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Drugs used in dementia in the elderly

Around 200 000 Australians have dementia, the most common cause is Alzheimer's disease (50% to 70% of cases).[1] Other causes include vascular dementia (10% to 20% of cases), dementia with Lewy bodies (up to 10%), fronto-temporal dementia and dementias due to Parkinson's disease, drug and alcohol abuse or head injury.[1,2] Dementia often has a combination of causes.[2]

Behavioural and mood problems become more common as dementia progresses. The umbrella term for these symptoms is behavioural and psychological symptoms of dementia. This *NPS News* looks at both the pharmacological and non-pharmacological management of these symptoms and, more broadly, dementia.

Non-pharmacological management of dementia

Non-drug strategies promote independence and can maintain cognitive and physical function in people with dementia. Individualise management and involve the patient, their family and carers wherever possible.[3]

The evidence for many non-pharmacological interventions is limited. However, good clinical practice suggests that regular physical and recreational activity, memory aides (e.g. calendars, schedules or memory books) and environmental modifications (e.g. visual prompts, motion-sensor lights) can be useful.[3,4]

Cognitive stimulation programs where patients participate in activities that involve some degree of cognitive processing, such as reminiscence, or word or card games, can improve cognition and quality of life.[4]

Pharmacological management of Alzheimer's disease

The cholinesterase inhibitors (donepezil, galantamine and rivastigmine) and the N-methyl-D-aspartate (NMDA) antagonist, memantine, are approved for use in Alzheimer's disease. These drugs are not approved for any other type of dementia.

The cholinesterase inhibitors and memantine do not alter the pathology of Alzheimer's disease.[2] At best, they may temporarily delay progression and improve symptoms according to subjective measurements or cognitive assessment tools (Table 1). There are two main assessment tools used to establish whether a patient is eligible for a cholinesterase inhibitor or memantine under the Pharmaceutical Benefits Scheme (PBS), the MMSE and the SMMSE.

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Pharmacological management of Alzheimer's disease (cont...)

Table 1: Selected dementia assessment tools

Assessment tool	Description	Comment
Cognition		
Mini–Mental State Examination (MMSE)[5] or Standardised Mini–Mental State Examination (SMMSE)[6]	30 point scale: lower scores indicate poorer function	Used widely in clinical practice
Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-cog)[7]	70 point scale: higher scores indicate poorer function	Usually only used in trials
Severe Impairment Battery (SIB)[8]	100 point scale: higher scores indicate poorer function	Usually only used in trials
Global overview		
Clinicial Global Impression of Change (CGIC)	7-point scale rating patient from very much improved (1) to very much worse (7)	Subjective overview of general patient functioning, cognition, behaviour and activities of daily living.
Clinician's Interview-Based Impression of Change (CIBIC)	7-point scale rating patient from very much improved (1) to very much worse (7)	Subjective overview of general patient functioning, cognition, behaviour and activities of daily living.

Prescribing drugs used in Alzheimer's disease

The cholinesterase inhibitors are PBS listed for mild to moderate Alzheimer's disease. This diagnosis must be confirmed by a specialist and the patient's baseline MMSE score must fall between 10 and 24, inclusive.[9]*

Memantine is PBS listed for moderately severe Alzheimer's disease. Again, this diagnosis must be confirmed by a specialist and the patient's baseline MMSE score must fall between 10 and 14, inclusive.[10]†

To continue either class of drug, the patient must demonstrate an improvement in cognitive function within 6 months of beginning therapy as measured by a 2-point increase from the baseline MMSE score.[9]

Cholinesterase inhibitors

Taking a cholinesterase inhibitor for 6 months produces an average difference in cognition scores of 2 to 3 points (on the ADAS-cog) compared with placebo.[11] This is lower than the 4-point difference which is commonly accepted as being clinically important on this scale.[12]

If 100 people take a cholinesterase inhibitor for 6 months and their symptoms are monitored using a subjective global assessment scale (the CIBIC or CGIC) then symptoms will:

- improve in 7 people because they are taking the drug
- improve in 17 people — but this would have happened even if they had not been taking the drug
- get worse in 76 people despite taking the drug.[11]

For some people, preventing worsening of symptoms will be a goal of treatment (although this would require a private script). If 100 people take a cholinesterase inhibitor for 6 months and their symptoms are monitored using a subjective global assessment scale (the CIBIC or CGIC) then symptoms will:

- stabilise or improve in 15 people because they are taking the drug
- stabilise or improve in 51 people — but this would have happened even if they had not been taking the drug
- get worse in 34 people despite taking the drug.[11]

Up to half of the patients taking cholinesterase inhibitors withdrew from trials because of adverse effects.[12] Gastrointestinal side effects such as anorexia, nausea, vomiting and diarrhoea are common, particularly during the first few days of treatment and following dose escalation. Patients may also experience insomnia, dizziness, cramps, vivid dreams, asthma and a slowed heart beat.[2] For every 10 patients treated, 1 will stop treatment because of an adverse event.[11]

* If the patient is from a different cultural background, has a learning or sensory disability, is illiterate or has very limited education an MMSE < 10 is acceptable. If the MMSE is ≥ 25, baseline ADAS-cog must be specified.

† If the patient is from a different cultural background, has a learning or sensory disability, is illiterate or has very limited education an MMSE < 10 is acceptable.

Prescribing drugs used in Alzheimer's disease (cont...)

The cholinesterase inhibitors are contraindicated in people with active peptic ulcer disease or gastrointestinal or urinary obstruction. Galantamine is contraindicated in patients with severe kidney or liver impairment. All cholinesterase inhibitors should be used with caution in patients with asthma or heart block.[13]

Memantine

Among patients with moderate to severe Alzheimer's disease, using memantine for 6 months produces an average difference in cognition scores of 3 points (on the 100 point SIB) compared with placebo.[14] The minimum clinically important difference on this scale has not been established, thus the clinical impact of using memantine is not known. The efficacy of memantine among patients with mild to moderate Alzheimer's disease is even smaller (less than 1 point on the SIB).[14]

Up to 12% of patients taking memantine withdrew from trials because of adverse effects.[12] The more common adverse effects of memantine include confusion, dizziness, drowsiness, headache, insomnia, agitation and hallucinations.[13]

Memantine is contraindicated in patients with renal impairment (creatinine clearance ≤ 50 mL/min) or a history of seizures.[13]

More information about memantine in Alzheimer's disease can be found in NPS RADAR: *Memantine (Ebixa) for moderately severe Alzheimer's disease*.

Combination therapy with memantine and a cholinesterase inhibitor

There is limited evidence to support combination therapy with memantine and a cholinesterase inhibitor.

One trial found that memantine was no better than placebo when added to a cholinesterase inhibitor in patients with mild to moderate Alzheimer's disease.[15] In contrast, a second trial reported memantine marginally improved cognition, function and behaviour, compared with placebo, in patients with moderate to severe Alzheimer's disease already taking donepezil.[16]

The PBS listing only allows for subsidy of either memantine or a cholinesterase inhibitor at any one time.

Pharmacological treatments and response to placebo

Much of the improvement seen with cholinesterase inhibitors and memantine in trials is a placebo response and is not due to the specific effect of these drugs. Up to a third of those on placebo had a clinically significant improvement (≥ 4-point increase in ADAS-cog) in trials of the cholinesterase inhibitors.[12] Up to a quarter of patients taking placebo showed clinical improvement in trials of memantine (defined as stabilisation or improvement on the subjective CIBIC scale **and** a cognitive or functional scale).[17,18]

Discontinuing treatment

A drug which initially produces a clinically meaningful improvement in symptoms will not remain effective as Alzheimer's disease progresses. Continuing a drug which is no longer effective could result in more harm from adverse effects than benefits. Stop drug treatment if slowing cognitive decline is no longer a goal (e.g. severe dementia). None of the cholinesterase inhibitors or memantine are PBS-listed for severe dementia (MMSE < 10).

Discuss the following with the patient, their family and carers when initiating therapy:

- cholinesterase inhibitors and memantine do not work for everyone and the response to the drug cannot be predicted
- drug therapy will be trialed for up to 6 months
- continuing the drug after 6 months requires demonstrated improvement in cognitive function as measured by an increase of at least 2 points from baseline on the MMSE[9]*
- even if the patient initially responds to the drug, it usually needs to be stopped if the patient progresses to severe dementia.

If the patient does not respond to the drug, or is no longer responding to the highest tolerated dose, discuss trying another drug or stopping therapy with the patient, family and carer. If stopping, explain that the drug is being stopped because it is no longer working and the risk of adverse effects makes it inadvisable to continue.

When stopping, lower the dose gradually. In a small study of aged-care residents with severe dementia, gradually tapering the dose of a cholinesterase inhibitor did not result in adverse clinical outcomes or sudden deterioration (although there was no control group).[19]

* Or an increase of ≥ 4 points on the ADAS-cog if the patient's baseline MMSE was ≥ 25.

Treatment for behavioural and psychological symptoms of dementia

Drug therapy should not be first-line for patients with behavioural and psychological symptoms of dementia.

Evaluate the patient to rule out disorders that may be causing pain or discomfort such as a urinary tract infection or constipation. Other non-drug strategies for addressing these symptoms include caregiver training, environmental modifications, orientation cues, glasses, hearing aids, physical activity, and light, music or pet therapy. The evidence for non-pharmacological interventions for addressing behavioural and psychological symptoms is limited. Where possible, interventions should be tailored to the individual and carers should be involved in the process.[20,21]

Antipsychotics

Reserve antipsychotics for patients with distressing agitation, aggression, delusions or psychoses that have not responded adequately to non-drug strategies. They can have a small beneficial effect on these symptoms but this must be weighed against an increased risk of mortality, stroke and extrapyramidal symptoms.[22–24]

If antipsychotics are used, start at a low dose and increase slowly. Both response to therapy and adverse events need to be monitored closely.[3] The reason for starting an antipsychotic should be well-documented. If there is insufficient improvement in the target symptoms the antipsychotic should be stopped.

Stable levels are needed for an antipsychotic to be effective, thus 'as required' (prn) dosing should be avoided. Intermittent dosing relies on the sedative effect of the drugs and does not reveal whether the antipsychotic has a specific effect on these behavioural and psychological symptoms.

The behavioural and psychological symptoms of dementia are mostly episodic and many patients do not show worsening behaviour after antipsychotics are withdrawn.[22,25] Antipsychotic prescription should be reviewed within 3 months and gradually withdrawn in a trial cessation. Taper the dose by 50% every 2 weeks and stop after 2 weeks on the minimum dose.[26]

Do not use conventional antipsychotics and avoid atypical antipsychotics in people suspected of having dementia with Lewy bodies (characterised by dementia with any two of complex visual hallucinations, fluctuating cognitive impairment or spontaneous motor parkinsonism) as these drugs can cause parkinsonism, further impair consciousness and increase the risk of mortality.[2,27]

More information about antipsychotics in dementia can be found in PPR 37: *Role of antipsychotics in managing behavioural and psychological symptoms of dementia*, NPS RADAR: *Risperidone for behavioural disturbances in dementia* and NPS News 51: *What's 'atypical' about the newer antipsychotics?*

Benzodiazepines

Benzodiazepines appear to increase the risk of hip fracture among older people by at least 50%.[28] They impair cognition and gait which can lead to falls. Benzodiazepines should be the last choice for treating behavioural and psychological symptoms as there is no good evidence for their use.[29]

The decision to prescribe benzodiazepines to older people should be based on regular evaluation of benefits and harms, and clearly defined and documented treatment goals. If benzodiazepines are prescribed, use short-acting agents and restrict use to no more than 2 weeks. Medication orders for 'as required' use should include the indication (e.g. for agitation) and dose (minimum hourly frequency of administration and maximum daily dose). Including the duration of therapy (e.g. 1 week) also provides an opportunity for review.

Anticholinergic drugs can worsen dementia

The cholinesterase inhibitors are thought to improve the symptoms of dementia by increasing the amount of acetylcholine in the brain. In contrast, the anticholinergic drugs block the action of acetylcholine and have been implicated in cognitive deterioration and delirium in the elderly.[30,31] For this reason, anticholinergic drugs should be avoided in people with dementia. A third of individuals taking cholinesterase inhibitors are also prescribed an anticholinergic drug despite the fact that these anticholinergic drugs directly oppose the actions of the cholinesterase inhibitors.[32]

Urinary incontinence is a common problem among people with dementia[30] and the cholinesterase inhibitors can also cause urinary incontinence.[13] However, the commonly used incontinence drugs (see Table 2) are anticholinergics. If a patient is experiencing urinary incontinence consider non-drug alternatives such as scheduled toileting, reducing caffeine intake and using incontinence pads.

Other classes of drugs that may have an anticholinergic effect include the antihistamines and some antidepressants and antipsychotics (Table 2).

Table 2: Examples of drugs with anticholinergic effects*[13,33]

Drugs for urinary incontinence
darifenacin, oxybutynin, propantheline, solifenacin, tolterodine
Antihistamines
brompheniramine, chlorpheniramine, dexchlorpheniramine, dimenhydrinate, diphenhydramine, pheniramine, promethazine, trimeprazine
Antispasmodics and antidiarrhoeals
belladonna alkaloids, hyoscine (butylbromide or hydrobromide), loperamide
Antipsychotics
chlorpromazine, clozapine, fluphenazine, olanzapine, pericyazine, trifluoperazine
Tricyclic antidepressants
amitriptyline, clomipramine, dothiepin, doxepin, imipramine, nortriptyline†, trimipramine
Drugs for parkinson's disease and extrapyramidal disorders
amantadine, benzhexol, benztropine, biperiden, orphenadrine
Bronchodilators
ipratropium (nebulised), tiotropium
Drugs for eye examinations
atropine, cyclopentolate, homatropine, tropicamide
Other
disopyramide, mianserin, pizotifen, prochlorperazine

* Consult the product information for other drugs that may have anticholinergic effects, or contact the NPS Therapeutic and Information Service (TAIS) on 1300 138 677 for further advice.

† Nortriptyline is often chosen for elderly people as it has the lowest potential to cause anticholinergic adverse effects compared with other tricyclics.

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References

1. Australian Institute of Health and Welfare. Dementia in Australia: national data analysis and development. Canberra: AIHW, 2007.
2. Therapeutic Guidelines: Neurology. Version 2, 2002.
3. Royal Australian College of General Practitioners. Care of patients with dementia in general practice: guidelines. Sydney: NSW Department of Health, 2003.
4. National Collaborating Centre for Mental Health. Dementia: a NICE–SCIE guideline on supporting people with dementia and their carers in health and social care. London: British Psychological Society, 2007
5. Folstein M, et al. J Psychiatr Res 1975;12:189–98.
6. Molloy D, et al. Am J Psychiatry 1991;148:102–5.
7. Rosen WG, et al. Am J Psychiatry 1984;141:1356–64.
8. Saxton J, Swihart AA. Clin Geriatr Med 1989;5:531–43.
9. Department of Health and Ageing. PBS for health professionals. Canberra, 2008. www.pbs.gov.au (accessed 1 May 2008).
10. Pharmaceutical Benefits Advisory Committee. Positive Recommendations made by the PBAC — March 2008. Canberra: Australian Government Department of Health and Ageing, 2008. http://www.health.gov.au/internet/main/publishing.nsf/Content/pbacrec-mar08-positive (accessed 5 May 2008).
11. Birks J. Cochrane Database Syst Rev 2006;(1):CD005593.
12. Qaseem A, et al. Ann Intern Med 2008;148:370–8.
13. Australian Medicines Handbook 2008.
14. McShane R, et al. Cochrane Database Syst Rev 2006;(2):CD003154.
15. Porsteinsson AP, et al. Curr Alzheimer Res 2008;5:83–9.
16. Tariot PN, et al. JAMA 2004;291:317–24.
17. Reisberg B, et al. N Engl J Med 2003;348:1333–41.
18. Bakchine S, Loft H. J Alzheimers Dis 2007;11:471–9.
19. Lee J, et al. J Am Med Dir Assoc 2007;8:243–7.
20. Ayalon L, et al. Arch Intern Med 2006;166:2182–8.
21. Drug Ther Bull 2007;45:81–5.
22. Ballard C, Waite J. Cochrane Database Syst Rev 2006;(1):CD003476.
23. Schneider LS, et al. Am J Geriatr Psychiatry 2006;14:191–210.
24. Schneider LS, et al. JAMA 2005;294:1934–43.
25. Ruths S, et al. Int Journal Geriatr Psychiatry 2008.
26. Department of Veteran's Affairs. Antipsychotics in dementia. 2007. http://www.dva.gov.au/health/veteransmates/pdf/M12L_Therapeutic%20Brief_FINAL.pdf.PDF (accessed 10 May 2008).
27. Drug Ther Bull 2003;41:1–4.
28. Cumming RG, Le Couteur DG. CNS Drugs 2003;17:825–37.
29. Warner J, et al. Dementia. BMJ Clinical Evidence. BMJ, 2006. http://clinicalevidence.bmj.com/ceweb/conditions/meh/1001/1001.jsp (accessed 6 May 2008).
30. Yap P, Tan D. Aust Fam Physician 2006;35:237–41.
31. Gill SS, et al. Arch Intern Med 2005;165:808–13.
32. Robinson M, et al. Co-administration of acetylcholinesterase inhibitors and anticholinergic drugs in the elderly (abstract 207). National Medicines Symposium 2008.
33. Rudolph JL, et al. Arch Intern Med 2008;168:508–13.

The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence.
Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.

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