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## Pharmacological Management of Alzheimer's Disease

Jane R Hecker, Carol A Snellgrove

### ABSTRACT

With the ageing of the population, Alzheimer's disease (AD) represents an individual and public health problem of enormous significance. Research is ongoing worldwide in the search for more effective treatments, including drugs to slow or prevent progression in AD. Three cholinesterase inhibitor drugs (donepezil, rivastigmine and galantamine) are currently subsidised in Australia for the management of core cognitive symptoms in mild to moderate AD. Other drugs are available for the secondary management of behavioural and psychological symptoms associated with AD. This article reviews the pharmacological management of AD, treatment efficacy, side effects, and practical issues in drug use.

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### INTRODUCTION

Dementia is a clinical syndrome characterised by progressive impairment in multiple cognitive and behavioural/psychological domains—primarily memory, language and speech, visuospatial ability, executive functioning, and mood/personality.<sup>1</sup> Most definitions, such as the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV) definition, require impairments be of sufficient severity to impact on social or occupational functioning. The prevalence of dementia increases exponentially from 1–2% among people aged 65 years to 30% among 90 year-olds. It is estimated that Alzheimer's disease (AD) accounts for up to 70% of dementia and is the main contributor to the steep increase in prevalence with age.<sup>2-4</sup> The recent availability of treatments for AD has provided the catalyst for the widespread development of memory clinics to enable proper assessment and pharmacological management for people with cognitive disorders.<sup>5</sup> Pharmacological management for AD can be divided into three major areas:

- preventative treatment;
- primary anti-dementia therapy for management of cognitive symptoms; and
- secondary treatment for management of behavioural and psychological symptoms of dementia.

### PREVENTATIVE TREATMENT

Epidemiological evidence supports a number of possible protective strategies, although direct prevention trials

are yet to provide clear evidence. The use of non-steroidal anti-inflammatory drugs to treat arthritis, and oestrogen replacement for post-menopausal women, have been associated with a reduced risk of AD. Physical activity appears beneficial, as does high dietary intake of anti-oxidant vitamins C and E, and vitamins B<sub>6</sub>, B<sub>12</sub> and folate.<sup>6,7</sup> Moderate intake of red wine appears protective.<sup>7</sup>

A number of studies are being conducted worldwide in patients with memory loss or mild cognitive impairment to test agents that may delay the onset of AD. Drugs under investigation for disease prevention include cholinesterase inhibitors, anti-inflammatory agents, antioxidants (including vitamin E) and oestrogens (in women).<sup>8</sup> However, the use of oestrogens has recently been made less viable by the findings of the Women's Health Initiative.<sup>9</sup>

Hypertension appears to be emerging as a risk factor for AD as well as vascular dementia.<sup>6,7,10,11</sup> Attention to modifying other vascular risk factors may have a role in AD as well as vascular dementia. Evidence suggests elevated homocysteine and reduced B<sub>12</sub> and folate levels are correlated with cognitive impairment. A link between cholesterol and amyloid metabolism in AD has been postulated, with long-term HMG-CoA reductase inhibitor (statin) studies showing reduced prevalence of AD in the statin treatment arms.<sup>6,12,13</sup>

### MANAGEMENT OF COGNITIVE SYMPTOMS

#### The Cholinergic Hypothesis

There is much evidence from animal and human research supporting a relationship between the cholinergic neurotransmitter system and memory and cognitive performance. Several lines of evidence implicate impaired cholinergic neurotransmission as contributing to the cognitive symptomatology of AD—progressive loss of cholinergic neurones in the basal forebrain nuclei; depletion of the enzyme choline acetyltransferase, which catalyses the synthesis of acetylcholine; and reduction in levels of brain acetylcholine. Attempts to increase cholinergic function in AD were based on the success of dopamine replacement in Parkinson's disease. The history of cholinergic pharmacology is characterised by the failure of acetylcholine precursors (e.g. choline, lecithin), releasing agents, and selective muscarinic agonists.<sup>8,14</sup>

#### Cholinesterase Inhibitors

The acetylcholinesterase inhibitors (AChEI) are the only licensed agents for primary treatment of AD. A large number of randomised controlled trials and major independent reviews including Cochrane meta-analyses,<sup>15-17</sup> a UK National Institute of Clinical Excellence appraisal,<sup>18</sup> and the American Academy of Neurology guidelines for dementia management<sup>19</sup> all support the use of

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cholinesterase inhibitors as symptomatic treatment in patients with mild to moderate AD. Clinical guidelines have also been published in Canada and Australia which support their use.<sup>20,21</sup> There are three AChEIs marketed in Australia—donepezil, rivastigmine and galantamine. The pharmacological characteristics and dosage schedules for each of these drugs are described in Table 1. The first AChEI developed (tacrine) is no longer available due to hepatic adverse effects.

### Evidence for Cholinesterase Inhibitors

AChEIs have been studied in over 20 multi-centre clinical trials involving over 9000 patients. Most of these studies have involved patients with mild to moderate severity AD, based on criteria of the National Institute of Neurological and Communicative Disorders and Stroke, and the Alzheimer's Disease and Related Disorders Association. Standard outcome measures for use in AD treatment trials as recommended by the US Food and Drug Administration included a cognitive measure, the Alzheimer's Disease Assessment Scale - Cognitive Subscale (ADAS-Cog), and a global scale such as Clinician Interview Based Impression of Change plus Caregiver Input (CIBIC-plus). Trials with AChEIs have shown gains of 2–4 points on the 70-point ADAS-Cog scale or 1–2 points on the 30-point Folstein Mini-Mental State Examination (MMSE) over six months—representative of a gain of six months function in this chronic disease. Based on the CIBIC-plus, about one-third of patients show significant improvement, detectable by a skilled clinician.<sup>14</sup> A benefit on activities of daily living has been demonstrated for all AChEIs, which is best described as a slowing of decline rather than an actual improvement.<sup>14</sup> Improvement in neuropsychiatric symptoms has also been shown with cholinesterase inhibitors, particularly in apathy, together with a delay in emergence of new behavioural symptoms. Variable patterns of improvement occur in anxiety, depression and hallucinations/delusions.<sup>14</sup>

Cholinesterase inhibitors are not curative, are not proven to prevent disease progression, and are not effective in all patients. Generally 50–70% of patients will achieve a symptomatic treatment response, either an improvement in cognitive or behavioural symptoms of AD, or alternatively, a stabilisation of disease progression. Due to the progressive nature of AD, a 'successful' treatment may be one that simply delays progression of symptoms rather than improves cognition. Stability is maintained for up to 12 months in clinical trials. No clearly identifiable factors predict response, including age, gender, apolipoprotein E (ApoE) genotype, and disease stage. Greater difference is measured between treatment and placebo groups in moderately-severe AD due to greater placebo decline at this stage.<sup>14</sup>

The clinical significance of these outcome measures is not automatically apparent from the trial data. While the cognitive and global scales used 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. Some patients treated with these agents do show a more significant level of clinical improvement. Commonly reported responses include identifiable improvement in attentiveness and alertness, involvement in conversational language, and initiation of activities of daily living, together with improvement in apathy and other behavioural symptoms. Recent research by Rockwood et al. describes benefit on clinically relevant individualised outcomes chosen by patients and caregivers, known as Goal Attainment Scaling.<sup>22</sup> Additional evidence is required to determine the specific value of these drugs in treating challenging behaviours in patients with AD. Caregiver time surveys measured in some more recent clinical trials (galantamine) have shown time savings, but further research is needed to study social and economic outcomes, including patient quality of life, caregiver stress and quality of life, impact on time to residential care, and cost-effectiveness of AChEIs.

**Table 1. Cholinesterase inhibitor profiles**

	<b>Donepezil</b>	<b>Rivastigmine</b>	<b>Galantamine</b>
Chemical group	Piperidine	Carbamate	Tertiary alkaloid (Daffodil derivative)
Mechanism of action	Reversible, non-competitive AChEI (highly selective)	Pseudo-irreversible, dual AChEI/BuChEI, G1 isoenzyme specific, selective for hippocampus, neocortex	Reversible, competitive, dual mode: selective AChEI plus allosteric nicotinic receptor modulator
Half-life	70 hours	2 hours	5-6 hours
Elimination	Renal and hepatic	Renal	Hepatic
Drug interactions	Low potential	Low potential	Low potential
Dose frequency	Daily	Twice daily	Twice daily
Form/Administration	Tablet - association to food not important. Morning administration can reduce vivid dreams/nightmares	Capsule or liquid - take with food to minimise nausea	Tablet - take with food to minimise nausea
Starting dose	5 mg daily	1.5 mg twice daily	4 mg twice daily
Recommended titration*	Titrate up to 10 mg at 4-6 weeks	4 weekly titration: 3 mg twice daily then 4.5 mg twice daily then 6 mg twice daily. Liquid allows flexibility for titration.	4 weekly titration: 8 mg twice daily then 12 mg twice daily (8 mg twice daily is the maximum subsidised dose in Australia)
Maximum dose	10 mg daily	6 mg twice daily	12 mg twice daily

\*re-titration is required if treatment is stopped for more than a few days, AChEI = acetylcholinesterase inhibitor, BuChEI = butyrylcholinesterase inhibitor

Although the majority of clinical trials studied mild to moderate AD over six-months duration, there is now supporting evidence in more severe dementia,<sup>23</sup> and the nursing home population,<sup>24</sup> supporting benefit over 12 months duration.<sup>25,26</sup> Dementias other than AD have been studied, with evidence of benefit in both dementia with Lewy bodies (rivastigmine)<sup>27</sup> and vascular dementia—galantamine,<sup>11</sup> and donepezil (unpublished observations).

### Guidelines for Prescribing Cholinesterase Inhibitors

Guidelines for prescribing AChEI drugs are described in Table 2. The Pharmaceutical Benefits Scheme (PBS) criteria for subsidy are under continuing negotiation and change, which has created some difficulties. Patients are eligible for a six-month trial of each cholinesterase inhibitor, followed by ongoing treatment if they demonstrate a positive response.

There have been no randomised, controlled, head to head studies comparing the different AChEIs, although a number of manufacturer-sponsored open-label studies have been presented at scientific meetings. The measurable short-term improvement with these drugs is comparable and the clinical relevance of pharmacological differences has not been established.<sup>14</sup> Decisions on choice of AChEI are predominantly driven by tolerability and ease of administration. If one drug is not tolerable or effective, a trial of an alternate agent can be worthwhile.

Side effects are similar across all drugs in this class and include expected cholinergic gastrointestinal effects—particularly nausea, diarrhoea, vomiting, abdominal pain, anorexia, and weight loss—which are usually dose-related and often transient. Non-specific side effects can include headache, fatigue, insomnia, dizziness, tremor, and muscle cramps. Urinary symptoms, particularly urinary incontinence and urgency, have been reported. Occasionally patients can develop agitation, hallucinations

or vivid and distressing dreams. A small increase in the incidence of syncope is potentially the most serious side effect. Side effects can be minimised by gradual dose titration, and may respond to dose reduction or cessation of the drug, if necessary.<sup>28</sup> AChEIs should not be used with other cholinomimetic drugs or anticholinergic agents. Dose modification for renal or hepatic impairment is generally not required. Cholinesterase inhibitors are currently subsidised until dementia becomes severe.

### Other Putative Cognitive Enhancers

Epidemiological evidence suggests that the antioxidant vitamin E may be a useful treatment for established AD. The single, large published study, restricted to patients with moderately-severe disease showed that vitamin E (1000 units twice daily) or selegiline (5 mg twice daily) both delayed the time to functional worsening of AD symptoms.<sup>29</sup> Opinion varies regarding the place of vitamin E in AD treatment—it is included as a guideline level treatment in the American Academy of Neurology recommendations,<sup>19</sup> although the Cochrane Review states that there is insufficient evidence.<sup>30</sup> Side effects are rare, but interaction with warfarin can lead to bleeding problems.

Ginkgo biloba, derived from the Chinese maidenhair tree, is a putative cognitive enhancer with reported anti-inflammatory and antioxidant properties. Randomised, controlled trials are small in number and demonstrate variable response, but overall evidence is weak.<sup>31,32</sup> The manufacture of ginkgo is unregulated, lacking standards for potency or purity. Although generally safe, ginkgo may cause bleeding and should be used with caution in patients receiving aspirin.<sup>19</sup>

Despite epidemiological support for a possible role in prevention of AD, treatment studies with both anti-inflammatories and oestrogen in patients with AD have not demonstrated significant benefit. Memantine, an

**Table 2. Guidelines for prescribing cholinesterase inhibitors in Alzheimer's disease**

1. Obtain accurate diagnosis of Alzheimer's disease from specialist physician or psychiatrist
2. Assess disease severity: AChEIs indicated for mild to moderate Alzheimer's disease only
3. Check general health status  
(bradycardia, heart block, asthma or active peptic ulcer are absolute contraindications, and must be resolved before using AChEIs)
4. Cease anticholinergic drugs, if possible
5. Counsel patient/family regarding realistic expectation of benefit/risk and identify treatment goals
6. Ensure compliance
7. Perform baseline cognitive assessment:
  - MMSE 10-24: eligible for PBS subsidy
  - MMSE >24: ADAS-Cog required
  - MMSE <10 and clinically mild-moderate Alzheimer's disease: CIBIS/CIBIC (for non-English speaking, low education, visual/hearing impairment and intellectually disabled)
8. Obtain PBS authority script (in writing) for six months initial treatment
9. Review by specialist or general practitioner at 1, 3 and 6 months

#### Notes:

- Clinical trials indicate that peak cognitive improvement is usually achieved 2-3 months following commencement of treatment. However, some patients may show benefit at later times.
- Switching between drugs is allowed for side effects or efficacy.
- Authority scripts available by phone approval except first script and first maintenance script.
- A trial of AChEI medication withdrawal is indicated when side effects are intolerable; the patient has reached severe Alzheimer's disease; despite treatment compliance there is the same steady rate of decline as before treatment; or there is an acceleration in the rate of decline in mood, cognition, function or behaviour, not explainable by an intercurrent illness.

AChEI = acetylcholinesterase inhibitor, MMSE = Mini-Mental State Examination, ADAS-Cog = Alzheimer's Disease Assessment Scale - Cognitive Subscale, CIBIC = Clinician Interview Based Impression of Change, CIBIS = Clinician Interview Based Impression of Severity, PBS = Pharmaceutical Benefits Scheme, CIBIC-plus = Clinician Interview Based Impression of Change plus Caregiver Input

N-methyl-D-aspartate (NMDA) receptor antagonist, improved cognition and global functioning in groups of patients with moderate to severe dementia, without adverse effects.<sup>33,34</sup> It can also be combined with AchEIs.<sup>35</sup> Memantine has been approved for the treatment of dementia in Europe for over ten years, where it is used in combination with AchEIs. Memantine is currently only accessible in Australia through the Special Access Scheme.

Current research into the molecular biology and genetics of AD promise to lead to the development of more powerful therapies that might delay disease progression or possibly prevent the development of AD. Certain enzymes involved in the metabolism of amyloid precursor protein ( $\beta$  and  $\delta$  secretases) and tau protein (glycogen synthase kinase-3) lead to the production of amyloid plaques and neurofibrillary tangles. Drugs under development include agents which block the effect of these enzymes and may prevent the amyloidogenic processing of amyloid precursor protein. Amyloid- $\beta$  immunisation has shown promising results in animal studies, but early clinical trials were withdrawn due to the development of meningo-encephalitis in a small percentage of study subjects. Future improvements in this technique are likely. Further genetic developments may lead to genetic manipulation of risk factor genes, altering their relationship with amyloid metabolism.

#### MANAGEMENT OF BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

Changes in personality and behaviour are commonly associated with AD, often becoming significant in the moderate and severe stages of dementia. These changes may be extremely disruptive to patients and caregivers in both home and residential care settings, resulting in reduced quality of life and increased costs of care. Behavioural and psychological symptoms associated with dementia (BPSD) have a multifactorial aetiology, including neurobiological, psychological and social contributors. Drugs which may target specific symptoms within the BPSD spectrum should be restricted to situations where other physical or medication-related causes have been identified and treated, the symptom is at least moderately distressing to either the patient or caregiver, the patient has failed a trial of non-drug strategies (e.g. behaviour therapy, environmental modification, music therapy, improved sleep hygiene), and the symptom is likely to be drug-responsive. General principles of BPSD drug management are summarised in Table 3.

##### Conventional Antipsychotics

Antipsychotics are the most commonly utilised class of drugs in the treatment of BPSD—for the treatment of agitation and psychotic symptoms. A meta-analysis of conventional antipsychotics (not atypical agents) showed only small benefit compared to placebo (18% improvement in agitation) and did not support superior efficacy of any specific agent. Side effects of this class of drugs are common amongst older patients and include extrapyramidal movement disorder; sedation; and tardive dyskinesia, which develops in one-third of patients at twelve months.<sup>36</sup> A randomised study comparing haloperidol 2–3 mg daily with lower doses, showed benefit in terms of reduction in aggression at 2–3mg, but no efficacy at lower doses.<sup>37</sup>

**Table 3. Principles of pharmacological management of behavioural and psychological symptoms of dementia**

1. Specify and quantify the problematic symptom(s) being targeted to allow objective assessment of drug efficacy. A behaviour chart recorded by the primary caregiver may be useful in monitoring symptoms before and after drug therapy.
2. Choose the therapeutic agent on the basis of the most appropriate treatment class for a particular symptom of a defined psychiatric syndrome, confirmed efficacy for relevant symptoms, and minimal side effect potential.
3. Commence with a low dose (one-third to half the usual adult starting dose, e.g. 0.25 mg risperidone twice daily, or 2.5 mg olanzapine daily).
4. Titrate dose gradually while monitoring response and side effects.
5. If no positive response is identified, cease medication and try an alternative.
6. Avoid the use of multi-drug therapy.
7. Re-evaluate both the drug regimen and the non-pharmacological strategies at three-monthly intervals.
8. Consider the patient's co-morbid medical problems and therapy.

##### Atypical Antipsychotics

A body of literature indicates that atypical antipsychotics have superiority over conventional agents in terms of side-effect profile, and possibly, efficacy.<sup>38</sup> However, the newer drugs (risperidone, olanzapine, quetiapine, ziprazadone) are more costly than conventional agents, and have the potential to cause weight gain (olanzapine) and derangement of glucose metabolism.<sup>39,40</sup> Risperidone has demonstrated efficacy for both psychotic symptoms and more general BPSD,<sup>41</sup> and has shown significant efficacy for aggression and psychotic symptoms compared to both placebo and haloperidol.<sup>42</sup> A multi-centre Australian study has confirmed the positive results of international trials.<sup>43</sup> A single study of olanzapine showed an inverted-U dose-response curve. The lowest dose (5 mg) produced the greatest effect on a composite score comprising agitation/aggression, hallucinations, and delusions, and was significantly superior to placebo.<sup>44</sup> Lack of PBS subsidy for these drugs in BPSD restricts their use.

##### Anxiolytics

Benzodiazepines are commonly used in the treatment of BPSD, and are used primarily for anxiety, agitation and sleep disturbance. However, few randomised trials have examined the use of anxiolytics in the elderly, and even fewer have looked at their use in BPSD. One study reported no difference in treatment outcomes with haloperidol compared to oxazepam in dementia patients.<sup>45</sup> Anecdotal evidence suggests that the non-benzodiazepine sedative, zolpidem, may be useful in restoring normal sleep.<sup>46</sup> The side-effect profile of benzodiazepines includes sedation, motor (ataxia) and cognitive impairment (amnesia and confusion) and potential withdrawal syndrome. An increase in falls can occur. Sleep architecture may also be altered, with inhibition of rapid eye movement (REM) and delta wave sleep. Therefore, benzodiazepines are poor choices for regular use in dementia, but can have a role for short-term management of anxiety or sleep disturbance. Preferred agents are those with short action and no active metabolite, including oxazepam and lorazepam.

## Antidepressants

It is important to treat depression in dementia, and a low threshold should exist for initiating treatment. Selective serotonin reuptake inhibitors (SSRIs) are the first-line antidepressants. A retrospective review of studies of SSRIs (citalopram and sertraline) in dementia has shown a significant effect on both psychosis and depression, suggesting that these agents could have antipsychotic potential in dementia patients. Improvements have also been suggested for aggression, anxiety and agitation.<sup>47</sup>

## Anticonvulsants

Lack of convincing evidence for anticonvulsants in the treatment of BPSD should limit their use to situations where first-line therapy has been ineffective. Low dose carbamazepine (300 mg daily) given to patients within an institutional setting has been associated with reduced patient agitation and aggression, and reduced staff time required to manage patients.<sup>48</sup> Side effects of carbamazepine include sedation, skin rash, headache, leucopenia, and mild elevation of liver function tests. Sodium valproate has been used in the treatment of aggressive behaviour in patients with dementia.<sup>49</sup> There are no studies of the newer anticonvulsants, although anecdotal benefit of gabapentin has been reported.<sup>50</sup>

## Cholinesterase Inhibitors

Studies report benefits, and anecdotal observations suggest that a small proportion of AD patients show substantial behavioural improvements when cholinesterase inhibitor therapy is commenced.<sup>51</sup> This can occur even in the absence of measurable cognitive benefit.

## Oestrogen

A small clinical trial<sup>52</sup> suggests that short-term oestrogen therapy may safely decrease the frequency and severity of BPSD, particularly in sexually disinhibited or very aggressive men. Oestrogen is generally tried where other options have failed.

## CONCLUSION

AD is a progressive neurodegenerative disease affecting a significant number of older people. The availability of AChEIs to stabilise the core cognitive symptoms of mild to moderate AD for up to twelve months has heralded a noticeable shift to a more positive attitude to the assessment and management of patients. Donepezil, rivastigmine, and galantamine are currently subsidised under PBS authority restrictions.

Important advances have also been made in the pharmacological management of behavioural and psychological symptoms of AD, improving the quality of life for both patients and caregivers. The continuing endeavour to elucidate preventative treatment is important if our approach to AD is to shift from palliative care.

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