Buying time:
Therapeutic interventions in Alzheimer's disease

Mary Tucker MB BS FRNZCGP

***Mary Tucker** is a general practitioner with a special interest in care of the elderly. She is a Senior Lecturer attached to the Goodfellow Unit of the University of Auckland and works with the distance learning modules of the Diploma in Geriatric Medicine.*

The ticking clock

Alzheimer's disease (AD), the commonest cause of dementia, progresses slowly and relentlessly over five to 20 years leaving the shell of the person that was and, reminiscent of Milton's *'Paradise Lost'*, leaving bitter memories for those who care for them, *'of what he was, what is and what must be worse.'*[1] Alzheimer's disease accounts for 55% of all cases of dementia, followed by vascular dementia (20%), Lewy body dementia (15%) and fronto-temporal dementia (5%) while other forms of dementia account for the remaining 5%.[2]

Neurotransmitters

The link between the role of acetylcholine in memory and the abnormalities in cholinergic neurotransmission in the Alzheimer brain was recognised in the 1970s and 80s. Defects in neurotransmission are secondary to the inflammatory damage and disruption of neuronal pathways caused by oxidative stress, lipid deposition and Abeta toxicity. Autopsy findings suggest that over 75% of the neuronal population in the basal forebrain nuclei may be lost in the end stage of AD resulting in an 80–90% loss of cholinergic activity in the most severely affected areas, (the hippocampus and temporal lobes), and a 40%–75% loss in the parietal cortex and frontal lobes.[3]

Alzheimer's disease accounts for 55% of all cases of dementia

Cholinergic deficits have been found in the limbic and paralimbic systems in AD and in Lewy body dementia, which shares many of the features of AD but in which fluctuations in cognitive function are marked and Parkinsonism, delusions and visual hallucinations are more common. Restoration of function in these areas, which are associated with emotional responses, may be responsible for the beneficial effect of acetylcholinesterase inhibitors on the behaviour of patients with dementia.[3,4]

More recently the role of N methyl-d-aspartate (NMDA) in neurotransmission has been recognised.[5] Glutamate is the principal excitatory neurotransmitter in the brain, stimulating a number of receptors including the NMDA receptor, which has been implicated in the learning and memory process. However, during neural injury, glutamate is increasingly released, which leads to overstimulation of neurons, chronic calcium influx and overload, activation of secondary messengers in the inflammatory process, and toxicity. Because the receptor is being overstimulated, the normal physiologic balance of calcium across the neuronal membrane is disrupted, and signal transduction of the learning and memory processes cannot occur. NMDA receptor antagonists protect against this over-stimulation.[6]

Buying time

Current therapies for Alzheimer's disease target abnormalities in the neurotransmitters. The available drugs are palliative, benefiting some patients for a period of time. They do not permanently halt the inexorable progress of the disease.[5] There is debate with regard to their cost effectiveness.[7,8] In Britain, the National Committee for Clinical Excellence (NICE) proposed in March 2005 that Acetylcholinesterase (AChE) inhibitors, approved for use in patients with mild to moderate Alzheimer's disease since 2001, should no longer be funded under

Figure 1. Acetylcholinesterase inhibitors

	Donepezil: Aricept	Rivastigmine: Exelon	Galantamine: Reminyl
Class of drug	Piperidine	Phenyl-carbamate	Phenanthrene alkaloid
Recommended dose	5 mg per day increasing after 1 month to 10mg per day	1.5mg bd increasing slowly over 6 months to 6 mg bd	4mg bd increasing slowly over 4 months to 12 mg bd
Enzyme inhibited **AChE** **BuChE**	 Yes –	 Yes Yes	 Yes –
Sustained inhibition of enzymes	–	Yes	–
Allosteric modulation of nicotinic ACh receptor	–	–	Yes
Cost to pharmacy: 1 month's therapy – GST not included. (June 2005)	5mg per day $181.76 10mg per day $186.45	3mg bd $166.10 6mg bd $166.10	4mg bd $167.86 8mg bd $167.86 12mg bd $186.03
Cost to patient	Add Pharmacy mark-up of 15–60%		

the National Health Service (NHS) on the grounds that, although there were proven cognitive gains, there was inconclusive evidence with regard to changes in quality of life and time of admission to a nursing home and that cost benefit calculations put these drugs beyond the means of the NHS. The proposal was greeted with anger by professionals, patient groups and drug manufacturers and will not be implemented.[9] The recommendations were based on the results of Randomised Controlled Trials (RCTs) which excluded potential responders and included non-responders. The RCTs showed that the 'average effect' of these drugs, while significant, was too small to produce meaningful impact on quality of life, reduction in time to admission to residential care or reduction in caregiver burden. Consideration of the 'average effect' obscures the fact that there is a wide variability in treatment effect and that, in a sizeable minority of patients (25%–27%), there is marked clinical benefit with an improvement, at the end of six months, equivalent to twice the annual rate of progression of the disease. Improvement in behavioural problems may also occur but was not measured in these trials. Identification of the sub-group of patients responsive to therapy, before commencement of therapy, although of utmost importance, is not yet possible. It is suggested that appropriately designed observational studies could provide efficacy estimates similar to those of RCTs, would complement their results and would allow the accumulation of large amounts of data in relatively little time thus facilitating the development of guidelines for the identification of potential responders to AChE inhibitor therapy.[10] It has also been suggested that patients with Lewy body dementia, which responds well to AChE inhibitors, may account for some of the dramatic responses to therapy while patients with co-morbid subcortical ischaemic cerebrovascular disease, which has also been shown to disrupt cholinergic transmission, may contribute to the response in other cases.[8]

Acetylcholinesterase (AChE) inhibitors...have been shown to temporarily improve, stabilise or reduce the rate of memory loss and other intellectual functions when compared with a placebo

Acetylcholinesterase inhibitors

Cognitive enhancement

Acetylcholinesterase (AChE) inhibitors increase acetylcholine levels in the brain and are recommended for symptom control in patients with mild to moderate cognitive impairment. They have been shown to temporarily improve, stabilise or reduce the rate of memory loss and other intellectual functions when compared with a placebo.[3] AChE inhibitors include tacrine (Cognex - 1993), donepezil (Aricept – 1997), rivastigmine (Exelon – 2000), and galantamine (Remilyl – 2001).[6] Tacrine is no longer used because of its short half life, the need for qid dosing and the risk of hepatotoxicity.[11]

In a meta-analysis of reports of trials involving the three AChE inhibitors most commonly used, (donepezil, galantamine and rivastigmine), Ritchie et al. examined the effects of these drugs on clinical outcomes and trial completion rates. All three drugs showed similar beneficial effects on cognitive tests when

Figure 2. Adverse effects of Acetylcholinesterase inhibitors and drug interactions

Adverse effects	Drug interactions	Special recommendations
GI side effects:	Anticholinergics	Potentiate succinylcholine-type
10–20% in 1st year of treatment:[11]	Succinylcholine	muscle relaxation.
Commonest:	Neuro-muscular blocking agents	Cardiac: caution in 'sick sinus syndrome'
Anorexia, nausea, vomiting diarrhea	Cholinergic agonists	& supraventricular conduction problems.
Muscle cramps, insomnia		History of peptic ulcer
Less common:		Receiving NSAIDs,
Headache, pain, common cold, dizziness		Bladder outflow obstruction
Bradycardia		History of epilepsy, asthma, or
		obstructive pulmonary disease.

compared with a placebo. The main differences lay in their side-effect profiles and, with donepezil and rivastigmine, the dose effect across the dosing levels studied.[12] Cholinergic side effects (anorexia, nausea, vomiting and diarrhoea) are common, but tolerance to these side effects often develops. Clinical trials show that these drugs produce the greatest benefit if started early in the course of the disease and that differences in levels of functioning between treated and untreated patients continue for several years. Withdrawal and re-initiation of treatment may result in loss of benefit.[13]

Although these drugs share the same mode of action they differ in other pharmacological properties. Rivastigmine inhibits both AChE and butyrylcholinesterase (BuChE). This may be of clinical relevance as the level of BuChE in some areas of the brain increases by 40–90% with the progression of AD whereas AChE activity decreases by 45%. As both these enzymes degrade AChE in the brain, dual inhibition by rivastigmine may be more effective than AChE specific inhibition by donepezil or galantamine and, for this reason, slow dose escalation is important, with four weeks between dose increases of rivastigmine in order to limit cholinergic side effects. For rivastigmine, AChE inhibition has been shown to be dose dependent and to be maintained over time whereas the level of AChE inhibition gradually falls with donepezil and galantamine. Galantamine binds to the Acetylcholine (ACh) receptor and also to the nicotinic acetylcholine receptor (nAChR) at an additional site that may produce allosteric receptor modulation with resultant increased ACh activity. These differences are clinically relevant as up to 50% of patients unsuccessfully treated with donepezil benefit from a switch to rivastigmine with symptomatic improvement, stabilisation or improved tolerability. Inability to tolerate donepezil did not predict similar problems with rivastigmine treatment. A switch to rivastigmine without a washout period was safe and well tolerated. Patients were less likely to experience cholinergic side effects such as nausea and vomiting after being switched from one AChE inhibitor to another.[14]

Commencement of therapy

Therapy with AChE inhibitors should be commenced in patients with mild (MMSE 21–26) to moderate (MMSE 10–20)[15] dementia following tests to exclude reversible causes of dementia and confirmation of the diagnosis on history, cognitive testing and CT scanning. Psychogeriatric assessment or assessment at a Memory Clinic is desirable for patients to confirm the diagnosis, especially for those with mild dementia. New research suggests that AChE inhibitors reduce loss of

Figure 3. Switching acetylcholinesterase inhibitors[14]

Who	Ineffective treatment from start } Increase dose and re-evaluate Initial response - subsequent deterioration } before considering change. Side effects – – – – Reduce dose before considering change Effective and no side effects: do not change drugs.
When	Assess after six months to allow dose escalation to optimum and assessment of clinical progress.
How	No side effects: no washout required. Side effects: washout 7–14 days Start low: increase four weekly if necessary after evaluation of response. Regular review of all symptoms as change may not be uniform Review clinical progress.

volume of the brain in patients with AD[16] and also inhibits the production of beta secretase and thus Abeta deposition[17] reinforcing the need for early diagnosis and commencement of therapy. In Britain, for AChE inhibitors to be subsidised the MMSE must be above 12.[15] In Australia, where guidelines are similar to those in Britain, patients may receive a subsidised six month trial of AChE inhibitors if a consultant geriatrician or psychogeriatrician confirms the diagnosis of AD, and patients score between 10 and 24 on the standardised mini-mental state examination; patients who score >=25 but have clinical features of AD should be evaluated further by the cognitive subsection of the AD assessment scale (ADAS-cog). To continue to receive subsidised prescriptions beyond six months, patients must show improvement of >=2 points on the mini-mental state examination (or a reduction of 4 points on the ADAS-cog), measured at any time over the initial prescription period.[18]

Patients should be medically stable when therapy is commenced as unstable medical conditions will cause functional deterioration and predispose the patient to delirium rendering assessment of the impact of AChE inhibitor therapy difficult.[19]

Titration of dose

The dose should be titrated to minimise side effects (predominantly gastrointestinal). In all cases the dose should be taken to the maximum dose tolerated and continued for at least three months before deciding whether there has been an adequate response.

Response to therapy

In 40% of patients there is a symptomatic improvement lasting approximately eight months followed by a decline that is slower than that of the placebo group for longer periods. No hard predictor of response or non-response has been identified. Global changes in cognition, behaviour, and functioning have been detected by both physicians and caregivers, indicating that even small measurable differences may be clinically significant.[20]

Duration of therapy

As there is no clear diagnostic test for Alzheimer's disease, a six month therapeutic trial of AChE inhibitors should be offered to all patients diagnosed as Alzheimer's disease and the response to therapy reviewed at six weeks and at three to four months. If there is deterioration at six months the drug should be discontinued and consideration given to a trial of another AChE inhibitor. If improvement is present at six months continue therapy, reviewing response at six monthly intervals and continuing until MMSE falls below 12 or there is no longer a therapeutic effect – usually after two years. Discuss the need to do so with patient and caregiver before commencing therapy.

Switching acetylcholinesterase inhibitors

If one drug is ineffective or produces intolerable side effects it should be discontinued and another tried as they belong to different therapeutic classes. Change from donepezil to rivastigmine is well documented.

Neuropsychological effects: Amelioration of behavioural disturbance

Behavioural problems, which are common in AD and Lewy body dementia, include psychosis, agitation, depression, anxiety, personality alterations, and neurovegetative changes. It has been noted that there is a similarity between anticholinergic toxicity (thought disorders, visual hallucinations and variable mood changes) and the neuropsychiatric symptoms of Alzheimer's disease and Lewy body dementia and that these patients are more prone to develop adverse effects when drugs with an anticholinergic action are prescribed than the non-demented elderly. The adverse effects of anticholinergic medication can be amelioriated by AChE inhibitors. Amelioration of behavioural changes may explain why relatives claim to see an improvement with AChE inhibitor therapy when cognitive testing shows no change. Behavioural problems in patients with Lewy body dementia, in particular visual hallucinations, respond well to therapy with AChE inhibitors.[3,4] Apathy is one of the symptoms most responsive to AChE inhibitor therapy – and this is also linked to cognitive improvement. It is suggested that the primary effect of AChE inhibitors may be on improvement in attention and executive function. Reducing behavioural disturbance in the patient is an important treatment goal as this behaviour is distressing both to the patient and to caregivers and may precipitate admission to institutional care.

Key Points

- AChE inhibitors produce the greatest benefit if started early in the disease.
- Offer a six month trial of AChE inhibitors to all patients diagnosed as AD
- Consider change to another AChE inhibitor for non-responders
- Reducing behavioural disturbance is an important treatment goal.
- Additional benefit may be gained by the addition of a NMDA antagonist.

NMDA receptor antagonists

Canadian studies suggest that 50% of individuals suffering from Alzheimer's disease can be classified as moderate (MMSE 10–20) to severe (MMSE <10) and this increases to 90% of those in institutions.[21] Memantine, which is the only drug approved for use in

moderate to severe Alzheimer's disease, is an uncompetitive NMDA receptor antagonist and is thought to protect neurons from glutamate overstimulation.[6] Small but significant reductions in functional and cognitive decline have been reported in two placebo-controlled randomised controlled trials, with increase in duration of independence of 1.3–4.1 months and delay in time to institutionalisation of 0.8–1 month. In patients with moderate to severe Alzheimer's disease, clinical trial data suggests that the addition of Memantine (10mg bd) to therapy of patients who were stable on an AChE inhibitor produced additional benefit.[11]

Available pharmacoeconomic data from Europe and the US support the use of Memantine as a cost-effective treatment in this patient population. Mean total per-patient costs were reduced by £1963 over two years (2003 costs) in the UK analysis and by €1687 over five years (2001 costs) in the Finnish analysis.[21]

Summary

In *'Buying time'* interventions which focus on neurotransmitter failure in patients with Alzheimer's disease are explored. Available drugs offer improved quality of life, for a time, to a significant number of patients and their caregivers. In the October issue of *NZFP*, *'Stopping the clock'*, Part 2 of this review of therapeutic options in Alzheimer's disease will explore ongoing research into therapies that may prevent the development of Alzheimer's disease or halt its progress.

References

1. Milton J. Paradise lost. In: Wain J, editor. The Oxford Anthology of English Poetry. Oxford: Oxford University Press; 2003. p. 307 (Book IV line 23–26).
2. Alzheimer's Society (UK). Policy Positions: Demography [homepage on the Internet]. London: Alzheimer's Society UK; [updated 2004 Jul; cited 2005 Jun 3]. Available from: http://www.alzheimers.org.uk/News_and_Campaigns/Policy_Watch/demography.htm.
3. Cummings JL. Cholinesterase inhibitors: A new class of psychotropic compounds. Am J Psychiatry 2000; 157(1): 4–15.
4. Cummings JL, Kaufer D. Neuropsychiatric aspects of Alzheimer's disease: the cholinergic hypothesis revisited. Neurology 1996; 47(4): 876–83.
5. Walker LC, Ibegbu CC, Todd CW, Robinson HL, Jucker M, LeVine H, 3rd, et al. Emerging prospects for the disease-modifying treatment of Alzheimer's disease. Biochem Pharmacol 2005; 69(7): 1001–8.
6. Reynolds J, Mintzer J. Alzheimer disease update: New targets, new options. Drug Benefit Trends 2005; 17(2): 83–95.
7. Clegg A, Bryant J, Nicholson T, McIntyre L, De Broe S, Gerard K, et al. Clinical and cost-effectiveness of donepezil, rivastigmine, and galantamine for Alzheimer's disease. A systematic review. Int J Technol Assess Health Care 2002; 18(3): 497–507.
8. Royall DR. The emperor has no clothes: dementia treatment on the eve of the aging era. J Am Geriatr Soc 2005; 53(1): 163–4.
9. Kmietowicz Z. NICE proposes to withdraw Alzheimer's drugs from NHS. BMJ 2005; 330(7490): 495.
10. Frisoni GB. Treatment of Alzheimer's disease with acetylcholinesterase inhibitors: bridging the gap between evidence and practice. J Neurol 2001; 248(7): 551–7.
11. Tariot PN, Federoff HJ. Current treatment for Alzheimer disease and future prospects. Alzheimer Dis Assoc Disord 2003; 17 Suppl 4: S105–13.
12. Ritchie CW, Ames D, Clayton T, Lai R. Metaanalysis of randomized trials of the efficacy and safety of donepezil, galantamine, and rivastigmine for the treatment of Alzheimer disease. Am J Geriatr Psychiatry 2004; 12(4): 358–69.
13. Cummings JL. Use of cholinesterase inhibitors in clinical practice: evidence-based recommendations. Am J Geriatr Psychiatry 2003; 11(2): 131–45.
14. Gauthier S, Emre M, Farlow MR, Bullock R, Grossberg GT, Potkin SG. Strategies for continued successful treatment of Alzheimer's disease: switching cholinesterase inhibitors. Curr Med Res Opin 2003; 19(8): 707–14.
15. National Institute for Health and Clinical Excellence (NICE). 2001/002 – NICE issues guidance on drugs for Alzheimer's disease [homepage on the Internet]. London: National Institute for Health and Clinical Excellence; [updated 2001 Jan 19; cited 2005 Jun 12]. Available from: http://www.nice.org.uk/page.aspx?o=14406.
16. Hashimoto M, Kazui H, Matsumoto K, Nakano Y, Yasuda M, Mori E. Does donepezil treatment slow the progression of hippocampal atrophy in patients with Alzheimer's disease? Am J Psychiatry 2005; 162(4): 676–82.
17. Zimmermann M, Borroni B, Cattabeni F, Padovani A, Di Luca M. Cholinesterase inhibitors influence APP metabolism in Alzheimer disease patients. Neurobiol Dis 2005; 19(1-2): 237–242.
18. Noble JM. Drugs for Alzheimer's disease. Guidelines for prescribing cholinesterase inhibitors in Australia are similar to those in UK. BMJ 2001; 323(7321): 1128.
19. DeLaGarza VW. Pharmacologic treatment of Alzheimer's disease: an update. Am Fam Physician 2003; 68(7): 1365–72.
20. Doody RS, Stevens JC, Beck C, Dubinsky RM, Kaye JA, Gwyther L, et al. Practice parameter: management of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2001; 56(9): 1154–66.
21. Plosker GL, Lyseng-Williamson KA. Memantine: a pharmacoeconomic review of its use in moderate-to-severe Alzheimer's disease. Pharmacoeconomics 2005; 23(2): 193–206.

Proactive support in primary care can avert admissions

'Despite our busy lives, few of us want to see our older relatives become a burden to the state. Our experience is that the involvement of an interested primary care team expressing concern is often enough to move relatives to act when action is required. In New Zealand substantial family input is reported to lighten general practitioners' load by reducing the need to resolve social issues. In the United Kingdom healthcare professionals must take the initiative, but when they do we have found that the family is not far behind.'

Jiwa M. BMJ 2004; 328: 350