

Graylands Hospital Drug Bulletin

Anti-dementia drugs: Are they worthwhile?

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Introduction

Dementia is a neurodegenerative disorder which leads to a decline in areas of cognition, including memory, communication, attention, thinking and judgement.^{1,2} The most common types of dementias are Alzheimer's disease (AD), vascular dementia and dementia with Lewy bodies. Dementia can also be present in other neurological disorders such as Parkinson's disease and Huntington's disease.

In February 2016, the National Health and Medical Research Council (NHMRC) approved the recommendations from the first Australian clinical practice guidelines for dementia. The guidelines and recommendations are available at this address:

<https://www.clinicalguidelines.gov.au/portal/2503/clinical-practice-guidelines-and-principles-care-people-dementia>

Non-pharmacological treatment should be first choice in managing dementia and includes measures such as adjusting the patients' environment to ensure patient safety, involving them in appropriate activities and providing support to the family and carers.³ The use of sedative and cholinergic drugs should also be reviewed and ceased if appropriate.^{1,3}

There are only two different classes of drugs that are currently marketed for the treatment of AD: anticholinesterase inhibitors (donepezil, galantamine and rivastigmine) and N-methyl-D-aspartate (NMDA) antagonists (memantine). These drugs do not prevent or cure the disease but

aim to slow the progression and improve symptoms relating to behaviour, function and cognition.¹ Beneficial effects from these drugs may only be seen after 3-6 months of therapy and adverse effects are common which can significantly reduce tolerance to treatment.⁴ Currently, the evidence only shows possible benefits of the use of these drugs in AD, dementia with Lewy bodies and Parkinson's disease dementia.⁵ The use of cognitive enhancers in mild cognitive impairment has not shown any benefits.⁶ This drug bulletin aims to investigate the value of anticholinesterase inhibitors and NMDA antagonists in AD.

| Anticholinesterase Inhibitors | NMDA antagonists |
|-------------------------------|--------------------|
| Donepezil (Aricept®) | Memantine (Ebixa®) |
| Galantamine (Reminyl®) | |
| Rivastigmine (Exelon®) | |

Table 1: Classes of drugs to treat AD

Anticholinesterase inhibitors

Although the exact aetiology of AD is unknown, decline in the activity of the enzyme responsible for the synthesis of the neurotransmitter acetylcholine (choline acetyltransferase) has been associated with decline in cognition.⁷ It is not considered a cause of AD but does provide a target for the treatment of AD.⁷

Anticholinesterase inhibitors prevent the breakdown of acetylcholine by acetylcholinesterases in the neuronal synapse, increasing the levels of acetylcholine.^{2,8} Oral donepezil and

galantamine, as well as rivastigmine patches are first line agents for AD. Oral rivastigmine is considered second line.¹⁴

The side effect profiles for the anticholinesterase inhibitors are very similar. The most frequently reported are gastrointestinal side effects which are dose-related and can be managed by either reducing the dose of the medication or slower titration. See **Table 2** for the precautions, contraindications and adverse effects of the acetylcholinesterase inhibitors. If treatment with these drugs is interrupted

outcomes.^{6,9,10} A dose of 10 mg has only been shown to be marginally more beneficial than a dose of 5 mg but is associated with an increased incidence of adverse effects and increased cost. A dose of 5 mg could, therefore, be a better option for patients.⁶ A trial of 23 mg daily failed to find superiority over lower doses on the predefined measures.^{7,10} Despite this, the United States Food and Drug Administration (FDA) have approved high dose (23 mg) donepezil for use in patients with AD. The use of this higher dose is not approved in Australia.

Table 2: Acetylcholinesterase inhibitors precautions, contraindications and adverse effects²

| | | |
|---------------------------|--|---|
| Precautions: | History of peptic ulcer disease, seizures, heart block, bradyarrhythmias, Parkinson's disease, asthma, obstructive pulmonary disease | Risk of aggravation |
| | Treatment with anticholinergic drugs | Antagonises action of anticholinesterases |
| | Treatment with drugs that can cause bradycardia | Increased risk of bradycardia and hypotension |
| Contraindications: | Gastrointestinal or ureteric obstruction | |
| | Active peptic ulcer | |
| Adverse effects: | Common: nausea, vomiting, diarrhoea, anorexia, abdominal pain, dyspepsia, headache, insomnia, vivid dreams, depression, fatigue, drowsiness, dizziness, tremor, weight loss, muscle cramps, urinary incontinence, increased sweating, hypertension, fainting | |
| | Infrequent/Rare: bradycardia, heart block, seizure, agitation, hallucination, confusion, GI haemorrhage | |

for several days, it is recommended that the patient recommence the medication at the initial starting dose to reduce the incidence of side effects.⁴

Donepezil

A recent meta-analysis showed that donepezil at doses of 5 and 10 mg can improve cognitive function compared to placebo at the 24-26 week mark by -1.95 and -2.48 weighted mean difference (WMD), respectively, using the ADAS-Cog scale.⁸ Improvements in global clinical state have been observed with both strengths and modest benefits in behaviours have been established. However, minimal, if any benefit, was observed for functional

It is recommended that donepezil (Aricept®) be commenced at a dose of 5 mg a day and maintained for at least one month to allow the earliest clinical responses to be assessed.¹¹ The Aricept® product information mentions that the dose may be increased to 10 mg even though there is no statistically significant evidence that a greater treatment effect is obtained from the use of the 10 mg dose.¹¹

Donepezil should be given in the evening; however, patients who experience insomnia or vivid dreams - or where adherence to medication in the evening is inconsistent - consider giving the medication in the morning.⁸

Galantamine

Evidence for improvement in cognitive function compared to placebo after six months has been shown from all strengths of galantamine.^{12,13} Based on the lack of a statistical dose-response relationship for efficacy and the relative incidence of side-effects at each dose, a Cochrane review recommended the *16 mg/day* dose as the most preferable initially.¹² The manufacturer, however, continues to recommend an 8 mg starting dose.¹³

Galantamine (Reminyl®) is a controlled-release capsule, available as an 8 mg, 16 mg or 24 mg strength. It should be noted that the majority of the studies viewed used immediate-release galantamine and twice-daily dosing. However, there appears to be similar efficacy and incidence of side-effects between twice-daily dosing and the prolonged-release once-daily dosing.¹³

The maximum dose of galantamine is 24 mg per day. Patients should try to take this medication with food in the morning and drink plenty of fluids whilst been treated with this medicine. If a patient has swallowing difficulties, the capsule can be opened, the pellets mixed with a small amount of yoghurt or apple puree and the mixture then swallowed without chewing the pellets.¹³

Galantamine is contraindicated when creatinine clearance is less than 10 mL/min, and in moderate hepatic impairment the dose should be reduced by half. It can cause serious skin reactions including Stevens-Johnson syndrome therefore, patients should be monitored for skin rash. Galantamine is substrate of CYP2D6 and CYP3A4. When using galantamine in combination with drugs that inhibit these enzymes, there is an increased risk of side-effects; a lower dose may need to be used.¹³

Rivastigmine

Some benefits have been seen with 6 to 12 mg orally per day and the 9.5 mg/24 hour patch compared to placebo. Benefit has been observed in areas of cognitive function (WMD -1.79 on ADAS-cog scale), activities of daily living and the physicians rated global impression of change but Rivastigmine at this dose, was unable to demonstrate improvement in behavioural symptoms or impact on carers.¹⁴ The patches were associated with a lower incidence of gastrointestinal side effects with similar efficacy to the oral formulation.¹⁴ Lower oral doses of 1 to 4 mg and the 4.6 mg/24 hour patch had much smaller benefits in cognition and had no difference on activities of daily living compared with placebo.^{9, 14, 15}

Rivastigmine (Exelon®) is available as a capsule and a patch. Since the rivastigmine patches are of similar efficacy to the oral form¹⁶ and have a lower incidence of side-effects, the patches are considered one of the first-line treatments in the treatment of Alzheimer's disease.¹⁵⁻¹⁷ A patient commencing rivastigmine patches should initially receive the 4.6 mg/24 hour patch and apply it once-daily for 24 hours. After four weeks, the 9.6 mg/24 hour patch can be used and this dose can be maintained if tolerated. Patches should be applied to the back, upper arm or chest, and the site of application should be rotated to avoid using the same area in a two-week period.¹⁵

Rivastigmine capsules should be taken twice-daily with morning and evening meals to reduce gastrointestinal side effects.¹⁷ Due to the high incidence of gastrointestinal side effects with oral rivastigmine, it is recommended the weight of the patient be monitored and significant weight loss be reported to medical practitioner.¹⁶ The recommended initial dosing schedule for the oral capsules is 1.5 mg twice-daily for two weeks and then increase to 3 mg twice-daily.

Further increases to 4.5 mg and then 6 mg should be considered at 4-weekly intervals if the previous dose is well tolerated.¹⁶

When switching from oral therapy to the transdermal patch, the patch should be applied the day after the last oral dose; a patient stabilised on a dose of 3-6 mg daily should be given then 4.6 mg/24 hour patch, whereas a patient stabilised on a dose of 9-12 mg can be given the 9.5 mg/24 hour patch.¹⁷

NMDA antagonists – Memantine

It is thought that AD is also associated with a loss of glutaminergic neurotransmission which may contribute to loss of cognitive function.⁷ Memantine is an N-methyl-D-aspartate (NMDA) antagonist which has been shown to reduce the degradation of glutaminergic neurons.¹⁸ Even though memantine has been shown to have symptomatic benefits, it has not been shown to slow or reverse the neurodegenerative processes of Alzheimer's disease.^{19, 20}

At a dose of 20 mg per day, it improves cognition (WMD -1.29), global assessment and activities of daily living but the improvement is only seen in patients with moderate to severe AD (MMSE of 15 or less).^{15, 21} However, the evidence for benefits in cognition is conflicting and the improvements seen are small and may not translate to any clinical significance.²¹ No benefits in behavioural symptoms have been confirmed; however, memantine may reduce the likelihood of patients becoming agitated.¹⁹ Patients with mild to moderate disease had minimal benefits in cognition and global assessment and no benefits seen in function and behaviour.¹⁹

Table 3: Memantine precautions, contraindications and adverse effects²

| | | |
|---------------------------|---|-----------------------|
| Precautions: | Treatment with other NMDA antagonists (amantadine, ketamine, dextromethorphan) | Increased CNS effects |
| Contraindications: | History of seizures | |
| Adverse effects: | Common: confusion, dizziness, drowsiness, headache, insomnia, agitation, hallucinations, dyspnoea, hypersensitivity | |
| | Infrequent: vomiting, anxiety, hypertonia, VTE | |
| | Rare: seizures, rash, renal failure, cholestatic hepatitis, heart failure, bradycardia | |

Memantine is currently only indicated for moderately severe to severe Alzheimer's disease. It should only be used in patients where there is an intolerance or contraindication to using an acetylcholinesterase inhibitor or a diagnosis of severe AD. **Table 3** outlines the precautions, contraindications and adverse effects that should be taken into to account when prescribing memantine. The usual regimen for commencing memantine is 5 mg daily for seven days, then 10 mg daily for seven days, then 15 mg daily for seven days then a 20 mg maintenance dose can be given from week four. Patients with a creatinine clearance of 5-29 mL/min the maintenance dose should be reduced to 10 mg per day. Patients should be warned that this medication may make them feel drowsy or dizzy.²⁰

Anticholinesterase inhibitor and NMDA antagonist combination

Few studies have looked at combination therapy using donepezil with memantine. These studies show that in Alzheimer's disease, the combination compared to donepezil alone is unlikely to have any additive benefits in cognition or functioning.

The combination of the two agents does not appear to significantly increase the risk of adverse effects.^{7, 22} The combination of drugs for dementia treatment is not subsidised by the PBS.

Drugs in development

Research into new drugs for dementia focusses on different pathways of neurodegradation involved in AD. One area that has been extensively researched is the processing of amyloid- β precursor protein (APP). APP can be processed two ways - one by β -secretase then γ -secretase which is the plaque forming pathway that produces $A\beta$, or the other by α -secretase then γ -secretase which is the non-plaque forming pathway. It has been proposed that an accumulation of $A\beta$ in the extracellular space can lead to aggregation and the formation of plaques which may play a role in neuron function in AD.²³ Currently no benefit has been shown from use of drugs with this mechanism of action. A proposed reason for the lack of benefit is a relative inability of the drug to cross the blood brain barrier.²³ Rosiglitazone and pioglitazone (DPP-4 inhibitors) may have a role in inhibiting β -secretase.²⁴⁻²⁶ Pioglitazone is likely to be the better option since it can more easily cross the blood brain barrier compared to rosiglitazone; however, studies were not able to show any benefit from either of these drugs.²⁶

There have been trials looking at the inhibition of γ -secretase by semagacestat in reducing $A\beta$ formation. Although results demonstrated reductions in $A\beta$ plasma concentrations and formation in the cerebrospinal fluid,²³ testing was prematurely ceased due to serious side-effects. No improvement or moderate worsening of cognition was seen in these studies.²³ γ -secretase is also involved in the Notch signalling pathway which is necessary for neuronal signalling; inhibiting this

pathway as well could account for the side-effects seen in the trial. Current research for γ -secretase inhibitors is in more targeted molecules for the APP pathway.²⁴⁻²⁶

Another target is in preventing the aggregation of $A\beta$ and reducing the stability of the aggregates. Tramiprosate was studied and found to reduce $A\beta$ levels in the cerebrospinal fluid; however, no change in cognitive function was noted compared to placebo after three months of therapy. Further analysis of the ADAS-cog scores showed possible improvement in memory, language and praxis skills.²⁴⁻²⁶ Iron, copper, zinc and possibly aluminium promote the aggregation of $A\beta$ as well as stabilising the formed plaques. Chelation of these metals is, therefore, a possible option to modify the progression of AD.²³

Another protein, tau has been investigated as a possible pathology in AD. Tau is involved in the formation and stabilisation of microtubules. The tau protein can become hyperphosphorylated which results in a dysfunctional protein, which is toxic to the neurons. Efforts to prevent phosphorylation of tau or prevent the aggregation of tau are being investigated.²⁷ Lithium and valproate inhibit an enzyme, GSK3b, which is involved in the phosphorylation of tau.²⁵ No improvement in cognitive function was seen with valproate and there is conflicting evidence whether it is able to reduce agitation in patients with AD.²⁶

Lithium was seen to reduce the incidence of developing AD in patients with psychotic illness but was not able to show any benefit in patients diagnosed with AD.²⁶ Methylthioninium chloride (methylene blue) interferes with tau aggregation and some promising results have been seen in reducing the cognitive decline in patients with AD at a dose of 60 mg. Leuco-methylthioninium is a new formulation that has recently been

developed with proposed better bioavailability and tolerability.²⁸

There have been studies around the use of anti-inflammatory drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin in AD. It is suggested that these agents have a role in reducing neuro-inflammation, and subsequently reducing neurodegeneration. Meta-analyses of randomised controlled trials have not been able to show any difference in cognition compared to placebo, there have been few benefits shown from observational studies. Currently, there is inadequate evidence to be able to recommend this therapy.^{23, 29} Consideration should also be given to the risk of bleeding and other adverse effects from these agents in the older population.

Autoantibodies for A β and tau have been found to be present in patients with AD. These autoantibodies could provide a diagnostic marker for AD as well as a possible treatment option in the future.²⁹ Currently, there are immunotherapies in early phase trials. There has been development of active vaccines and monoclonal antibodies targeting A β and tau pathways. There have been a few failed trials due to lack of efficacy and occurrence of severe side-effects. Safer agents have been developed (including using human donor autoantibodies) and research in preclinical animal models is underway.^{27, 29}

More recent research has identified synapse loss may be the method of cognitive decline in AD.³⁰ In mouse models, C1q, the initiating protein of the classical complement cascade, is increased and associated with synapses before overt plaque deposition. It has also been suggested that mild cognitive impairment occurs before onset of plaques.³⁰ Inhibition of C1q, C3 or the microglial complement receptor CR3 reduces the number of phagocytic microglia, as well as the extent of early synapse loss. Microglia in

the adult brain, when challenged with synaptotoxic, soluble A β oligomers, engulf synapses in the absence of plaque aggregates. Inhibiting C1q, C3 or CR3 activity rescues synaptic loss and dysfunction.³⁰ If these theories are correct, targets for drug development may shift to complement and microglia.

Conclusion

Currently available drugs for the treatment of AD have shown to modestly improve cognition compared to placebo. These drugs are unable to affect the underlying disease progression but may slow cognitive decline. The clinical significance of a slight improvement on the assessment scales is unclear and may not necessarily indicate real-life improvement. If no benefit with these drugs is observed, they should be ceased. Currently there is the most evidence for using donepezil; however, the effectiveness of the different drugs appears to be very similar so choice of agent is directed largely by patient factors. There is a strong need for more effective treatments for AD to be developed.

Drugs currently marketed are available on the Pharmaceutical Benefits Scheme (PBS) for AD only. Patients have to meet the criteria set out by the PBS in order to obtain the drug at the subsidised price. Refer to Appendix 1.

This Drug Bulletin was written by Kim Bennett and was reviewed by the Graylands Pharmacy Department

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Appendix 1: PBS prescribing of drugs for AD

PBS criteria for INITIAL prescribing of drugs for Alzheimer's disease:

| | | PBS criteria | |
|--|---|---|--|
| | | Condition confirmed by, or in consultation with a specialist/consultant physician Treatment must be the sole PBS-subsidised therapy for this condition | |
| Drug | Indication | Baseline MMSE or SMMSE of 10 or more | Baseline MMSE or SMMSE of 9 or less |
| Donepezil Rivastigmine Galantamine | Mild to moderately severe Alzheimer's disease | Baseline MMSE or SMMSE of 10 or more | Baseline MMSE or SMMSE of 9 or less |
| Memantine | Moderately severe Alzheimer's disease | Baseline MMSE or SMMSE of 10-14 | Baseline MMSE or SMMSE of 9 or less |
| <p>Donepezil (Aricept®) Tablets: 5 mg & 10 mg, x 28.</p> <p>Rivastigmine (Exelon®) Capsules: 1.5, 3, 4.5 & 6 mg, x 56. Patches: 4.6 & 9.5 mg/24 hours, x 30.</p> <p>Galantamine (Reminyl®) Capsules: CR 8, 16 & 24 mg, x 28.</p> <p>Memantine (Ebixa®) Tablets (scored): 10 mg, x 56. Tablets (scored): 20 mg, x 28.</p> | | No additional criteria | <p>A patient unable to obtain a score of 10-14 for reasons other than Alzheimer's disease must fit one or more of the groups listed on the PBS which must be specified on the authority application.</p> <p>Patients need to be assessed using the Clinicians Interview Based Impression of Severity scale and include the baseline MMSE or SMMSE.</p> |

Note: Patient MUST receive 6 months of initial subsidised therapy to qualify for subsidised on-going treatment.

Authority can be obtained by either:

- Initial phone authority for 1 month quantity and 1 repeat (ie 2 months therapy) followed by a written authority for 1 month quantity and 3 repeats (ie 4 months therapy) (total of 6 months therapy); or
- Written authority for 1 month quantity and 5 repeats (total of 6 months therapy).

PBS criteria for CONTINUING treatment with drugs for Alzheimer's disease:

| |
|--|
| Patient must have received six months of sole PBS-subsidised INITIAL therapy with the particular drug. |
| Patient must demonstrate a clinically meaningful response to initial treatment. |
| Treatment must be the sole PBS-subsidised therapy for this condition. |

- A comprehensive assessment must be undertaken and documented to establish that continuing treatment will produce worthwhile benefit
- Treatment should cease if there is no agreement of benefit as there is always the possibility of harm from unnecessary use
- Re-assessments should be undertaken and documented every 6 months.

The prescription for 1 month quantity and 5 repeats should be endorsed with a streamline code:

- **4219** for Donepezil, Galantamine or Rivastigmine
- **4214** for Memantine

For more information, visit the PBS website: <http://www.pbs.gov.au/browse/body-system?depth=3&codes=n06d#n06d>

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