7 indicating a worsening). When considered as a group, ChEIs show statistically significant benefits over placebo at six months. The number needed to treat (NNT) is estimated at 12 for minimal improvement and seven for stabilization or better. The number needed to harm (NNH) is 12 for one additional patient to experience an adverse effect. Other benefits from physician focus

groups have also been reported in terms of increased attention, initiative, social interactions and involvement in domestic activities.\textsuperscript{13}

Most trials studying memantine have been conducted in patients with moderate-to-severe dementia, and this drug is recommended for these patients.\textsuperscript{14,15} However, recent studies suggest that this drug may have added benefits if combined to ChEIs in milder forms of AD. In a few studies with patients with moderate-to-severe AD, the results showed statistically significant benefits in cognition, function and global impression with memantine used alone or with a ChEI, at six months.\textsuperscript{16,17}

In conclusion, ChEIs and memantine demonstrated modest, but real effects in terms of cognition, behavior and global effect at six months.

Two 12-month randomized donepezil trials have shown sustained benefits in terms of function and global assessment.\textsuperscript{18,19} Extension trials have looked at long-term effects and shown some benefits. Despite their observational nature and lack of true placebo, these studies suggest that ChEI benefits may extend beyond six to 12 months and provide physicians with the rationale for continuing therapy beyond this period of time.

Other molecules that have been studied recently and have not shown convincing or sustained benefits include vitamin E, Omega-3 acids, statins, ginkgo biloba, non-steroidal anti-inflammatory drugs (NSAIDs) and Chinese moss.

Even if there are medications available to offer these patients, it is important to keep in mind the key role of non-pharmacologic interventions, including home safety assessments, caregiver well-being, exercise, and maintaining social and intellectual activities. Prevention should also be addressed in the general approach to dementia, but it exceeds the scope of this article. We will simply emphasize the importance of optimally controlling vascular risk factors.

**ChEI Side Effects**

The most common side effects associated with ChEIs are gastrointestinal related, such as anorexia, nausea and loose stools. Other side effects include leg cramps, nightmares, bradycardia, syncope and incontinence. A Cochrane review has shown that these adverse events were significantly more common with ChEIs than with placebo (72\% vs. 57\%).\textsuperscript{7,12} However, it is well known to clinicians that starting ChEI therapy at a low dose and slowly increasing it decreases the

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**Table 1**

<table>
<thead>
<tr>
<th></th>
<th>Donepezil</th>
<th>Galantamine</th>
<th>Rivastigmine</th>
<th>Memantine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of Action</strong></td>
<td>AChEI</td>
<td>* AChEI *</td>
<td>* AChEI *</td>
<td>NMDA antagonist</td>
</tr>
<tr>
<td></td>
<td></td>
<td>* allostERIC *</td>
<td>* butyrylcholinesterase *</td>
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<td></td>
<td></td>
<td>modulator of inhibitor</td>
<td>inhibitor</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Cytochrome P450, 2D6, 3A4</td>
<td>Cytochrome P450 2D6, 3A4</td>
<td>Urine esterase</td>
<td>Renal</td>
</tr>
<tr>
<td><strong>Elimination Half-life</strong></td>
<td>70 hours</td>
<td>7 to 8 hours</td>
<td>1 to 2 hours</td>
<td>60 to 80 hours</td>
</tr>
<tr>
<td><strong>Daily Dosage</strong></td>
<td>5 mg, 10 mg</td>
<td>8 mg, 16 mg, 24mg</td>
<td>* 3 mg, 6 mg, 9 mg or 12 mg (2 divided oral doses) *</td>
<td>5 mg, 10 mg, 15 mg, 20 mg (1 or 2 doses)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>* 5 cm\textsuperscript{2} and 10 cm\textsuperscript{2} (transdermal patch) *</td>
<td></td>
</tr>
<tr>
<td><strong>Minimal Effective Daily Dose</strong></td>
<td>5 mg</td>
<td>16 mg</td>
<td>* 6 mg orally (2 divided doses) *</td>
<td>10 mg (1 or 2 doses)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>* 10 cm\textsuperscript{2} (transdermal patch) *</td>
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</table>

The incidence of these side effects. The prevalence of side effects is estimated at 20% when the drug is slowly titrated, and side effects are most often mild and transient in nature.7

The only absolute contraindication to ChEI therapy is hypersensitivity to one of its components. When considering treatment options for patients with heart conduction diseases (other than right bundle branch block), physicians should be cautious as these patients were excluded from clinical trials. A safe and reasonable approach before starting ChEI treatment is for patients to have an electrocardiogram, especially in individuals with a history of heart disease. As previously mentioned, adjustments to memantine doses are necessary in patients with chronic renal failure.

**Initiation and Discontinuation of Treatment**

All patients diagnosed with dementia should be offered a trial of treatment. The choice of agent should be based on adverse-effect profiles, ease of use, familiarity and the patient’s beliefs.20 According to *The Third Canadian Consensus on Diagnosis and Treatment of Dementia*, treatment should be discontinued in the following circumstances:

- the patient experiences intolerable side effects;
- comorbidities make continued use of the agent either unacceptably risky or futile (e.g., terminally ill); or
- the patient’s dementia progresses to a stage where there is no significant benefit from continued therapy.20

Upon discontinuation of treatment, patients should be carefully monitored for evidence of a significant decline in their cognitive status, functional abilities, or the development/worsening of behavioral challenges. If the patient presents with these challenges, the attending physician should consider reintroducing the medication.

**Monitoring response.** Every patient’s response to therapy is unique—their expectations should be realistic and their responses monitored according to these goals. A structured clinical evaluation is usually recommended at three months after initiation as this corresponds to the timing of maximal effect observed in clinical trials. Patients can be monitored every six to 12 months thereafter.

**Managing disease progression.** When a patient’s symptoms continue to deteriorate despite ChEI treatment, the clinician has several options. First, they must make sure that the maximal effective and tolerated dose is being used. If this is the case and there is still no benefit, the patients can be switched to another ChEI. Even though these drugs belong to the same general class, the differences in the individual characteristics of each make it reasonable to use this approach. However, such a switch is not recommended in individuals who show loss of benefit several years after initiation of treatment as this is most likely due to progression of the disease. There is no rationale to adding another ChEI to the patient’s current treatment as doing so usually increases side effects with little additional benefit. If the patient’s disease is moderate-to-severe, memantine can be added in combination to ChEI or taken alone. If there is a sudden decline in the patient’s status, delirium should always be ruled out before attributing the decline to disease progression.

**Cost effectiveness.** Few cost-effectiveness studies have been conducted and usually show no benefit or disadvantage of donepezil for any healthcare resource. Prediction models have also been developed, but it is difficult to draw pragmatic conclusions that can be readily translated into clinical practice.21

**Disease-modifying Treatments**

As previously mentioned, currently available agents do not alter the disease process, but rather alleviate the patient’s symptoms. Research is now focused on developing disease-modifying therapies that act either on the amyloid or tau pathology through different therapeutic approaches.

**Anti-amyloid treatments.** Optimizing clearance of Aβ42 with immunologic therapy is being studied with passive and active immunization. After cases of severe side effects were associated with the use of active immunization (several cases of meningoencephalitis), a
second-generation vaccine was developed and is now being studied.\(^2^2\) Other immunologic studies for which the results of phase III trials are pending include passive immunization with infusion of monoclonal antibodies against amyloid (e.g., bapineuzumab and intravenous immunoglobulin).\(^2^3\)

The decrease of Aß production and aggregation are other mechanisms that can help target amyloid pathology. The medical community had a lot of hope for tramiprosate, a molecule that inhibits amyloid aggregation, but the molecule failed to show efficacy in a phase III trial.

Further, studies using a gamma-secretase inhibitor have been disappointing due to this agent’s non-selectivity and complete inhibition. This drug is also often associated with serious side effects due to interference with lymphocyte differentiation that alters the structure of intestinal goblet cells.

Tarenflurbil was the first agent in a class of drugs that modulated gamma-secretase activity. A large 18-month phase III trial showed no benefit of treatment and the development program was discontinued.\(^2^4\) In August this year, Eli Lilly and Company announced that it was stopping its trials of a gamma-secretase inhibitor due to adverse effects present in results from a Phase III trial. A plausible explanation for this failure is that oral administration produced insufficient brain concentrations to reduce α to a meaningful extent.

β-secretase inhibitors are not expected to incur the same safety risk as γ-secretase inhibitors and are considered to be the most promising target of all, but such medications have not yet been developed.

Anti-tau treatments. One of the components of methylthioninium chloride, a tau phosphorylation inhibitor, is a form of methylene blue—this has an effect on tau aggregation and mitochondrial function, which is likely to play an important role in treating AD.\(^2^5\) A phase II trial of this drug in 2008 showed very promising results, reporting that it slowed the progression of AD by 81% over a year,\(^2^6\) and we are eagerly waiting for phase III trials. Other anti-tau agents studied in pilot trials include lithium and valproate. These trials were either negative or associated with prohibitive side effects. Paclitaxel has also not yet shown efficacy.

Other mechanisms. Animal studies showing potential beneficial effects of latrepirdine, an antihistaminic medication with mitochondrial stabilizing properties, were first shown in Russian research in 2000. In 2008, results from a phase II clinical trial published in The Lancet were also very promising.\(^2^7\) However, in March 2010, Pfizer and Medivation announced the disappointing results of two phase III studies. In the CONNECTION trial, latrepirdine did not meet its co-primary or secondary efficacy endpoints compared to placebo. Co-primary endpoints were measures of cognition (ADAS-COG) and global function (CIBC-plus). A possible explanation for this failure to demonstrate efficacy was a lack of decline in the placebo group. Latrepirdine was well tolerated in the CONNECTION study and in a separate phase III safety and tolerability study, confirming the drug’s tolerability when used alone or in combination with approved AD medications. Latrepirdine is being studied in four other ongoing randomized, double-blind, placebo-controlled phase III studies.

Conclusions
Research in the past 10 years has rapidly evolved and currently allows physicians to offer symptomatic treatment to patients using ChEIs and/or memantine therapy. More recently, growing knowledge of the pathophysiology of AD has helped develop new targets for treatment. Despite the disappointing results of the recent phase III trials, we can still hope that future research will discover novel disease-modifying agents in the next few years. The continuous progress in the field of the diagnosis of AD allows us to believe that we may soon be able to diagnose AD at a very early stage, thus treating the disease before the accumulation of pathologic protein. One day, we will look back at the past ten years as the beginning of a new era for AD patients. Until then, research must go on.

All patients diagnosed with dementia should be offered a trial of treatment. The choice of agent should be based on adverse-effect profiles, ease of use, familiarity and the patient’s beliefs.\(^2^0\)
References:


