Cholinesterase inhibitors and Alzheimer's disease

HELEN CREASEY MB BS, FRACP

Cholinesterase inhibitors may lead to improvement in the symptoms of Alzheimer's disease, but there is no direct evidence that they alter the long term outcome.

What are cholinesterase inhibitors?

Cholinesterase inhibitors block cholinesterases, enzymes that break down acetylcholine in the synaptic space, thereby allowing acetylcholine to act longer on the post-synaptic receptor. Acetylcholine is a major neurotransmitter for memory, attention and concentration.

When should they be used?

At present cholinesterase inhibitors are only available on the PBS for Alzheimer's disease. (However, there is some evidence of possible benefit in dementia with Lewy bodies and in vascular related dementias.) Most studies have looked at patients with Mini Mental State Examination (MMSE) scores from 10 to 24; a few have included nursing home patients or those with MMSE scores less than 10. Although the current advice is to use these drugs early, there is no direct evidence that this is either necessary or more beneficial than later use.

Dr Creasey is Staff Specialist Geriatrician, Centre for Education and Research on Ageing, Concord Repatriation Hospital, Concord, NSW.

Obtaining authority

Current PBS guidelines are complex and require written application for authority approval both to start and to continue the drugs. The application letter must include confirmation of the diagnosis as well as current performance and/or a specific category if baseline MMSE is less than 10. The authority permits one month's therapy and five repeats.

Confirmation of diagnosis

A specialist/consultant physician or psychiatrist must confirm the diagnosis of Alzheimer's disease.

Current performance

The relevant cognitive test score or scores at baseline must be given. There are two major divisions based on MMSE scores: patients with scores at or above 10 and those with scores below 10.

For patients with scores from 10 up to 24 no further testing is required. For those with scores above 24, an Alzheimer's Disease Assessment Scale Cognitive subscale (ADAS-Cog) score (0 to 70) is also required. While most GPs should be able to perform a MMSE, the ADAS-Cog requires specific forms, tools and training, and may more easily be supplied by the diagnosing specialist or a memory clinic.

For patients with a MMSE score below 10, a specific category (see below) must be supplied for PBS approval.

Category

Approval will be given for patients with MMSE scores below 10 if any of the following factors account for poor MMSE performance.

- Language difficulties: nonEnglish speaking background
- Language difficulties: major dysphasic symptoms
- Cultural difficulties (Aboriginal or Torres Strait Islander)
- Perceptual difficulties, e.g. blind, deaf
- Limited education, e.g. less than six years of schooling, illiterate and/or innumerate
- Long standing intellectual disability.

Continuing treatment

To continue the drugs beyond six months requires a further written application. This must report retesting results showing a gain of at least 2 points on MMSE (when baseline MMSE is above 10), or a 4-point improvement in ADAS-Cog.

Patients with a baseline MMSE below 10 must be shown to be 'very much improved' or 'much improved' as defined on the Clinician's Interview-Based Impression of Change (CIBIC). The CIBIC is a specific scale based on formal assessment, across a variety of domains, using structured interviewing of the carer and patient separately, each taking about 20 minutes. It is a 7-point scale, ranging from 'very much improved' to 'marked worsening'.

(Like the ADAS-Cog, it is usually performed by a specialist or a memory clinic.) If the changes do not meet these levels, continuation of treatment will not be approved.

How are they used?

There are three acetylcholinesterase inhibitors available: donepezil (Aricept), rivastigmine (Exelon) and galantamine (Reminyl). All medications should be started at the lowest available dose and increased gradually.

For donepezil start the patient on 5 mg at night, and if tolerated after one month then increase the dose to 10 mg nightly. Rivastigmine is started at 1.5 mg twice daily and increased, if tolerated, at not less than two-weekly intervals by 3 mg a day to a maximum dosage of 6 mg twice daily (i.e. over at least eight weeks). For galantamine, start at 4 mg twice daily, and if tolerated after one month then increase the dosage to 8 mg twice daily. Although galantamine has been tested in dosages up to 16 mg twice daily, this dosing is not available on the PBS.

Lack of efficacy with one drug may be followed by trial of a second drug, but this practice has little scientific basis. Second drug trials are reasonable when the maximum drug dosage is not achieved in a patient because of side effects.

What needs monitoring?

Assessment of MMSE, ADAS-Cog or CIBIC within 6 months is required to apply for continuation of PBS authority. It is probably not helpful to repeat testing before three months, since maximal effect is seen four to six weeks after maximum dosage is achieved. If no improvement is seen at three months, another drug in the group may be tried, with a short wash out period (one to two days between medications).

Usually side effects manifest early, and close monitoring of the patient on a weekly or fortnightly basis during the titration phase is suggested.

Common side effects

These drugs are cholinergic and potentially will increase any cholinergic activity. Effects of this may be seen in the cardiac, respiratory, gastrointestinal, genitourinary and central pathways. Gastrointestinal side effects are common and include anorexia, weight loss, nausea, vomiting, flatus, reflux and diarrhoea. Urinary urgency and frequency, changes in sleep pattern and nasal drip are also common. Sleep disturbance is more common in patients taking donepezil; however, donepezil has the least gastrointestinal side effects and requires only once daily dosing. Rivastigmine produces the most gastrointestinal problems. Common side effects should be sought regularly during titration.

Important precautions and interactions

Uncommon but more hazardous (or potentially so) cholinergic effects include gastrointestinal ulceration and bleeding, pancreatitis, syncope from arrhythmias (especially bradycardia), incontinence (bowel and/or bladder), urine retention, worsening of asthma or chronic obstructive pulmonary disease (COPD), delirium, seizures and parkinsonism. The drugs have not been tested in pregnancy, during lactation or in children.

Rivastigmine dosage needs to be modified in patients with liver disease. Donepezil and galantamine potentially may interact with the metabolism of other drugs; however, no clinically important interactions have been documented and many commonly used drugs have been co-administered without significant interactions. All three medications may enhance the action of cholinesterase neuromuscular blockers and caution should be taken with anaesthesia. All anticholinergic drugs will reduce the action of cholinesterase inhibitors.

Hazardous side effects are more likely in patients who have underlying chronic diseases such as sick sinus syndrome, COPD, peptic ulcer disease or an unstable bladder, and in those who are frail with multiple medical problems and medications.

Clinical use: the author's views

Cholinesterase inhibitors do not prevent progression of the patient's underlying dementia. It is important that the patient and/or carers understand this and are supported, as needed, as the dementia worsens. The drugs should never be prescribed without also implementing patient and carer support programs. These may be provided by the GP but may also involve others such as aged care assessment teams (ACATs) and Alzheimer's Australia groups (www.alzheimers.org.au).

Although the evidence of benefit is statistically significant, the size of the benefit is clinically small and studies have not included a patient point of view. While carers often seek treatment, patients may not be willing and conflicts can result. Anxiety or depression may develop, in either patient or carer, if treatment effect does not meet expectation.

Conditions potentially exacerbated by cholinesterase inhibitors should be specifically screened for prior to starting these drugs, and again at follow up. Even late symptoms that could be attributed to dementia, such as incontinence, may be due to these drugs; this can be established by trial of drug withdrawal. There is no defined time to stop these drugs, but a patient who becomes dependent for self-care in a nursing home probably does not benefit from continued use. MT

Declaration of interest

Dr Creasey has no current involvement with the pharmaceutical industry pertaining to these drugs other than attending educational meetings. She has been on the advisory boards and involved in trials for all three drugs.