Pharmacological treatment of cognitive deficits in Alzheimer’s disease

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The growing number of people with dementia poses a significant challenge to our society. The commonest cause of dementia is Alzheimer’s disease (AD), which accounts for over half of cases.\(^1\) As a number of pharmacological agents have been proposed for treating AD, it is timely to review the clinical and published evidence for each. This article outlines the benefits, risks and practical considerations associated with specific treatments for the cognitive symptoms of AD. Drugs for treating non-cognitive symptoms, such as depression and psychosis associated with dementia, are reviewed elsewhere.\(^2\)

There is no evidence from randomised trials of preventive measures for AD. Epidemiological data suggest that antioxidants, statins, anti-inflammatory drugs and oestrogen replacement therapy may be associated with a lower prevalence of the disease.\(^3\) Some of these agents may improve or maintain clinical status for a limited period (6–12 months). As AD is a progressive disease, a “successful” treatment may be one that simply delays the progression of symptoms or slows the rate of decline.\(^4\)

**Study methods**

The United States Food and Drug Administration (FDA) requires studies to follow a standard format.\(^5\) They must be parallel, randomised, double-blind, placebo-controlled trials of at least 24 weeks duration, evaluated by changes of a predetermined level on widely accepted cognitive tests (such as the Alzheimer’s Disease Assessment Scale — cognitive subscale\(^6\) [ADAS-Cog; range, 1–70; higher score = worse]), and a global outcome measure (such as the Clinician Interview Based Impression of Change with Caregiver Input).\(^7\) Scores on the ADAS-Cog in patients with moderate Alzheimer’s disease increase by approximately 7–11 points per year. The FDA recommends that the criterion for a response to a drug be an improvement on the ADAS-Cog of at least four points.

**Cholinergic agents**

Agents believed to enhance central nervous system cholinergic function have been the focus of most research examining the pharmacological management of AD. Two main classes of agents have been investigated: cholinesterase inhibitors (ChEIs) and cholinomimetics. Cholinomimetics are not currently licensed for use anywhere because of adverse effects or insufficient efficacy in trials.

**Donepezil**

Donepezil has been shown to have a statistically significant beneficial effect in cognitive and global outcomes in patients with mild to moderate AD in five randomised controlled trials (RCTs) and has been discussed in three sys-

**Abstract**

- Clinical trials and independent reviews support the use of cholinesterase inhibitors for treating the symptoms of patients with mild to moderate Alzheimer’s disease (AD).
- Before initiating cholinesterase inhibitor therapy, patients should be thoroughly assessed, and the diagnosis confirmed, preferably by a specialist.
- Compliance with cholinesterase inhibitor therapy should be monitored and the response (in global, cognitive, functional and behavioural domains) reassessed after 2–3 months of treatment.
- Vitamin E may be protective against AD, and therapy with 1000 IU twice daily may be considered.
- There is insufficient evidence to support the use of other antioxidant agents, anti-inflammatory agents, monoamine oxidase B inhibitors, folate/homocysteine or antihypertensive drugs in patients with AD, or hormone replacement therapy in affected women.
was tolerated by fewer than 50% of patients, mainly because of gastrointestinal upset or hepatic toxicity. It was withdrawn in 2000.

**Summary**

Clinical trials and major independent recent reviews, including the Cochrane reviews and the National Institute for Clinical Excellence (NICE) appraisal, all support the use of the cholinergic agents donepezil, rivastigmine and galantamine as symptomatic treatments in patients with mild to moderate AD (E1). There is no strong evidence to support an effect on disease progression or symptomatic efficacy beyond six to 12 months, at least partly because ethical considerations preclude long-term, placebo-controlled research studies. There are uncontrolled data supporting continuation beyond 12 months, but evidence is still tentative.

The clinical significance of the reported benefits has been questioned. While scales used in these studies have proven reliability and validity, they may not reflect clinically relevant outcomes for patients and their carers. Clinical trial results often hide the heterogeneity of response suggested in clinical practice. However, clinical experience appears to support the benefit of the cholinesterase inhibitors. Between 50% and 60% of patients show benefit, with improvement relative to baseline continuing in many cases for 6-12 months or more, and a minority of patients improve more dramatically. Responders can not be predicted before treatment. Commonly reported responses include identifiable improvement in attention, conversational language and activities of daily living, together with abatement of apathy and behavioural symptoms (E4). There is accumulating evidence that cholinesterase inhibitors reduce non-cognitive symptoms such as psychosis and apathy in AD.

Evidence to support greater efficacy of one drug over another within this class awaits head-to-head RCTs. There is emerging open-label-trial evidence that some patients failing to respond to one agent may respond to another.

Evidence for the cost-effectiveness of these drugs is reviewed in the NICE appraisal, with consideration of nine available economic evaluation studies. No clear conclusions were reached.

**Anti-inflammatory drugs**

Epidemiological evidence suggests that anti-inflammatory drugs may prevent or delay the onset of AD, but there is insufficient evidence that they are effective in its treatment. Several of these drugs may lead to life-threatening complications, such as gastrointestinal bleeding. It is not yet recommended that anti-inflammatory drugs be used to treat AD.

**Antioxidant agents**

**Vitamin E (α-tocopherol)**

Epidemiological evidence suggests vitamin E, an antioxidant, may be protective against AD. One RCT indicated a benefit using 1000 IU twice daily in delaying the time to clinical decline (E2). Side effects with vitamin E are infrequent.
2: Rules for prescribing cholinesterase inhibitors under the Pharmaceutical Benefits Scheme

Subsidised donepezil and rivastigmine became available through the Pharmaceutical Benefits Scheme (PBS) in February 2001, and galantamine will become available from November 2001, with several provisos:

1. Therapy with these drugs is only to be commenced in patients with a diagnosis of Alzheimer’s disease (AD), confirmed by an appropriate specialist.
2. Patients must have mild to moderate AD, defined as a mini-mental state examination (MMSE) score of ≥ 10.
3. The score on either the MMSE or Alzheimer’s Disease Assessment Scale – cognitive subscale (ADAS-Cog) (for those with an MMSE score > 24) must be recorded (testing does not need to be done by a specialist).
4. Continuation under the PBS requires demonstrated evidence of cognitive improvement (MMSE score at least 2 points better or ADAS-Cog score at least 4 points better).
5. Patients are not to continue to receive subsidised medication once their MMSE score is below 10.

— diarrhoea may occur and vitamin E may interact with warfarin and lead to bleeding problems.

Ginkgo biloba

This product is derived from the leaves of a Chinese tree and is said to have anti-inflammatory, antioxidant and antiplatelet-aggregation properties. A meta-analysis, which found four trials (among 50 papers reviewed) to be acceptable, reported a small but significant benefit in cognitive performance, which translated into a 3% difference on ADAS-Cog at three to six months (E1). The number needed to treat for one patient to have a four-point decrease on ADAS-Cog in AD patients is about 6.3 (E2). Compared with cholinesterase inhibitors, the level of evidence for ginkgo is weak and data are lacking. Although generally considered safe, ginkgo may cause bleeding and should be used with caution in patients receiving anticoagulant drugs.

Brahmi (Bacopa monniera)

This Ayurvedic preparation is marketed as a herbal “memory booster”, with a putative antioxidant mechanism of action. There are no clinical data to support a benefit for patients with AD.

Oestrogen

Most data for the use of oestrogen in the treatment of AD have been epidemiological, although there are plausible reasons why oestrogen may be beneficial. A recent placebo-controlled trial found no cognitive benefit over one year of treatment (E2), although the addition of oestrogen to tacrine and donepezil appeared to improve cognition more than either cholinesterase inhibitor alone (E3).

Monoamine oxidase B inhibitors

Selegiline (L-deprenyl)

The effects of selegiline (L-deprenyl), an irreversible MAO-B inhibitor with selectivity for monoamine oxidase B at its usual clinical dose (10 mg/day), has been examined in at least 15 RCTs since 1987. A recent review concluded that the evidence for beneficial effects (on memory function, and on mood and behaviour), while promising, is as yet insufficient to recommend routine clinical use (E1). In Australia selegiline is currently only available under the Pharmaceutical Benefits Scheme for treating Parkinson’s disease.

Lazabemide

The development of lazabemide, a reversible monoamine oxidase inhibitor with antioxidant activity, as a treatment for AD appears to have ceased.

Folate/homocysteine

There is tantalising epidemiological evidence to suggest that a reduction of serum homocysteine levels through ingestion of folic acid may be protective against the development of AD. However, there is as yet no RCT evidence to indicate any benefit of folic acid in the prevention or treatment of AD.

Antihypertensive drugs

Recent epidemiological evidence indicates an association between atherosclerosis and subsequent development of AD. Blood pressure may be higher in the preclinical phase of AD but normalises once the disease has manifested itself. Although normalising blood pressure may reduce the risk of developing AD, there is no specific role for antihypertensive agents in the treatment of cognitive symptoms.

New drugs

A number of exciting developments hold promise. Memantine, an uncompetitive N-methyl-D-aspartate (NMDA) antagonist, has shown significant improvements on global and behavioural scales in patients with AD and vascular dementia. However, the evidence in favour of memantine is not yet sufficiently robust to justify its use in routine clinical practice (E2). There has been enormous publicity for vaccinating AD by injection or nasal spray of β-amyloid designed to stimulate antibodies that will attack plaques in the brain. While results in mice have been impressive, both pathologically and behaviourally, and safety trials in normal human volunteers have been satisfactorily, evidence for efficacy in humans with AD awaits trials now in progress. The identification of β and δ secretases, the enzymes responsible for the abnormal degradation of amyloid precursor protein and the production of the toxic β protein and amyloid plaques, has led to the development of compounds to block these enzymes. These may shortly be available for clinical trials.
3: Profiles of cholinesterase inhibitors

**Donepezil (Aricept)**
*Action:* A piperidine-based selective acetylcholinesterase inhibitor which is highly selective for acetylcholinesterase in the central nervous system (CNS). It significantly inhibits brain cholinesterase, but has no effect on either cardiac muscle or smooth muscle in the intestine and has only a limited effect on pectoral muscle.48

*Dosing:* Donepezil should be initiated at a once-daily dose of 5 mg and increased to 10 mg after one month, provided there are no untoward effects. Donepezil is available in 5 mg and 10 mg tablets. Available evidence implies a further small but significant benefit with the higher dose, which is tolerated by approximately 90% of patients.49

*Adverse effects:* At 10 mg/day, nausea (17% of patients), diarrhea (17%) and vomiting (10%) may occur.48 These predictable cholinergic effects are generally transient and occur mostly on initiation or up-titration of the drug. Some patients also experience muscle cramps (8%), fatigue (8%) and dizziness (8%), as well as vivid dreams or nightmares. Dose reduction or morning administration may alleviate some of these adverse events. Donepezil must be used with caution in patients with sick sinus syndrome, other supratentorial conduction abnormalities, peptic ulcer, asthma or obstructive airways disease.

**Rivastigmine (Exelon)**
*Action:* Rivastigmine is a cholinesterase inhibitor that inhibits both acetylcholinesterase and butryrycholinesterase, which may theoretically be advantageous, as CNS butryrycholinesterase levels are raised in individuals with Alzheimer's disease (AD).

*Dosing:* Initiate at 1.5 mg twice daily for two weeks and titrate upwards; thereafter in monthly steps, to the highest well tolerated dose, to a maximum of 6 mg twice daily. Capsules are available in 1.5 mg, 3 mg, 4.5 mg and 6 mg strengths. Rivastigmine must be given twice daily because of its short elimination half-life, and this may compromise compliance in patients with AD. The treatment effect is clearly dose responsive and patients should be titrated to their highest well tolerated dose.

*Adverse effects:* At 6–12 mg/day, most frequently reported side-effects include nausea (47%), vomiting (31%), diarrhea (19%), headaches (17%), dizziness (21%), abdominal pain (13%), fatigue (9%) and malaise (5%). The slightly higher rate of side effects for rivastigmine may be counterbalanced by its shorter half-life. Side effects reported were usually mild to moderate and often transient at the time of dose and increase during the titration phase (up to 12 weeks duration).51 Gradual titration, with at least four weeks at each dose, and taking the drug with food is important to reduce side effects and maximum tolerance for patients. Dose can be increased more gradually or at only one of the daily dose intervals initially to improve tolerance in some patients. Analysis of the unpublished results in the Cochrane review favoured thrice-daily dosing, although low outcomes reached clinical significance.52

**Galantamine (Reminyl)**
*Action:* Galantamine is a selective, competitive and reversible acetylcholinesterase inhibitor with a dual mode of action through allosteric modification of presynaptic nicotinic receptors.

*Dosing:* Tablet sizes are 4 mg and 8 mg, with a liquid preparation (4 mg/mL) which is useful for titration. Dose can be titrated from 4 mg twice daily to 8 mg twice daily over four weeks after assessing tolerability and benefit. The dose should be adjusted in patients with moderate to severe hepatic impairment, starting with 4 mg daily. There is no rebound effect after abrupt discontinuation of treatment.

*Adverse effects:* With 8 mg twice daily, most side effects occurred in the first four weeks and were typical of this class of drug, including nausea (5.7%), vomiting (3.6%), diarrhea (5%), anorexia (5.7%), agitation (15%).52 No dose adjustment is required for mild to moderate renal impairment (creatinine clearance rate >9 ml/min), but galantamine is contraindicated in patients with severe renal impairment. The incidence of gastrointestinal side effects was low and adverse events were mild, suggesting galantamine is well tolerated when the dose is slowly escalated.

Practical recommendations for management

Once AD is diagnosed, cholinesterase inhibitor therapy should be considered. Vitamin E should also be considered. As yet, we do not recommend that women consider hormone replacement therapy.2

**Using cholinesterase inhibitors**

*Initiating ChEI therapy:* This requires thorough assessment, and preferably specialist confirmation of the diagnosis (see Box 2). It is important to counsel patients and their families about realistic potential benefits of these agents and to obtain consent for treatment. The dose should be titrated in steps, as shown in Box 3. Compliance should be monitored and response monitored by considering global, cognitive, functional and behavioural domains. Side-effects with all agents are predominantly gastrointestinal, often transient, dose-related, and reversible on cessation of treatment.

*Monitoring progress:* The patient should be reviewed clinically after two to three months of treatment with the maximum well-tolerated dose, and every three months thereafter. The need for continued therapy should be reviewed through the systematic assessment of cognition and function within six months. It is advisable to use standard brief cognitive tests on a regular basis (eg, Mini Mental State Examination, and a standardised assessment of function, such as Instrumental Activities of Daily Living [ADLACS]).31 Cognitive testing should not be repeated more frequently than every three months, as there are learning practice effects. It is difficult to determine improvement or decline when scores approach the upper or lower bounds of a test. Peak cognitive effect in both the rivastigmine and donepezil studies occurred at about three months, but in the Cochrane review of rivastigmine the peak effect on the CIBIC and Progressive Deterioration Scale occurred after more than six months.

*Ceasing ChEI therapy:* There are no clear data on when therapy ceases to be beneficial. It is reasonable to continue ChEI therapy for patients who have shown improvement or stabilisation in cognitive, functional or behavioural domains. Indications for a trial of medication withdrawal include:

- intolerable adverse effects;
- the patient having reached the severe stage of AD;
- ongoing benefits appearing questionable to a clinician or independent observer;

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4: Important messages for patients and carers

- Cholinesterase inhibitors offer modest but significant benefits in about two-thirds of patients with Alzheimer's disease.
- Benefit in a patient may be temporary stabilisation or improvement: eventually the benefit will wear off.
- Cholinesterase inhibitors provide symptomatic relief only: they are not cures and they do not attack the underlying disease.
- Drug treatment is only one component of AD treatment.
- New drugs are being developed which hold hope of arresting or reversing AD.

Competing interests

Henry Brodaty has been a consultant, sponsored speaker and/or investigator for Eisai, Pfizer, Novartis, Janssen, Seprx, Lundbeck, Neurathapeutics/Credocoma, SmithKline Beecham, Hoechst Marion Roussel, and Quinlans.

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Karyn Boundary is on the drug advisory board for Janssen, Lundbeck and Novartis. She has performed sponsored clinical drug trials for Pfizer, Eisai, Janssen, Novartis, Boehringer Ingelheim, Neurathapeutics/Credocoma, Aventis, Sanofi-Synthelabo, and has received honoraria from Eisai, Pfizer, Novartis, and Boehringer Ingelheim.

Jane Hecker has performed sponsored clinical drug trials for Eisai/Pfizer, Sandzio/Novartis, Parke-Davis/Novartis Us Ltd, Roche/Protagdin, Eli Lilly, Boehringer Ingelheim, Neurathapeutics/Credocoma and Janssen-Cilag. She is on the pharmaceutical advisory boards for Novartis, Janssen-Cilag and Bristol-Myer-Squibb, and has received honoraria from Janssen-Cilag, Eli Lilly and Boehringer Ingelheim.

John Snowdon is on the dementia drug advisory board for Janssen-Cilag Australia. He has been a sponsored speaker and/or investigator for Janssen-Cilag, Eli Lilly and Pfizer, and has received financial support to attend educational meetings from Neurath, and Lundbeck.

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References


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