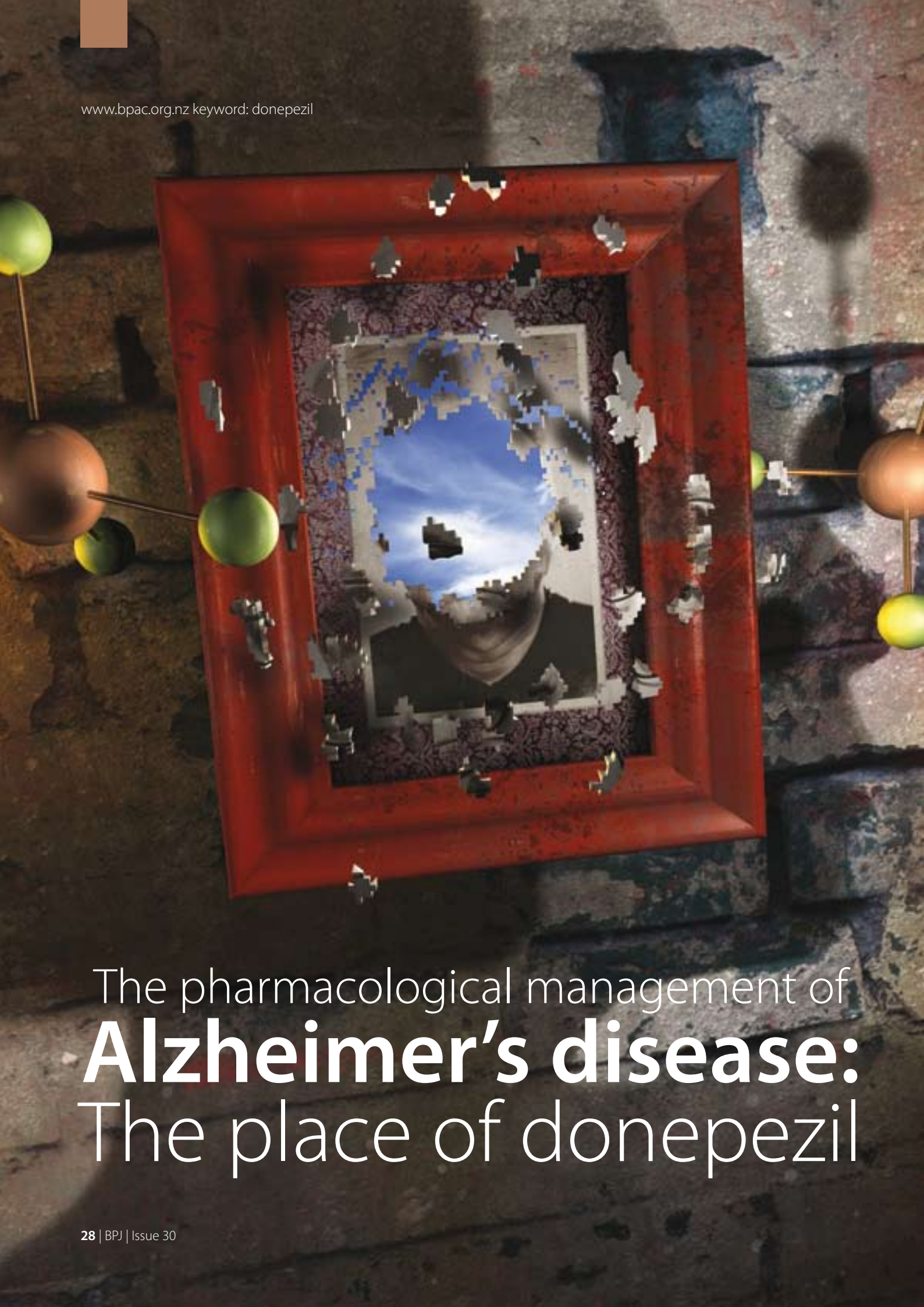
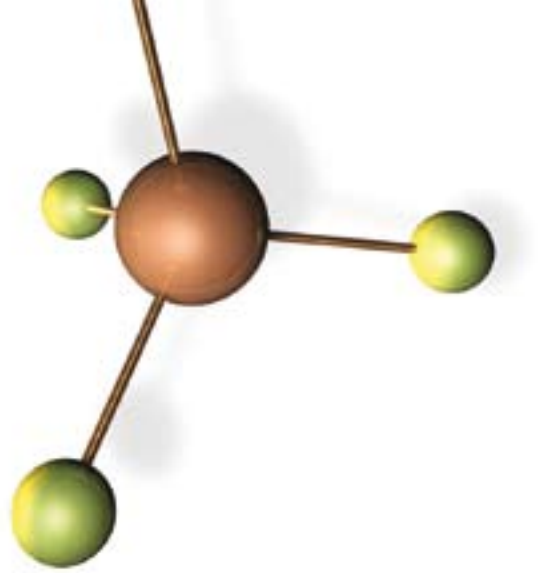
www.bpac.org.nz keyword: donepezil



The pharmacological management of **Alzheimer's disease:** The place of donepezil



Donepezil to be funded for the treatment of Alzheimer's disease

As the world's population ages, the number of people affected by Alzheimer's disease, the most common form of dementia, will rise rapidly. There is currently no treatment available that can prevent the onset of Alzheimer's disease or its progression. Management is focused on symptomatic treatment using lifestyle, behavioural and pharmacological methods, where appropriate. The aim of treatment is to improve quality of life for both the person with Alzheimer's disease and their family.

PHARMAC recently announced that donepezil, a medicine used in the management of Alzheimer's disease, will be funded on the Pharmaceutical Schedule from November 1, 2010. The Donepezil-Rex brand (donepezil hydrochloride) will be available for prescription by any prescriber, and will not require Special Authority approval or specialist recommendation.

Donepezil is a specific and reversible inhibitor of acetylcholinesterase, registered in New Zealand for the symptomatic treatment of Alzheimer's disease and vascular dementia. Some guidelines recommend that donepezil (and other acetylcholinesterase inhibitors) only be used in

* The Mini Mental State Examination (MMSE) is a commonly used test of cognition. The MMSE is not specific for Alzheimer's disease and is confounded by age and education level. It should be used only as an aid to assessment and not as an explicit guide to treatment.

Key Concepts

- Management of Alzheimer's disease focuses on slowing the progression of symptoms through lifestyle, behavioural and sometimes pharmacological methods.
- Donepezil is an acetylcholinesterase inhibitor used in the management of Alzheimer's disease. From November 1, 2010, Donepezil-Rex will be funded on the Pharmaceutical Schedule, without the need for Special Authority.
- Donepezil and other acetylcholinesterase inhibitors treat the symptoms of Alzheimer's disease and in some people improve symptoms related to cognition, behaviour and function. They may delay the need for full-time institutional care. There is no evidence to suggest that they prevent the onset or the ultimate progression of Alzheimer's disease.
- Before prescribing donepezil GPs are advised to discuss this with a practitioner experienced in the treatment of dementia and in the use of acetylcholinesterase inhibitors.
- Patients using cognitive enhancers such as donepezil should be reviewed regularly for treatment response and adverse effects.

Cost-effectiveness of donepezil in Alzheimer's disease

Estimates of the cost-effectiveness of donepezil need to make several assumptions around the effects of treatment on progression to full-time care. The extent that acetylcholinesterase inhibitors delay rest home placement is uncertain, as the evidence is incomplete and ambiguous.

The AD2000 study, published in 2004, concluded that donepezil provided very minimal clinical benefits and was not cost-effective in people with mild or moderate disease.[7] However, due to low recruitment and methodological issues, many subsequent reviews or analyses have not incorporated the results of the AD2000 study.

In the National Institute for Clinical Excellence (NICE) guidelines from the United Kingdom it was concluded that donepezil and other acetylcholinesterase inhibitors are cost-effective, but only in people with moderate Alzheimer's disease, and this is the basis of their recommendation for the use of these medicines.[2] The main benefits are associated with assumed cost savings due to delayed full-time institutional dementia care and support.

There is also debate about the cost-effectiveness of donepezil in people with mild Alzheimer's disease, and whether there are benefits in starting acetylcholinesterase inhibitors, both on clinical and economic grounds. While the AD2000 trial did not report any benefits in people with mild disease, other more recent cost-effectiveness models for donepezil in mild to moderate Alzheimer's disease, support their use in the early stages of the disease.[6]

The lack of clarity regarding cost-effectiveness reinforces the need to regularly review and assess the response to donepezil and to stop treatment if it appears ineffective or is not tolerated.

moderate Alzheimer's disease (rated by a MMSE* score of 10 – 20).[1,2] However there is evidence that donepezil has a positive effect in some people with severe[3,4] and mild Alzheimer's disease.[5] In practice, donepezil may be used in any patient with Alzheimer's disease, ranging from the newly diagnosed to those with severe disease.

Donepezil is considered to be cost-effective in moderate Alzheimer's disease (see sidebar) and there are emerging views that cost effectiveness may also extend to patients with mild disease (MMSE 21 – 26) mainly due to assumed reduced costs related to institutionalisation and care.[6]

It is recommended, due to the complexity of Alzheimer's disease and dementia treatment in general, that only clinicians with experience in treating dementia should initiate therapy. In practice this may be difficult but it is advisable to discuss treatment with a specialist and to become familiar with local protocols and practices. GPs may work in conjunction with the care team to assess the response to therapy, as the GP is more likely to be familiar with the patient over a longer time period.

The use of acetylcholinesterase inhibitors in Alzheimer's disease

Alzheimer's disease is associated with a decrease in activity of the cholinergic system in the brain. Pharmacological treatments for Alzheimer's disease are based on inhibition of acetylcholinesterase, which increases the concentration of acetylcholine in the brain, resulting in increased cognitive function in some people. This class of drugs have also been shown to have some effect on other forms of dementia, including vascular dementia.[8]

There are currently three acetylcholinesterase inhibitors available and registered in New Zealand for the treatment of Alzheimer's disease – donepezil (Donepezil-Rex, Aricept, Donezil), galantamine (Reminyl) and rivastigmine (Exelon). Donepezil-Rex is the only acetylcholinesterase inhibitor that will be funded on the Pharmaceutical Schedule at this time.

Are acetylcholinesterase inhibitors effective?

Acetylcholinesterase inhibitors improve symptoms related to cognition, behaviour and function for some people with Alzheimer's disease.[5] However, there is no evidence to show that they slow the underlying progression of the disease.[1, 2] Minor improvements in daily activity scores and cognition test results have been observed such as an improvement of one to two points on the 30 point MMSE test. For some people with Alzheimer's disease this may mean that they have improved memory and ability to perform daily tasks, improved quality of life and reduced need for care.

The results of acetylcholinesterase inhibitor therapy are variable, but on average, patients may expect about six months of preserved cognitive function. Clinically relevant improvement has been measured (using cognitive tests) in approximately 39% of patients taking donepezil versus 22% taking a placebo.[2] Increasing the dose of the acetylcholinesterase inhibitor may result in a greater improvement for some patients, however adverse effects may become intolerable.[2,5]

Comparing donepezil to other non-funded acetylcholinesterase inhibitors

All three acetylcholinesterase inhibitors available in New Zealand are similarly effective in treating the symptoms of Alzheimer's disease and are associated with similar adverse effects. Lack of response to one drug does not necessarily mean that benefit will not be derived from another.

Galantamine

Like donepezil, galantamine is a selective inhibitor of acetylcholinesterase, however it also enhances the action of acetylcholine on nicotinic receptors. Nicotinic cholinergic receptors are thought to be important in regulating cognitive functions such as attention. Galantamine has a longer half-life than donepezil, which could mean that severe adverse effects persist for longer.[2] However, there have been no significant clinical differences demonstrated between the effect and tolerability of galantamine and donepezil.

Cognitive testing in Alzheimer's disease and its role in defining progression

Cognitive tests are used to monitor both the progression of Alzheimer's disease and the treatment effect of pharmacological agents. The two most commonly used tests in New Zealand are the Mini Mental State Examination (MMSE) and Addenbrooke's Cognitive Examination-Revised (ACE-R).

The MMSE is a brief test (approximately ten minutes) that can be used for screening for cognitive impairment and for estimating severity and progression of Alzheimer's disease and other forms of dementia. The maximum score on the MMSE test is 30. Age and education levels may influence scores. Scores above 20 can suggest mild cognitive impairment, scores between 11 and 20 suggest moderate cognitive impairment and scores of ten or below suggest severe cognitive impairment. These scores are suggested in the context that a patient has already been clinically diagnosed with Alzheimer's disease and a level of cognitive impairment is to be ascertained.

The ACE-R is a simple and effective test that can be administered by any clinician.[9] It has been suggested that it can detect dementia earlier than MMSE though neither test should be used as a means of diagnosing Alzheimer's disease. Both tests are useful in assessing patients and helping family and caregivers to understand disease progression.

An online copy of ACE-R can be found at several websites including: **www.stvincents.ie/dynamic/File/Addenbrookes_A_SVUH_MedEl_tool.pdf**

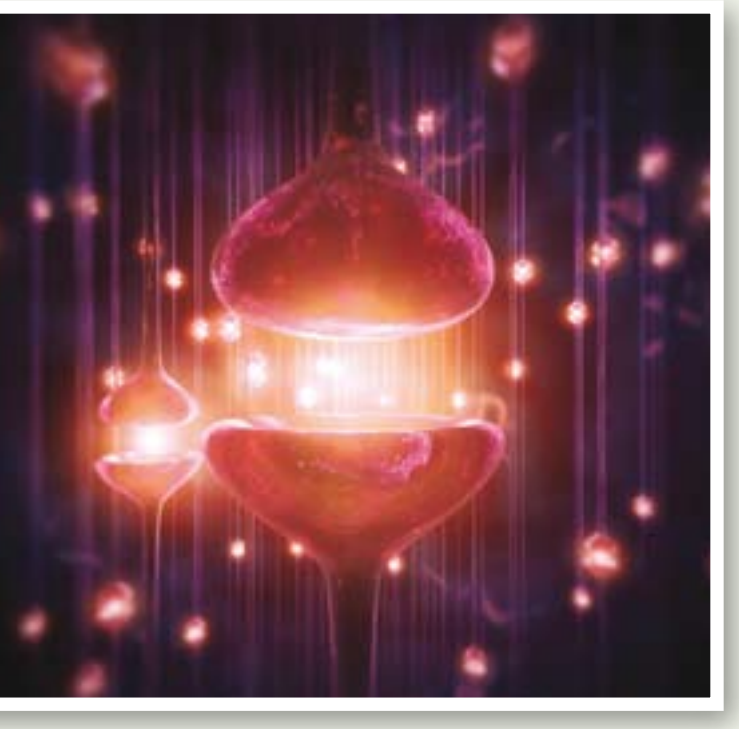
The Alzheimer's disease Assessment Scale-cognitive subscale (ADAS-cog) is used for measuring cognitive impairment and is frequently used as the outcome measure in clinical studies.

Memantine

Memantine is a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist, which is also used for the symptomatic treatment of Alzheimer's disease.[10] It is thought that malfunction of glutaminergic neurotransmission at NMDA receptors may contribute to symptom expression and progression of Alzheimer's disease. Memantine partially blocks NMDA receptors, inhibiting over-stimulation by the excitatory neurotransmitter glutamate.[10] This action can result in a small symptomatic improvement in cognition, mood and the ability to perform daily tasks, similar to the functional gain observed in some people taking acetylcholinesterase inhibitors.

The adverse effects of memantine are usually mild and may include influenza-like symptoms, headaches, muscular pain and dizziness.

In general, it is considered that the limited evidence of benefit for memantine is outweighed by the economic costs involved with the treatment.[2, 11] Memantine is not currently funded in New Zealand.



Rivastigmine

Rivastigmine is less selective than donepezil and targets both acetylcholinesterase and butyl-cholinesterase inhibitors.[5] However this increased inhibition does not appear to result in a clinically different effect than donepezil. Clinical trials used to study rivastigmine have only lasted 24 weeks in duration, therefore it is unproven whether treatment gains would last longer than six months. Rivastigmine is available as a transdermal patch preparation, which may be preferable for people who have experienced intolerable adverse gastrointestinal effects with an oral acetylcholinesterase inhibitor.

Initiating donepezil and assessing treatment response

Clear treatment goals should be set before commencing an acetylcholinesterase inhibitor. As donepezil is the only acetylcholinesterase inhibitor that is to be funded, it is recommended to trial this medicine first. Other acetylcholinesterase inhibitors may be trialled if there is no response to donepezil, however this will depend on whether the cost of treatment is able to be met.

Individual response to donepezil can not be predicted. The duration of treatment should be for as long as the patient is seen to benefit. The benefits of continuing donepezil should be assessed through the use of periodic evaluations of the patient's overall and cognitive function.

Initiating donepezil

Practice points

- Before initiating donepezil in a person with Alzheimer's disease it is strongly recommended that a practitioner experienced in the treatment of dementia is consulted.
- Donepezil should not be considered unless a clear diagnosis of Alzheimer's disease has been made. There is no evidence that donepezil is beneficial in people with mild cognitive impairment or that it delays the progression to Alzheimer's Disease.[12]

- Clearly defined treatment aims should be set e.g. decreased carer burden and stress, increased time until long-term care is needed, stabilisation of memory or cognition, decline in specific behaviours.
- Once the decision has been made to prescribe donepezil, it is recommended that treatment is commenced at 5 mg/day (once daily dosing, usually taken at night). This dose should be maintained for at least one month before clinical response is assessed. Monitor for adverse effects.
- If tolerated the dose may be increased to 10 mg/day. Treatment response should be reassessed at three months and again at six months.
- Reduce the dose to 5 mg/day if adverse effects become intolerable or improved clinical benefit is not apparent.
- If no benefit is observed at either dose, donepezil should be discontinued.

Best Practice Tip: Some DHB areas have specialised "memory clinics" where patients with Alzheimer's disease can be diagnosed and treated and families can be supported in understanding the changes and challenges likely to take place after diagnosis. Contact your local DHB for details of this service.

Assessing response to treatment

It is important to explain to both the patient and their family that pharmacological therapy for Alzheimer's disease is largely symptomatic. Acetylcholinesterase inhibitors can improve quality of life and cognitive function in many patients, but these gains are only temporary. Family and caregivers are often involved in observing for treatment response and adverse effects.

Potential adverse effects should be discussed prior to treatment as they can affect the way treatment goals are set. For example, if the goal for therapy is to increase the quality of life then the extent of the adverse effects can play a large role in deciding if, and when, to cease therapy.

Cognitive improvement[2]

- Assess cognitive function and activities of daily living prior to starting treatment using cognitive tests such as MMSE or ACE-R and self-reported and family observation of behaviours
- Assess initial treatment response after one month
- After three months at the highest tolerated dose, assess cognitive response to therapy
- If cognitive test scores indicate improvement (or no deterioration) and there is evidence of functional or behavioural improvement, continue treatment
- Treatment for longer than six months should be based on clear response and adequate ability for monitoring of the patient

Adverse effects, precautions and drug interactions

Mild cholinergic adverse effects such as vomiting and nausea affect approximately 20% of people taking acetylcholinesterase inhibitors. Other adverse effects associated with donepezil may include fatigue, dizziness, headache, syncope, bradycardia, agitation, confusion, dyspepsia, increased sweating and tremor.

Adverse effects are dose dependent, usually of short duration, and resolve spontaneously or after dose reduction. Adverse effects may be minimised by initiating treatment at a low dose, i.e. 5 mg donepezil, and increasing the dose gradually, i.e. after one month.

N.B. Each acetylcholinesterase inhibitor has a slightly different adverse effect profile. Refer to the manufacturer's data sheets.

Precautions to the use of donepezil include: asthma, COPD, epilepsy or seizure disorder, urinary retention and a history of peptic ulcers.

As donepezil and other acetylcholinesterase inhibitors may cause bradycardia, particular caution is required in prescribing to people with significant bradycardia, sick sinus syndrome or other superventricular cardiac

Pharmacological treatments should be used as part of a wider management plan for Alzheimer's disease

Management of Alzheimer's disease involves treatment of cognitive, behavioural and psychological issues. Acetylcholinesterase inhibitors such as donepezil can have a beneficial effect on cognitive symptoms, patient function, behaviour and reduce the burden on caregivers, but they are not a cure. The wider management of patients with Alzheimer's disease includes educating patients, their caregivers and family on the nature of the disease and how to deal with the inevitable decline in the patient's cognitive function and their ability to care for themselves. The role of clinicians in this education process and in the overall management of the disease is important.

For more information about identifying early signs of cognitive decline in older people, see BPJ 23 (Sept 2009); "Having a Senior Moment".

conduction disturbances, such as sinoatrial or atrioventricular block.

Drug interactions

All acetylcholinesterase inhibitors have the potential to increase the risk of bradycardia with beta blockers, digoxin, amiodarone and calcium channel blockers. The actions of other anticholinergic drugs, e.g. oxybutinin and benztropine, may be antagonised.

Donepezil is metabolised in the liver but there appear to be few clinically significant drug interactions involving the cytochrome p450 system. There is a possibility that enzyme inhibitors, e.g. fluoxetine, paroxetine and erythromycin, may increase drug concentrations of donepezil, and enzyme inducers, e.g. phenytoin and carbamazepine, may reduce drug concentrations. However, such interactions do not appear to be clinically significant.

Discontinuing donepezil

Treatment with donepezil or any other acetylcholinesterase inhibitor should be discontinued if:

- Significant adverse effects occur
- There is poor adherence to the treatment regimen or monitoring requirements
- Treatment goals are not achieved or major deterioration in the patient's condition occurs

After donepezil is discontinued beneficial effects usually abate gradually. There is little evidence to suggest a rebound effect after abrupt cessation of donepezil, however in practice this is sometimes observed. Sudden loss of cognitive function is possible and patients should be supported and monitored prior to, and during, the cessation period.

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What's up with the men folk?

A call for successful initiatives in getting men to attend general practice

The average life expectancy of males in New Zealand is four years less than females – 78.2 years versus 82.2 years. Life expectancy for Māori males is 8.6 years less than other males in New Zealand. Men are more likely to have cardiovascular disease, high cholesterol and higher rates of many common cancers, yet anecdotal reports suggest that they are much less likely than women, to attend general practice and talk to a GP or practice nurse about their health.

In Part One of our men's health series, we outline some national programmes and campaigns that promote men's health. In Part Two, we hope to bring you some insight, solutions and success stories from your primary care colleagues.

Men's health initiatives in New Zealand

One Heart Many Lives

One Heart Many Lives is a cardiovascular disease primary prevention programme, targeting Māori and Pacific men. It aims to raise both awareness of cardiovascular disease and its causes and decrease the level of cardiovascular risk among men. The main message is that the health of one person affects the lives of many others.

One Heart Many Lives is currently operating in Northland, Hawke's Bay, Whanganui, Taranaki and Lakes DHB. Each area adds unique characteristics to the national programme, making it their own.

www.oneheartmanylives.co.nz

Mana Tāne Ora o Aotearoa

Mana Tāne Ora o Aotearoa, the National Māori Men's Health Coalition, was formed to raise awareness of Māori men's health issues by profiling relevant health and social services targeting men's health.

Mana Tāne Ora o Aotearoa was established at the inaugural Māori men's health conference in 2009. The coalition is creating, developing and sharing innovative practices in Māori men's health, and expanding on successful models, programmes and services. It supports the sharing of successful practices and effective outcomes with the wider sector, providing a forum for information exchanges and facilitating research and best practice guidance.

www.taneora.co.nz

Movember

Movember is an international campaign that aims to raise funds and awareness for men's health. In New Zealand, Movember supports the Cancer Society (prostate cancer) and Mental Health Foundation (Out of the Blue depression campaign).

Men from around New Zealand can join the campaign and seek sponsorship from family, friends and colleagues, while they grow a moustache during the month of November.

Since 2006, more than 50,000 people have participated and $4 million has been raised in New Zealand.

http://nz.movember.com/

Men's Sheds

The Men's Sheds movement started in Australia to connect men with their communities and society, and is now growing throughout New Zealand.

Men's sheds offer a place for men to gather for friendship, to discuss health issues and to learn new skills. Men's sheds can help in addressing isolation, loneliness and depression.

www.menzshedaotearoa.org.nz

The Men's Health Challenge – Te Mātātaki Hauora Tāne

Men are more frequently diagnosed with cancer than women and also more likely to die from it. The Cancer Society of New Zealand has developed Te Mātātaki Hauora Tāne, a men's health challenge aimed at encouraging men, especially those aged over 50 years, to be more proactive about their health. Men are encouraged to complete a "scorecard" of health risk factors and make an appointment to see a health professional if they have identified two or more risks.

www.cancernz.org.nz/information/mens-health

Blue September

Blue September is a New Zealand campaign for the promotion of prostate cancer awareness. It encourages men to think about prostate cancer and to discuss it with their GP.

In New Zealand, around 2500 men are diagnosed with prostate cancer every year and 600 men die from it. Promoters of Blue September believe that this mortality rate can be halved by:

- Men taking responsibility for their health
- Men having regular health and prostate checks from at least age 40 years
- Early detection
- Early treatment

A Māori man's risk of dying of prostate cancer is double that of a non-Māori man. It is thought that an unwillingness to recognise the risks of prostate cancer and a reluctance to talk to their GP about it are significant factors in this disparity.

The Blue September campaign supports the Prostate Cancer Foundation of New Zealand.

www.blueseptember.org.nz

www.prostate.org.nz

Men's Health Week

Men's Health Week is an international campaign that was recently held for the first time in New Zealand in June 2010. It aims to encourage men to improve their lifestyle, wellbeing and all areas of their physical, mental, emotional and sexual health. It promotes awareness of important male specific preventable health issues, daily exercise and a regular health checkup.

www.menshealthweek.co.nz

We would like to hear from you!

- Do men attend your practice less than women?
- What do you think are some of the reasons why men do not attend general practice?
- What initiatives could your practice adopt to encourage men to attend general practice?
- Is it a good idea to promote "men's health checks" to encourage males of all ages to attend general practice?
- Do you have a "success story" that you would like to share with others?

Please email: **editor@bpac.org.nz** or write to: Editor, Best Practice Journal, P.O. Box 6032, Dunedin