

# Progress update: Pharmacological treatment of Alzheimer's disease

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**Abstract:** A number of drugs have been approved for the treatment of Alzheimer's disease (AD) and a larger number are being studied as possible therapies. The current mainstays of the pharmacotherapy of AD are the cholinesterase inhibitors (donepezil, galantamine, rivastigmine) and memantine. They collectively have acceptable tolerability and proven but modest efficacy. The agents being studied include dietary supplements (eg, vitamin E), herbal preparations (eg, Ginkgo biloba), medications approved for other indications (eg, HMG-CoA reductase enzyme inhibitors) and research drugs. In this review we discuss in detail the approved agents and review a number of the unapproved therapies that are currently available to the practitioner. While our era offers much more in the way of therapeutics for AD, it is clear that more work still needs to be done.

**Keywords:** Alzheimer's disease, drug therapy, cholinesterase inhibitors

## Introduction

Alzheimer's disease (AD) is the commonest type of dementia encountered in older patients. While there are a variety of effective non-pharmacological approaches to this condition, in this review we will limit ourselves to the pharmacotherapy of AD. We will not deal with those agents used primarily for the behavioral and psychological symptoms of dementia (eg, antidepressants, antipsychotics). We'll start with agents approved for the indication of AD in Canada. Then, we'll discuss select agents available to physicians that have been (or are being) studied for AD. This will include dietary supplements, herbal preparations and prescribed medications where their use for a dementia would be considered "off-label" (ie, the practice of prescribing drugs for a purpose outside the scope of the drug's approved indication). We will mention briefly drugs only available within research studies at the current time.

## Agents approved for the treatment of Alzheimer's disease

### Cholinesterase inhibitors

The first cholinesterase inhibitor (ChEI) approved for AD was tacrine in 1993. This class of drugs is the most widely prescribed one for the mild to moderate stages of AD. Donepezil, galantamine and rivastigmine are the ChEIs that are now most commonly used. These drugs are felt to correct the cholinergic deficit seen with AD where there is the loss of acetylcholine producing neurons in the brain. The ChEIs increase acetylcholine concentrations by blocking the action of the enzyme cholinesterase, which catalyzes the hydrolysis of acetylcholine into choline and acetic acid. While donepezil, galantamine and rivastigmine all inhibit the enzyme acetylcholinesterase, galantamine (by binding to an allosteric site on nicotinic receptors) and rivastigmine (through inhibition of butyrylcholinesterase) have additional mechanisms of action. Their significance remains uncertain.

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Cochrane reviews (Birks 2000; Loy 2005; Birks 2006; Birks and Harvey 2006), meta-analyses (Lanctôt et al 2003; Ritchie et al 2004; Rockwood 2004; Whitehead et al 2004), and qualitative systematic reviews (Clegg et al 2002; Wolfson et al 2002; Thompson et al 2004; Kadoszkiewicz et al 2005) have all examined the available data on the ChEIs. Cognitive, global, functional, behavioral and other outcomes have been measured in the randomized controlled trials (RCTs) of these agents.

The cognitive measure most often used in AD studies has been the Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-Cog). It includes eleven items (ie, spoken language, comprehension of spoken language, recall of test instructions, word finding, following commands, naming objects, construction – drawings, ideational praxis, orientation, word recall and word recognition) and is scored out of 70 (higher scores indicate greater impairment). The Mini-Mental State Examination (MMSE) is often performed as a secondary cognitive outcome measure. Global assessments of subjects in the dementia drug studies have often been done using scales such as the Clinicians' Interview-Based Impression of Change with Caregiver Input (CIBIC-Plus). A systematic baseline assessment is done that examines the domains ordinarily considered part of the clinical evaluation of a patient with dementia. At subsequent visits subjects are graded on a 1–7 scale relative to this baseline assessment. One indicates marked improvement, seven marked worsening and four no change. Basic and/or instrumental activities of daily living have been evaluated using a variety of scales such as the Alzheimer Disease Cooperative Study ADL Inventory (ADCS-ADL). This is a caregiver rated questionnaire of 23 items. Scores can range from 0 to 78. Higher scores indicate better functioning. When examined behavior has most often been assessed by the Neuropsychiatric Inventory (NPI). This evaluates the research subject for common neuropsychiatric disturbances found with AD (ie, delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behavior, night-time behavior disturbances, and appetite and eating abnormalities). Data on frequency, severity and caregiver distress are collected. The total possible score is 144 with higher scores indicating more problems.

The ChEIs have shown consistent, albeit modest, benefits of treatment on cognition and global clinical state. After treatment for approximately 6 months the advantage seen with a ChEI compared to placebo on the 70-point ADAS-Cog scale was 2.66 points (95% CI 3.02 to 2.31,  $p < 0.00001$ ;

data from 10 studies) and 1.37 points (95% CI 1.13 to 1.61,  $p < 0.00001$ ; data from 9 studies) on the 30-point MMSE (Birks 2006). On the CIBIC-Plus scale significantly more of those treated with a ChEI compared to placebo showed an improvement (428/1755 or 24% vs 277/1647 or 17%, OR 1.56, 95% CI 1.32 to 1.85,  $p < 0.00001$ ) (Birks 2006). Improved functional and behavioral outcomes have also been seen with active treatment (Trinh et al 2003; Birks 2006). Less decline (compared to placebo) rather than an actual improvement in functional abilities has been the typical finding. For example, in a 5-month RCT of galantamine subjects who received 16 mg/ day of galantamine showed on average a 0.7 point decline from baseline on the 78-point ADCS-ADL while those receiving placebo dropped 3.8 points ( $p < 0.001$ ) (Tariot et al 2004). As for behavior, on the 144-point NPI ChEI therapy was associated with on average a 2.44 point (95% CI 4.12 to 0.76,  $p = 0.004$ ) advantage compared to placebo (Birks 2006). Based on the available evidence, a number of reputable bodies have concluded that ChEIs are efficacious for mild to moderate AD (Doody, Stevens, et al 2001; Patterson et al 2001; Birks 2006; Burns and O'Brien 2006; Waldemar et al 2007). The US Food and Drug Administration recently (October 13, 2006) approved donepezil for the treatment of severe dementia in patients with AD. This was based on two RCTs conducted in Sweden (Winblad et al 2006) and Japan (unpublished).

The methodological limitations of the published studies (eg, reporting more than one outcome without correcting for multiple comparisons, absence of final outcome measures on subjects who had withdrawn) were specifically noted in one of the systematic reviews (Kadoszkiewicz et al 2005). Because of the modest benefits seen coupled with the methodological limitations of the studies, the authors questioned the effectiveness of these agents. Most other commentators have concluded that the likely impact of these methodological concerns do not invalidate the findings of the RCTs. The debate continues, though, about the clinical significance of the benefits seen with ChEIs. It has been argued that undue emphasis has been placed on statistical tests of significance rather than the practical importance of the benefits seen. The controversial AD2000 study was designed to determine whether treatment with donepezil produced "worthwhile improvements" in socially relevant outcomes like nursing home placement (Courtney et al 2005). No significant benefits were seen with donepezil compared to placebo in institutionalization rates at the end of the trial (42% vs 44% at 3 years;  $p = 0.4$ ) or in progression

of disability. Notwithstanding a number of optimistic pharmacoeconomic models, doubt remains about the cost-effectiveness of ChEIs (Green et al 2005). Recently the National Institute for Health and Clinical Excellence (NICE) and the Social Care Institute for Excellence (SCIE) in the United Kingdom recommended that ChEIs be restricted to patients with AD of a moderate severity as it was felt that the drugs were cost-effective only in this group (National Institute for Health and Clinical Excellence 2006). The manufacturers of donepezil (Eisai and Pfizer) disagreed with this restriction (as do many others) and have applied for a judicial review of the process used to reach this decision (Anonymous 2006).

If AEs occur with a ChEI, the agent can be either discontinued (if the side effects are judged to be disabling and/or dangerous) or the dose can be decreased (if the side effects are judged to be minor in severity) with an option to retry the higher dose after two to four weeks if the lower dose is well tolerated. The most common AEs encountered with the ChEIs are gastrointestinal symptoms such as anorexia, nausea, vomiting and diarrhea (Hogan et al 2002; Birks 2006). Gastrointestinal AEs in the RCTs were more likely to occur at the commencement of therapy (or when the dosage was increased), at the higher dose ranges and tended to be transient. They appeared to be more common with rivastigmine than donepezil (Birks 2006). Slower titration and ensuring that rivastigmine is taken with food decreases the risk of gastrointestinal side effects. A transdermal rivastigmine patch is being developed in the expectation that it will show similar efficacy to the oral form but with fewer AEs (Priano et al 2006). If nausea and/or vomiting occur with the use of a ChEI, the prescribing clinician should review how the medication is being taken (eg, dose, frequency, with or without food, evidence of an unintentional over-dose) and consider modifying the prescription (eg, lower the dose), reassigning responsibility for administration (eg, if the patient cannot correctly follow the directions given), changing the directions given (eg, take with food) or stopping the agent. While anti-emetics can be used for nausea and/or vomiting, a number of them (eg, dimenhydrinate, prochlorperazine) have anticholinergic properties. The concurrent use of anticholinergics and ChEIs might be associated with both worse cognitive outcomes (Lu and Tune 2003) and a lower likelihood of persisting with ChEI therapy (Kogut et al 2005). Weight loss did occur during the RCTs of the ChEIs but a study directly addressing this concern found that there wasn't an increased risk for weight loss (compared to patients with

AD not receiving a ChEI) with long-term use of these agents (Gillette-Guyonnet et al 2005).

Dizziness has been reported with donepezil, galantamine and rivastigmine. If disabling, the ChEI could be stopped or the dose reduced. Syncope, while rare, has been associated with the use of these agents. The loss of consciousness might arise from an arrhythmia. It is well known that ChEIs can lead to sinus bradycardia (Hogan et al 2002). Case reports of syncope from a complete atrioventricular block with ventricular tachyarrhythmia (Newby et al 2004) and the cardioinhibitory type of carotid sinus hypersensitivity have been reported with donepezil (Suleyman et al 2006). Noninvasive evaluation can usually identify the probable cause of syncope in AD patients being treated with a ChEI (Bordier et al 2005). Management could include the implantation of a pacemaker, depending on what is found (Bordier et al 2003). The presence of unexplained syncope would be a contraindication to the use of a ChEI.

Donepezil has been associated with sleep disturbances, vivid dreams/nightmares and hypnopompic hallucinations (Hogan et al 2002). There is a higher likelihood of insomnia occurring with the higher doses of donepezil (Birks and Harvey 2006). Rivastigmine and galantamine appear to be less likely to cause sleep disturbances. Management options for this problem would include switching to another ChEI.

An interesting potential problem with the ChEIs is that of a prescribing cascade. Here an adverse reaction to one drug leads to the prescription of a second drug to deal with the AE. For example, the use of ChEIs was associated with an increased risk of receiving a new prescription for an anticholinergic drug to manage urinary incontinence (Gill et al 2005). The use of the anticholinergic agent in this setting may represent the tail end of a prescribing cascade. Another example would be the higher use of hypnotics in AD patients treated with donepezil (Stahl et al 2003). Clinicians should always consider the possible contributing role of ChEIs to new or worsening medical concerns in treated patients. The use of a second agent to treat an AE will expose the patient to the potential risk of an adverse drug – drug or drug – disease interaction.

Indirect comparisons of the relative efficacy and tolerability of the ChEIs across clinical trials must be done with great caution as they are based on the questionable assumption that the trials were done in similar settings and on equivalent populations using comparable measures of efficacy and toxicity (Ioannidis 2006). The published trials that directly compared one ChEI to another had serious methodological limitations and/or showed no significant

differences in the primary outcome measures selected (Hogan et al 2004; Bullock et al 2005; Birks 2006). It is generally felt that the ChEIs have similar efficacy. Selection of which ChEI to use should be based on adverse effect (AE) profile, ease of use, familiarity with the agents and/or beliefs about the importance of the differences in their pharmacokinetics and other mechanisms of action.

Because of an unsatisfactory response and/or intolerable AEs, a patient on one ChEI may want to “switch” to a different one (Auriacombe et al 2002; Bullock and Connolly 2002; Emre 2002; Gauthier et al 2003; Bartorelli et al 2005; Sadowsky et al 2005; Wilkinson and Howe 2005; Dantoine et al 2006). If a switch is being made on the basis of an unsatisfactory response, patients can abruptly discontinue the first ChEI and start taking the second agent quickly afterwards (eg, the next day) without a washout period. They would start at the usual starting dose of the second agent followed by upward titration at the recommended rate. The approach would be different if the change is being made because of AEs. After stopping the first agent the second one would generally not be started until a week or two after resolution of the AE. A number of open-label, time-series studies on switching have been done and they indicate that it can be safely done (Auriacombe et al 2002; Gauthier et al 2003; Bartorelli et al 2005; Wilkinson and Howe 2005; Dantoine et al 2006). While benefits have been claimed, the available studies would have to be viewed as methodologically weak and not convincing. None have looked at switching to donepezil. A presentation at the 7th International Conference on Alzheimer’s and Parkinson’s Disease indicated that switching from donepezil to memantine was well tolerated whether it was done abruptly (donepezil discontinued one day with memantine started the next day and titrated up to 20 mg/d over three weeks) or gradually (donepezil dropped from 10 mg/d to 5 mg/d for two weeks before stopping; memantine then started and titrated upwards to 20 mg/d over three weeks). There is the potential of harm with switching. It can be associated with deterioration in the patient’s condition and there has been a case report of a fatality from aspiration pneumonia in a patient switched from donepezil to rivastigmine (Taylor et al 2002). The decision to make a switch should be based on the judgment of the prescribing physician about the relative benefits and risks of making a change and the wishes of the patient (or their proxy). In routine practice switching from one ChEI to another appears to be a relatively rare (<5% of treated patients) event (Dybicz et al 2006).

An area of continuing uncertainty is when to stop a ChEI. These decisions should be individualized and based

on the balance between benefits and harm for the patient. Stopping to see if there was in fact a treatment benefit, which becomes evident during the washout period, has become contentious. Studies suggest that interrupting therapy for a number of weeks can result in cognitive and/or functional losses that cannot be fully recaptured – even if the ChEI is restarted (Doody, Geldmacher et al 2001). Notwithstanding this, medications for the treatment of the cognitive and functional manifestations of AD should be discontinued when:

1. The patient and/or their proxy decision maker decides to stop;
2. The patient refuses to take the medication;
3. The patient is sufficiently nonadherent with the medication that continued prescription of it is viewed as futile and it is not possible to establish a system for the administration of the medication to rectify the problem;
4. There is no response to therapy after a reasonable trial (eg, 3–6 months);
5. The patient experiences intolerable side effects;
6. The co-morbidities of the patient make continued use of the agent either unacceptably dangerous or futile (eg, terminally ill); or
7. The patient’s dementia has progressed to a stage where there is no significant benefit from continued therapy.

If therapy is stopped, patients should be carefully monitored and if there is evidence of a significant decline in their cognitive status, functional abilities or the development/worsening of behavioural challenges consideration should be given to quickly re-instating therapy.

## Memantine

Neuronal excitotoxicity from glutamatergic neurotransmission is felt to be involved in the pathogenesis of AD. Memantine is a low to moderate affinity uncompetitive antagonist to the glutamatergic N-methyl-D-aspartic acid (NMDA) receptors. It inhibits the prolonged influx of  $\text{Ca}^{2+}$  ions that forms the basis of neuronal excitotoxicity. Because of its low affinity memantine allows for normal functioning of the receptor as it can still be activated by the relatively high concentrations of glutamate released immediately following depolarisation of presynaptic neurons. There is also some evidence from cell studies that memantine might decrease tau phosphorylation and thereby inhibit neurofibrillary degeneration (Chohan et al 2006).

A Cochrane Systematic Review concluded that there was a small beneficial effect of memantine at six months



in moderate to severe AD and a marginal benefit in those with mild to moderate disease (McShane et al 2006). A RCT published subsequent to the Review reported that the agent was safe and effective for mild to moderate AD (Peskind et al 2006). Notwithstanding this publication, memantine has generally been recommended as an option for patients with moderate to severe stages of AD only (Farlow and Cummings 2007; Schmitt et al 2007, Waldemar et al 2007) as the treatment effects seen with mild to moderate AD have not been consistently significant (Cosman et al 2007).

While memantine can be used as monotherapy for AD, it has a different mechanism of action than the ChEIs. Combination therapy with a ChEI would seem to be a rational option. An adult rat study, though, showed that co-administration of high doses of memantine (10–30 mg/kg) and donepezil (5–10 mg/kg) given intraperitoneally potentiated a NMDA antagonist type neurotoxic reaction in the brains of the study animals (Creeley et al 2006). The clinical significance of this finding is uncertain. Published human studies of combination therapy have been favorable. A RCT showed additional benefit when memantine was added to chronic donepezil therapy in patients with moderate to severe AD (Tariot et al 2004). When treatment response was defined as stabilization on individual outcome measures the combination resulted in significantly higher response rates than donepezil alone with the number needed to treat (NNT) ranging from 8–10 (van Dyck et al 2006). Two open-label studies found that the combination of rivastigmine and memantine was both safe and possibly beneficial (Dantoine et al 2006; Riepe et al 2006). The combination of galantamine and memantine also appears to be well tolerated (Grossberg et al 2006). The available human data indicates that combining memantine with a ChEI is safe and may lead to additional benefits for patients with moderate to severe AD.

As with the ChEIs there is uncertainty about the clinical significance of the benefits seen with this agent. In 2005 the Canadian Expert Drug Advisory Committee (CEDAC) recommended that memantine not be listed on the formularies of the Canadian government-funded drug benefit programs on the grounds that the clinical importance of the changes seen with memantine has not been established. The Committee was not convinced by the pharmacoeconomic model submitted by the manufacturer. Likewise the National Institute for Health and Clinical Excellence in the United Kingdom has recommended that memantine not be offered to those with AD unless it was

part of a well designed clinical trial (National Institute for Health and Clinical Excellence 2006).

## Select agents not approved for the treatment of Alzheimer's disease

### Antioxidants

Oxidative stress (a harmful condition that occurs when there is an excess of free radicals, a decrease in antioxidant levels, or both) may play a role in the pathogenesis of AD. Vitamin E is an antioxidant that has been studied as a possible therapy for AD. A 2-year, randomized, placebo-controlled trial of the effects of selegiline (10 mg a day), alpha-tocopherol (vitamin E, 2000 IU a day) or both on subjects with moderate AD was conducted. As their primary outcome measure the investigators looked at the time till the occurrence of any of the following: death, institutionalization, loss of the ability to perform basic activities of daily living, or severe dementia (Sano et al 1997). In their unadjusted analyses, there were no statistically significant differences in outcome among the four groups. In analyses that included the base-line score on the MMSE as a covariate, those on vitamin E showed a significant ( $p = 0.001$ ) delay in the time to the occurrence of the primary outcome. The estimated increase was 230 days. There was no apparent benefit on either of the two cognitive measures (ADAS-Cog, MMSE) they used. For the specific outcome of institutionalization vitamin E therapy showed a significant treatment effect. In a RCT of subjects with amnesic Mild Cognitive Impairment (which is felt be many to be a precursor of AD) participants were assigned to 2000 IU of vitamin E daily, 10 mg of donepezil daily, or placebo and then followed for up to three years (Petersen et al 2005). The primary outcome was progression to possible or probable AD. No benefit from vitamin E was found. There is insufficient evidence of efficacy for vitamin E in the treatment of AD to justify its use (Tabet et al 2000). Of additional concern is the recent finding that high dose vitamin E (400+ IU daily) supplementation is associated with an increased mortality risk (Miller et al 2005).

The purported beneficial actions of Ginkgo biloba for dementia include vasodilatation, reduced blood viscosity, modifications in neurotransmitter systems and reducing levels of oxygen free radicals (Birks et al 2002). A Cochrane Review of the agent concluded that it was both safe and promising. Concerns were expressed about the soundness of the earlier studies. The more methodologically rigorous trials have shown inconsistent results (Birks et al 2002). Since the publication of the Review two placebo-controlled trials of Ginkgo for AD have appeared. One was

interpreted as being positive (Kanowski and Hoerr 2003) while the other showed no significant benefit (van Donigen et al 2003). An underpowered six-month study compared Ginkgo and donepezil (Mazza et al 2006). While the authors concluded that donepezil and Ginkgo had similar efficacy, the study was too small to permit such a conclusion. It is well tolerated. In the RCTs of Ginkgo there were fewer reported withdrawals because of AEs than what was seen with the ChEIs (Kurz et al 2006). There might be a small risk of bleeding. A number of case reports have described a temporal association between using Ginkgo and a bleeding event (Bent et al 2005). In most of these cases other risk factors for bleeding were identified. Patients using Ginkgo, particularly those with known bleeding risks (eg, concurrent use of warfarin or antithrombotics), should be warned about a possible increase in the chances of a hemorrhage. Additional concerns about Ginkgo include variability in the quality of the agents available for purchase (Garrard et al 2003) and the excessive claims made for its effectiveness (Morris and Avorn 2003). In other words, "Let the buyer beware" (caveat emptor). There is currently insufficient evidence to recommend either for or against the use of Ginkgo biloba in AD.

Idebenone is related to coenzyme Q10, an intermediate in the oxidative phosphorylation pathway. While it has a number of potential mechanisms of action it does appear to be an antioxidant, inhibiting lipid peroxidation by scavenging free radicals. A 1-year RCT of 536 subjects with probable AD compared three doses of the agent with a placebo group. There was no significant benefit seen with treatment in the pre-specified four-group analysis. When all three idebenone dosages were grouped together and compared with placebo there was a small (1.9 points) difference on the ADAS-Cog that was statistically significant ( $p = 0.02$ ). No significant benefits were seen on the other outcome measures. The authors concluded that the effect on the ADAS-Cog was of insufficient magnitude to be clinically significant (Thal et al 2003).

## Folic acid, vitamin B6 and vitamin B12

In the Framingham Study cohort a higher plasma homocysteine level was found to be a risk factor for the development of AD (Seshadri et al 2002). The risk of developing AD nearly doubled with a plasma homocysteine level greater than 14  $\mu\text{mol}$  per liter. Possible mechanisms for the association include accelerated development of atherosclerosis, neuronal excitotoxicity from the activation of NMDA receptors, hypomethylation, increases in oxidative stress and increases

in  $\beta$ -amyloid toxicity. Most elevations in homocysteine are felt to be from inadequate folate, vitamin B12, and/or vitamin B6 intake. Data on the effects of folic acid, vitamin B6 and/or vitamin B12 on patients with AD are limited. No cognitive benefit from folic acid (with or without vitamin B12) has been seen in demented individuals (Malouf et al 2003). No trials of vitamin B6 involving people with dementia have been done (Malouf and Grimley Evans 2003). Finally, two RCTs of people with dementia and low serum vitamin B12 levels treated with Vitamin B12 supplementation found no evidence of a significant treatment effect on cognitive function (Malouf and Aersosa 2003). Though a low risk intervention, the routine administration of folate, B6 and/or B12 supplements to individuals suffering from AD cannot be endorsed at the present time (Balk et al 2007). Those with documented deficiencies, though, should be treated.

## Anti-inflammatory agents

Inflammation is felt to be part of the pathological cascade that leads to AD. While there is epidemiological evidence that patients on anti-inflammatory agents have a reduced incidence of AD (McGeer et al 1996; Wolfson et al 2002), the RCTs employing anti-inflammatory drugs as therapy for AD have been disappointing to date. An early study of indomethacin did show some promise but AEs were common (Rogers et al 1993) and additional studies were not done. The use of this agent cannot be recommended for AD (Tabet and Feldman 2002). Studies that examined celecoxib, diclofenac, naproxen and rofecoxib have been negative (Scharf et al 1999; Aisen et al 2003; Reines et al 2004; Firuzi and Praticò 2006). At the present time the use of a NSAID for the treatment of AD cannot be recommended.

NSAIDs may work by mechanisms other than cyclooxygenase (COX) inhibition. Some (eg, diclofenac, sulindac, indomethacin, flurbiprofen, ibuprofen) but not all NSAIDs have been found to affect A $\beta$  deposition and metabolism (Imbimbo 2004). It is possible that the negative NSAID trials to date may be due to selecting the wrong NSAID.

Flurizan<sup>TM</sup> is the R-enantiomer of flurbiprofen and appears to lower A $\beta$ 42 production by selectively modulating  $\gamma$ -secretase activity, shifting the metabolism of amyloid precursor protein towards the production of shorter, less toxic fragments. It is felt to lack significant COX inhibiting activity and has little in the way of gastrointestinal AEs. Promising results have been obtained and a Phase III clinical trial is currently underway.

A study of prednisone (20 mg for one month then 10 mg for one year) in 132 patients failed to show any significant

benefit (Aisen et al 2000). A RCT of hydroxychloroquine was also negative (van Gool et al 2001).

## Inhibitors of the HMG-CoA reductase enzyme

In vitro and animal studies have demonstrated that treatment with cholesterol-lowering drugs reduces the production of A $\beta$ . Some of the large RCTs of inhibitors of the HMG-CoA reductase enzyme (ie, "statins") have included secondary cognitive outcomes. The MRC/BHF Heart Protection Trial (simvastatin was the agent used) found no benefit with active treatment on the likelihood of either cognitive decline or developing a dementia (Heart Protection Study Collaborative Group 2002). The PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) trial also could not demonstrate any cognitive benefit with pravastatin (Shepherd et al 2002). Simvastatin was examined in a 26-week study of individuals with mild to moderate AD. With active treatment there was a small but significant reduction of A $\beta$ 40 in the cerebrospinal fluid of mild AD subjects. The mean MMSE score in the placebo group dropped from 17.1 to 14.4. In the simvastatin group, the mean MMSE score declined marginally from 17.8 to 17.2. At the end of the treatment period the difference in MMSE scores between the two groups was significant ( $p < 0.02$ ) (Simons et al 2002). A 12 month placebo controlled pilot trial of atorvastatin 60 mg in 71 patients with mild to moderate AD showed statistically significant improvement on the ADAS-Cog at 6 months and a positive trend at 12 months (Sparks et al 2005). A phase III trial is currently on-going. There was no evidence of any significant interaction between statins and galantamine in a small study (Winblad et al 2007). Though a promising area, HMG-CoA reductase enzyme inhibitors are not recommended for the treatment of AD at the present time.

## Estrogen and androgen hormone therapy

A Cochrane review examined the effect of hormone replacement therapy on cognition in women suffering from a dementia. Five double-blind RCTs were examined in detail. Short-lived and clinically insignificant beneficial effects with conjugated equine estrogens (CEE) were found on the MMSE (CEE 0.625 mg/d only), Trail-Making Test-B (CEE 0.625 mg/d only) and digit span backwards (CEE 1.25 mg/d only). Cued delayed recall of a word list was improved after two months of treatment with transdermal diestradiol. Control subjects did significantly better on delayed recall (one month), finger tapping (12 months) and on the Clinical Dementia Rating scale. After correction for

multiple testing only the short-term effect of transdermal estrogen remained statistically significant (Hogervorst et al 2006). Hormone replacement therapy (estrogens combined with a progestagen) or estrogen replacement therapy (estrogen alone) is not recommended for the cognitive impairments of women with AD.

Androgens can influence brain function directly through androgen receptors or indirectly through estradiol (testosterone is converted to estradiol by aromatase) (Henderson and Hogervorst 2004). In vitro and animal studies indicate that androgen depletion is associated with higher brain levels of beta-amyloid, hyperphosphorylation of tau protein and decreased neuronal survival after exposure to a toxin (Almeida and Flicker 2003; Ramsden et al 2003; Henderson and Hogervorst 2004). Studies of healthy older men suggest that therapy with testosterone has a weak and inconsistent association with better visuospatial and memory scores on testing (Almeida and Flicker 2003). Some but not all studies have shown an association between reduced testosterone levels and a diagnosis of AD (Moffat et al 2004). Two small intervention studies that included subjects with AD have been done. Ten hypogonadal nursing home patients with AD were randomized to either IM testosterone enanthate 200 mg every two weeks or placebo (Tan and Pu 2003). Unblinded assessments at three, six and nine months showed improvements on the ADAS-Cog, MMSE and the Clock Drawing Test. One patient became aggressive and developed hypersexual behavior. No other problems were noted. The second study was a randomized, double-blind, placebo-controlled six-week trial that examined the effects of weekly IM injections of 100 mg of testosterone enanthate on subjects with Mild Cognitive Impairment or AD (a total of 15 subjects with AD were enrolled) (Cherrier et al 2005). Improvements in spatial memory/ability and verbal memory were seen with testosterone therapy. No adverse effects were encountered. Both groups of researchers felt that additional studies were required. There is insufficient evidence to recommend the use of androgens (eg, testosterone) to treat men with AD.

## Other agents

A large number of compounds with diverse proposed mechanisms of action are being or have been tested as potential therapies for AD. A partial listing (in alphabetical order) would include: A $\beta$  aggregation inhibitors; acetyl-L-carnitine; active or passive beta-amyloid immunization; Alzhemed™; ampakines; 3-amino-1-propanesulfonic acid (3APS); aniracetam; BMY21,502; bapineuzumab;

besipiridine; cerebrolysin; clioquinol; cytidinediposphocholine (CDP-choline); D-cycloserine; DGAVP; dapsone; dehydroepiandrosterone; dimebon; doxycycline and rifampin; erythropoietin; extract of *Melissa officinalis*; gamma-aminobutyric acid (GABA) receptor antagonists; garlic;  $\gamma$ -secretase inhibitors; glycogen synthase kinase inhibitors; growth hormone releasing hormone; huperzine A; Hydergine™; ispronicline; lecozotan; lethicin; lithium carbonate; melatonin; milacemide; neramexane; muscarinic receptor agonists; nerve growth factor (NGF) gene therapy and mimics; nicergoline; nicotinic receptor modulators; nicotine; nimodipine; paclitaxel; peroxisome proliferator-activated receptor (PPAR)- $\gamma$  agonists; phosphatidyl serine; phosphodiesterase inhibitors; physostigmine; piracetam; propentofylline; rosiglitazone; selegiline; serotonin receptor antagonists; velnacrine; and, vinpocetine.

The studies that have been completed have yielded negative or inconclusive results. None of these agents have been approved for the treatment of AD in Canada. Their use can not be recommended at this time except as part of a well-designed drug trial.

## Conclusion

With so many drugs being looked at the optimist in me is hopeful for the future, the cynic feels that the large number being considered indicates that nothing truly works and the realist reflects that after the modern era of AD pharmacotherapy opened over twenty years ago in 1986 with the *New England Journal of Medicine* report on tetrahydroaminoacridine (Summers et al 1986) we are still left with a very limited armamentarium. The somewhat disappointing results seen to date might reflect the degree of brain damage that has occurred before the drugs are used. It is estimated that in AD neurodegeneration starts 20–30 years before the appearance of the first clinical symptoms (Goedert and Spillantini 2006). It might be a question of too little and too late.

## References

- Aisen PS, Davis KL, Berg JD, et al. 2000. A randomized controlled trial of prednisone in Alzheimer's disease. *Neurology*, 54:588–93.
- Aisen PS, Schafer KA, Grundman M, et al. 2003. Effects of rofecoxib or naproxen vs placebo on Alzheimer disease progression: a randomized controlled trial. *JAMA*, 289:2819–26.
- Almeida OP, Flicker L. 2003. Testosterone and dementia: too much ado about too little data. *J Br Menopause Soc*, 9:107–10.
- Anonymous. 2006. NICE faces legal challenge over restriction on dementia drugs. *BMJ*, 333:1085.
- Auriacombe S, Pere JJ, Loria-Kanza Y, et al. 2002. Efficacy and safety of rivastigmine in patients with Alzheimer's disease who failed to benefit from treatment with donepezil. *Curr Med Res Opin*, 18:129–38.
- Balk EM, Raman G, Tatsioni A, et al. 2007. Vitamin B6, B12, and folic acid supplementation and cognitive function: a systematic review of randomized trials. *Arch Intern Med*, 167:21–30.
- Bartorelli L, Giraldi C, Saccardo M, et al. 2005. Effects of switching from an AChE inhibitor to a dual AChE-BuChE inhibitor in patients with Alzheimer's disease. *Curr Med Res Opin*, 21:1809–18.
- Bent S, Goldberg H, Padula A, et al. 2005. Spontaneous bleeding associated with Ginkgo biloba – a case report and systematic review of the literature. *J Gen Intern Med*, 20:657–61.
- Birks J. 2006. Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database Syst Rev*, (1):CD005593.
- Birks J, Grimley Evans J, Iakovidou V, et al. 2000. Rivastigmine for Alzheimer's disease. *Cochrane Database Syst Rev*, (4):CD001191.
- Birks J, Grimley EV, Van Dongen M. 2002. Ginkgo biloba for cognitive impairment and dementia. *Cochrane Database Syst Rev*, (4):CD003120.
- Birks J, Harvey R. 2006. Donepezil for dementia due to Alzheimer's disease. *Cochrane Database Syst Rev*, (1):CD001190.
- Bordier P, Garrigue S, Barold SS, et al. 2003. Significance of syncope in patients with Alzheimer's disease treated with cholinesterase inhibitors. *Europace*, 5:429–31.
- Bordier P, Lanusse S, Garrigue S, et al. 2005. Causes of syncope in patients with Alzheimer's disease treated with donepezil. *Drugs Aging*, 22:687–94.
- Bullock R, Connolly C. 2002. Switching cholinesterase inhibitor therapy in Alzheimer's disease – donepezil to rivastigmine, is it worth it? *Int J Geriatr Psychiatry*, 17:288–9.
- Bullock R, Touchon J, Bergman H, et al. 2005. Rivastigmine and donepezil treatment in moderate to moderately-severe Alzheimer's disease over a 2-year period. *Curr Med Res Opin*, 21:1317–27.
- Burns A, O'Brien J. 2006. on behalf of the BAP Dementia Consensus Group Clinical practice with anti-dementia drugs: a consensus statement from British Association for Psychopharmacology. *J Psychopharmacol*, 20:732–55.
- Cherrier MM, Matsumoto AM, Amory JK, et al. 2005. Testosterone improves spatial memory in men with Alzheimer disease and mild cognitive impairment. *Neurology*, 64:2063–8.
- Chohan MO, Iqbal K. 2006. From tau to toxicity: Emerging roles of NMDA receptor in Alzheimer's disease. *J Alzheimers Dis*, 10:81–7.
- Clegg A, Bryant J, Nicholson T, et al. 2002. Clinical and cost-effectiveness of donepezil, rivastigmine, and galantamine for Alzheimer's disease. A systematic review. *Int J Technol Assess Health Care*, 18:497–507.
- Cosman KM, Boyle LL, Porsteinsson AP. 2007. Memantine in the treatment of mild-to-moderate Alzheimer's disease. *Expert Opin Pharmacother*, 8:203–14.
- Courtney C, Farrell D, Gray R, et al. 2004. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. *Lancet*, 363:2105–15.
- Creeley CE, Wozniak DF, Nardi A, et al. 2006. Donepezil markedly potentiates memantine neurotoxicity in the adult rat brain. *Neurobiol Aging*, [Epub ahead of print].
- Dantoine T, Auriacombe S, Sarazin M, et al. 2006. Rivastigmine monotherapy and combination therapy with memantine in patients with moderately severe Alzheimer's disease who failed to benefit from previous cholinesterase inhibitor treatment. *Int J Clin Pract*, 60:110–18.
- Doody RS, Geldmacher DS, Gordon B, et al. 2001. Open-label, multicenter, phase 3 extension study of the safety and efficacy of donepezil in patients with Alzheimer's disease. *Arch Neurol*, 58:427–3.
- Doody RS, Stevens JC, Beck C, et al. 2001. Practice parameter: management of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*, 56:1154–66.
- Dybiz SB, Keohane DJ, Erwin WG, et al. 2006. Patterns of cholinesterase-inhibitor use in the nursing home setting: a retrospective analysis. *Am J Geriatr Pharmacother*, 4:154–60.
- Emre M. 2002. Switching cholinesterase inhibitors in patients with Alzheimer's disease. *Int J Clin Pract Suppl*, (127):64–72.
- Farlow MR, Cummings JL. 2007. Effective pharmacologic management of Alzheimer's disease. *Am J Med*, 120:388–97.



- Firuzi O, Praticò D. 2006. Coxibs and Alzheimer's disease: should they stay or should they go? *Ann Neurol*, 59:219–28.
- Gauthier S, Emre M, Farlow MR, et al. 2003. Strategies for continued successful treatment of Alzheimer's disease: switching cholinesterase inhibitors. *Curr Med Res Opin*, 19:707–14.
- Garrard J, Harris S, Eberly LE, Matiak A. 2003. Variations in product choices of frequently purchased herbs: caveat emptor. *Arch Intern Med*, 163:2290–5.
- Gill SS, Mamdani M, Naglie G, et al. 2005. A prescribing cascade involving cholinesterase inhibitors and anticholinergic drugs. *Arch Intern Med*, 165:808–13.
- Gillette-Guyonnet S, Cortes F, Cantet C, et al. 2005. Long-term cholinergic treatment is not associated with greater risk of weight loss during Alzheimer's disease: data from the French REAL.FR cohort. *J Nutr Health Aging*, 9:69–73.
- Goedert M, Spillantini MG. 2006. A Century of Alzheimer's Disease. *Science*, 314:777–81.
- Green C, Picot J, Loveman E, et al. 2005. Modeling the cost effectiveness of cholinesterase inhibitors in the management of mild to moderately severe Alzheimer's disease. *Pharmacoeconomics*, 23:1271–82.
- Grossberg GT, Edwards KR, Zhao Q. 2006. Rationale for combination therapy with galantamine and memantine in Alzheimer's disease. *J Clin Pharmacol*, 46:17S–26S.
- Heart Protection Study Collaborative Group. 2002. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*, 360:7–22.
- Henderson VW, Hogervorst E. 2004. Testosterone and Alzheimer disease. Is it men's turn now? *Neurology*, 62:170–1.
- Hogan DB, Patterson C. 2002. Progress in clinical neurosciences – treatment of Alzheimer's disease and other dementias – review and comparison of the cholinesterase inhibitors. *Can J Neurol Sci*, 29:306–14.
- Hogan DB, Goldlist B, Naglie G, et al. 2004. Comparison studies of cholinesterase inhibitors for Alzheimer's disease. *Lancet Neurol*, 3:622–6.
- Hogervorst E, Yaffe K, Richards M, et al. 2002. Hormone replacement therapy to maintain cognitive function in women with dementia. *Cochrane Database Syst Rev*, (3):CD003799.
- Imbimbo BP. 2004. The potential role of non-steroidal anti-inflammatory drugs in treating Alzheimer's disease. *Expert Opin Investig Drugs*, 13:1469–81.
- Ioannidis JPA. 2006. Indirect comparisons: the mesh and mess of clinical trials. *Lancet*, 368:1470–2.
- Kaduszkiewicz H, Zimmermann T, Beck-Bornholdt HP, et al. 2005. Cholinesterase inhibitors for patients with Alzheimer's disease: systematic review of randomised clinical trials. *BMJ*, 331:321–7.
- Kanowski S, Hoerr R. 2003. Ginkgo biloba extract EGb 761 in dementia: intent-to-treat analyses of a 24-week, multi-center, double-blind, placebo-controlled, randomized trial. *Pharmacopsychiatry*, 36:297–303.
- Kogut SJ, El-Maouche D, Abughosh SM. 2005. Decreased persistence to cholinesterase inhibitor therapy with concomitant use of drugs that can impair cognition. *Pharmacotherapy*, 25:1729–35.
- Kurz A, Van Baelen B. 2004. Ginkgo biloba compared with cholinesterase inhibitors in the treatment of dementia: a review based on meta-analyses by the Cochrane Collaboration. *Dement Geriatr Cogn Disord*, 18:217–26.
- Lancôt KL, Herrmann N, Yau KK, et al. 2003. Efficacy and safety of cholinesterase inhibitors in Alzheimer's disease: a meta-analysis. *CMAJ*, 169:557–64.
- Loy C, Schneider L. 2006. Galantamine for Alzheimer's disease and mild cognitive impairment. *Cochrane Database Syst Rev*, (1):D001747.
- Lu CJ, Tune LE. 2003. Chronic exposure to anticholinergic medications adversely affects the course of Alzheimer disease. *Am J Geriatr Psychiatry*, 11:458–61.
- Malouf M, Grimley EJ, Areosa SA. 2003. Folic acid with or without vitamin B12 for cognition and dementia. *Cochrane Database Syst Rev*, (4):CD004514.
- Malouf R, Grimley Evans J. 2003. The effect of vitamin B6 on cognition. *Cochrane Database Syst Rev*, (4):CD004393.
- Malouf R, Areosa SA. 2003. Vitamin B12 for cognition. *Cochrane Database Syst Rev*, (3):CD004326.
- Mazza M, Capuano A, Bria P, Mazza S. 2006. Ginkgo biloba and donepezil: a comparison in the treatment of Alzheimer's dementia in a randomized placebo-controlled double-blind study. *Eur J Neurol*, 13:981–5.
- McGeer PL, Schulzer M, McGeer EG. 1996. Arthritis and anti-inflammatory agents as possible protective factors for Alzheimer's disease: A review of 17 epidemiologic studies. *Neurology*, 47:425–32.
- McShane R, Areosa Sastre A, Minakaran N. 2006. Memantine for dementia. *Cochrane Database Syst Rev*, (2):CD003154.
- Miller ER, Pastor-Barriuso R, Dalai D, et al. 2005. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med*, 142:37–46.
- Moffat SD, Zonderman AB, Metter EJ, et al. 2004. Free testosterone and risk for Alzheimer disease in older men. *Neurology*, 62:188–93.
- Morris CA, Avorn J. 2003. Internet marketing of herbal products. *JAMA*, 290:1505–9.
- National Institute for Health and Clinical Excellence. 2006. NICE technology appraisal guidance 111. Donepezil, galantamine, rivastigmine (review) and memantine for the treatment of Alzheimer's disease [online]. Accessed January 15, 2007. URL: <http://www.nice.org.uk/TA111>.
- Newby VJ, Kenny A, Grant I, et al. 2004. Donepezil and cardiac syncope: case report. *Int J Geriatr Psychiatry*, 19:1110–12.
- Patterson C, Gauthier S, Bergman H, et al. 2001. The recognition, assessment and management of dementing disorders: conclusions from the Canadian Consensus Conference on Dementia. *Can J Neurol Sci*, 28 (Suppl 1):S3–16.
- Peskind ER, Potkin SG, Pomara N, et al. 2006. Memantine treatment in mild to moderate Alzheimer disease: a 24-week randomized, controlled trial. *Am J Geriatr Psychiatry*, 14:704–15.
- Petersen RC, Thomas RG, Grundman M, et al. 2005. Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med*, 352:2379–88.
- Priano L, Gasco MR, Mauro A. 2006. Transdermal treatment options for neurological disorders: impact on the elderly. *Drugs Aging*, 23:357–75.
- Ramsden M, Shin TM, Pike CJ. 2003. Androgens modulate neuronal vulnerability to kainite lesion. *Neuroscience*, 122:573–8.
- Reines SA, Block GA, Morris JC, et al. 2004. Rofecoxib: no effect on Alzheimer's disease in a 1-year, randomized, blinded, controlled study. *Neurology*, 62:66–71.
- Riepe MW, Adler G, Ibach B, et al. 2006. Adding memantine to rivastigmine therapy in patients with mild-to-moderate Alzheimer's disease: results of a 12-week, open-label pilot study. *Prim Care Companion J Clin Psychiatry*, 8:258–63.
- Ritchie CW, Ames D, Clayton T, et al. 2004. Meta-analysis of randomized trials of the efficacy and safety of donepezil, galantamine, and rivastigmine for the treatment of Alzheimer disease. *Am J Geriatr Psychiatry*, 12:358–69.
- Rockwood K. 2004. Size of the treatment effect on cognition of cholinesterase inhibition in Alzheimer's disease. *Journal of Neurology Neurosurgery and Psychiatry*, 75:677–85.
- Rogers J, Kirby LC, Hempelman SR, et al. 1993. Clinical trial of indomethacin in Alzheimer's disease. *Neurology*, 43:1609–11.
- Sadowsky CH, Farlow MR, Atkinson L, et al. 2005. Switching from donepezil to rivastigmine is well tolerated: results of an open-label safety and tolerability study. *Prim Care Companion J Clin Psychiatry*, 7:43–8.
- Sano M, Ernesto C, Thomas RG, et al. 1997. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. *N Engl J Med*, 336:1216–22.
- Scharf S, Mander A, Ugoni A, et al. 1999. A double-blind, placebo-controlled trial of diclofenac/misoprostol in Alzheimer's disease. *Neurology*, 53:197–201.

- Schmitt F, Ryan M, Cooper G. 2007. A brief review of the pharmacologic and therapeutic aspects of memantine in Alzheimer's disease. *Expert Opin Drug Metab Toxicol*, 3:135–41.
- Schneider LS, Dekosky ST, Farlow MR, et al. 2005. A randomized, double-blind, placebo-controlled trial of two doses of ginkgo biloba extract in dementia of the Alzheimer's type. *Curr Alz Res*, 2:541–55.
- Seshadri S, Beiser A, Selhub J, et al. 2002. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. *N Engl J Med*, 346:476–83.
- Shepherd J, Blauw GJ, Murphy MB, et al. 2002. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet*, 360:1623–30.
- Simons M, Schwärzler F, Lütjohann D, et al. 2002. Treatment with simvastatin in normocholesterolemic patients with Alzheimer's disease: a 26-week randomized, placebo-controlled, double-blind trial. *Ann Neurol*, 52:346–50.
- Sparks DL, Sabbagh MN, Connor DJ, et al. 2005. Atorvastatin for the treatment of mild to moderate Alzheimer disease: preliminary results. *Arch Neurol*, 62:753–7.
- Stahl SM, Markowitz JS, Gutterman EM, et al. 2003. Co-use of donepezil and hypnotics among Alzheimer's disease patients living in the community. *J Clin Psychiatry*, 64:466–72.
- Suleyman T, Tevfik P, Abdulkadir G, et al. 2006. Complete atrioventricular block and ventricular tachyarrhythmia associated with donepezil. *Emerg Med J*, 23:641–2.
- Summers WK, Majovski LV, Marsh GM, et al. 1986. Oral tetrahydroaminoacridine in long-term treatment of senile dementia, Alzheimer type. *N Engl J Med*, 315:1241–5.
- Tabet N, Birks J, Grimley Evans J, et al. 2000. Vitamin E for Alzheimer's disease. *Cochrane Database Syst Rev*, (4):CD002854.
- Tabet N, Feldman H. 2002. Indomethacin for the treatment of Alzheimer's disease patients. *Cochrane Database Syst Rev*, (2):CD003673.
- Tan RS, Pu SJ. 2003. A pilot study on the effects of testosterone in hypogonadal aging male patients with Alzheimer's disease. *Aging Male*, 6:13–17.
- Tariot PN, Solomon PR, Morris JC, et al. 2000. A 5-month, randomized, placebo-controlled trial of galantamine in AD. *Neurology*, 54:2269–76.
- Tariot PN, Farlow MR, Grossberg GT, et al. 2004. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. *JAMA*, 291:317–24.
- Taylor AM, Hoehns JD, Anderson DM, et al. 2002. Fatal aspiration pneumonia during transition from donepezil to rivastigmine. *Ann Pharmacother*, 36:1550–3.
- Thal LJ, Grundman M, Berg J, et al. 2003. Idebenone treatment fails to slow cognitive decline in Alzheimer's disease. *Neurology*, 61:1498–502.
- Thompson S, Lancôt KL, Herrmann N. 2004. The benefits and risks associated with cholinesterase inhibitor therapy in Alzheimer's disease. *Expert Opin Drug Saf*, 3:425–40.
- Trinh NH, Hoblyn J, Mohanty S, et al. 2003. Efficacy of cholinesterase inhibitors in the treatment of neuropsychiatric symptoms and functional impairment in Alzheimer disease: a meta-analysis. *JAMA*, 289:210–16.
- van Dongen, van Rossum E, Kessels A, et al. 2003. Ginkgo for elderly people with dementia and age-associated memory impairment: a randomized clinical trial. *J Clin Epidemiol*, 56:367–76.
- Van Dyck CH, Schmitt FA, Olin JT, et al. 2006. A responder analysis of memantine treatment in patients with Alzheimer disease maintained on donepezil. *Am J Geriatr Psychiatry*, 14:428–37.
- van Gool WA, Weinstein HC, Scheltens PK, et al. 2001. Effect of hydroxychloroquine on progression of dementia in early Alzheimer's disease: an 18-month randomised, double-blind, placebo-controlled study. *Lancet*, 358:455–60.
- Waldemar G, Dubois B, Emre M, et al. 2007. Recommendations for the diagnosis and management of Alzheimer's disease and other disorders associated with dementia: EFNS guideline. *Eur J Neurol*, 14:e1–26.
- Whitehead A, Perdomo C, Pratt RD, et al. 2004. Donepezil for the symptomatic treatment of patients with mild to moderate Alzheimer's disease: a meta-analysis of individual patient data from randomised controlled trials. *Int J Geriatr Psychiatry*, 19:624–33.
- Wilkinson DG, Howe I. 2005. Switching from donepezil to galantamine: a double-blind study of two wash-out periods. *Int J Geriatr Psychiatry*, 20:489–91.
- Winblad B, Kilander L, Eriksson S, et al. 2006. Donepezil in patients with severe Alzheimer's disease: double-blind, parallel-group, placebo-controlled study. *Lancet*, 367:1057–65.
- Winblad B, Jelic V, Kershaw P, et al. 2007. Effects of statins on cognitive function in patients with Alzheimer's disease in galantamine clinical trials. *Drugs Aging*, 24:57–61.
- Wolfson C, Oremus M, Shukla V, et al. 2002. Donepezil and rivastigmine in the treatment of Alzheimer's disease: a best-evidence synthesis of the published data on their efficacy and cost-effectiveness. *Clin Ther*, 24:862–86.
- Wolfson C, Perrault A, Moride Y, et al. 2002. A case-control analysis of nonsteroidal anti-inflammatory drugs and Alzheimer's disease: are they protective? *Neuroepidemiology*, 21:81–6.