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13 July 2012

PBS Post-Market
Department of Health and Ageing
MDP 900
GPO Box 9848
CANBERRA ACT 2601

Dear Sir/Madam

Re: Review of PBS anti-dementia drugs to treat Alzheimer's Disease: rivastigmine, galantamine and memantine

We thank you for the opportunity to contribute to the above review. Our submission summarises the research we have undertaken and our advice to health professionals about the use of cholinesterase inhibitors generally and for the treatment of Alzheimer's disease.

NPS previously ran a therapeutic program – *Treating the symptoms of dementia* (August 2008) – and as part of this we reviewed the literature on the use of cholinesterase inhibitors for Alzheimer's disease. In addition we recently completed formative research for our proposed 2013-14 program on *Medicines in the elderly* which looked at this issue.

Cholinesterase inhibitors are not recommended for mild cognitive impairment; they do not slow progression to Alzheimer's disease and are associated with significant side effects.

A 2006 Cochrane review of cholinesterase inhibitors for Alzheimer's disease followed on from Cochrane reviews of the individual drugs.[1] This was a review of 13 trials (involving 7298 patients) which met the inclusion criteria — double-blind RCT of ≥ 6 months' duration, designed to evaluate the efficacy and tolerability of a cholinesterase inhibitor in patients with Alzheimer's disease, in which a cholinesterase inhibitor was compared with placebo or another cholinesterase inhibitor. Patients were diagnosed as having probable Alzheimer's disease using accepted criteria such as ICD-10, DSM and NINCDS-ADRDA. To be eligible for inclusion the cholinesterase inhibitor had to be administered at a dose recommended by the manufacturer: donepezil 10 mg daily, galantamine 24 mg daily in two divided doses or rivastigmine 6–12 mg daily in two doses. Only one trial comparing two different cholinesterase inhibitors met the inclusion criteria.

The mean age at baseline was between 72–75 years, except for one study in the very elderly (where the mean age was 86 years). Dementia was described as mild to moderate in 10 trials, mild in one and severe in two. Analyses were performed on an ITT basis. The ITT population consisted of those who provided complete data at endpoint (observed cases or OC) plus the LOCF population. Dropouts (mainly due to adverse events) totalled approximately 30% of the treatment group and 18% of the placebo population. Most studies reported analyses of both the ITT-LOCF and OC data sets so that the effects of dropouts could be assessed.[2]

The review found the three cholinesterase inhibitors 'efficacious for mild to moderate Alzheimer's disease', with no evidence of any differences between them with respect to efficacy. The Cochrane review of cholinesterase inhibitors for Alzheimer's disease concludes that, despite the slight variations in the mode of action of the three cholinesterase inhibitors, there is no evidence of any difference between them with

[1] Birks J. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev 2006:CD005593
[2] Barenholtz Levy H. Self-administered medication-risk questionnaire in an elderly population. Ann Pharmacother 2003;37:982-7

respect to efficacy.[3] Other published systematic reviews of trial data and clinical guidelines have reached the same conclusion.[4,5,6]

A published review of the literature relating to withholding, discontinuing and withdrawing medications in patients with advance dementia, suggests that physicians should not commence acetylcholinesterase inhibitors in advanced dementia and, if patients are already taking these drugs, they should contemplate cautious discontinuation although they currently have little guidance as to when and how to do so.[7]

In reviewing the evidence for the NPS dementia program, our specialist advisory group discussed a number of issues related to use of these drugs, including:

- The beneficial effect of the drug is most obvious when the decline is steepest. Therefore one has to look at the ADAS-Cog score. With the MMSE, the effect of these drugs is more apparent in those with MMSE scores less than 20, with some effect seen when the MMSE is between 20 and 25.
- One of the misconceptions surrounding the use of cholinesterase inhibitors and memantine is that some benefit will be missed if these drugs are not initiated early on in the disease.
- It is difficult to decide when to cease cholinesterase inhibitors. General consensus would be to consider cessation if after a period of three months on the initial drug there is no improvement, but clarity is required about what classifies as 'no improvement'. Is it a decline or stagnation in rating scales?
- Timing of cessation of cholinesterase inhibitors and memantine needs careful consideration, especially for patients being moved into residential care. Monitoring during cessation is also essential.

Six-month studies in Alzheimer's patients suggest that between 5-15 patients need to be started on cholinesterase inhibitor treatment in order to detect a significant improvement in one patient that would not have been evident on placebo. With such high cost therapy showing only modest benefit, there is considerable debate about the cost effectiveness of this group of medications. They produce only modest improvements overall, with NNTs of 12 and 10 for one patient to have global improvement, or a ≥ 4 point change in ADAS-Cog, respectively.

Treatment of people with mild and moderate Alzheimer's disease with cholinesterase inhibitors for 6 months improves cognition scores an average 2 to 3 points (on the 70 point ADAS-cog) compared with placebo.[6] A 4-point difference is commonly accepted as being clinically significant.

While some patients may benefit, only 37% to 41% show a clinically significant response to treatment (4 point change in ADAS-cog or 1-4 score in CIBIC) and this response is unpredictable, with equivalent rates of 22-27% for placebo.[5] Efficacy needs to be continually assessed.

In August 2008 NPS published a review of the use of memantine for moderately severe Alzheimer's disease in NPS RADAR. In summary, our advice to health professionals at the time was:

- Memantine was listed for use in moderately severe Alzheimer's disease in contrast to cholinesterase inhibitors for use in mild to moderate Alzheimer's disease
- Short term trials found moderate improvements in scores on rating scales of cognitive, psychological and behavioural functioning but the clinical importance of these outcomes had not been established

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[3] Birks J. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev 2006:CD005593

[4] American Psychiatric Association. Treatment of Patients with Alzheimer's Disease and Other Dementias, Practice Guideline. 2007 http://www.psychiatryonline.com/content.aspx?aid=152139 (accessed 17 March 2008).

[5] Qaseem A, Snow V, Cross JT. Current pharmacologic treatment of dementia: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. Ann Intern Med 2008;148:370-8

[6] Perras C, Shukla VK, Lessard C, et al. Cholinesterase inhibitors for Alzheimer's disease: a systematic review of randomized controlled trials [Technology report no 58]. Ottawa: Canadian Coordinating Office for Health Technology Assessment, 2005 www.cadth.ca/media/pdf/217_cholinesterase_tr_e.pdf

[7] Parsons C, Hughes CM, Passmore AP, Lapane KL. Withholding, discontinuing and withdrawing medications in dementia patients at the end of life: a neglected problem in the disadvantaged dying? Drugs Aging 2010;27:435-49

- Review patients regularly and discontinue therapy after six months if there was no improvement
- There was limited evidence to support combination therapy with memantine and a cholinesterase inhibitor, and PBS subsidisation was limited to use of either memantine or a cholinesterase inhibitor.

In November 2011 *NPS RADAR* included advice to health professionals about the changes to authority listings for the use of donepezil, galantamine, rivastigmine and memantine for Alzheimer's disease. This highlighted the modest effects of these treatments and that treatment is not appropriate for everyone. We also recommended using MMSE or the Standardised Mini-Mental State Examination (SMMSE) to assess patient's eligibility for PBS subsidy of these medicines, and emphasised the need for ongoing review and discontinuation of treatment in the event of poor adherence, significant adverse effects or lack of stabilisation or improvement in symptoms. We flagged that effectiveness of long term use has not been established, with limited evidence of effectiveness with any of the medicines beyond one year.

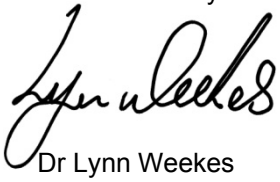
In our view, the PBS restriction continuation rule and subsidisation limitations currently in place should continue but only if there is stronger enforcement and monitoring for compliance. There is evidence of use outside these restrictions, generally relating to continuation of use beyond the recommended period.

Prescribing cascades present a real risk for older patients, and occur when a new medicine is prescribed to 'treat' an adverse drug reaction (ADR) associated with another medicine, in the belief that the drug is needed to treat a new medical condition. Adverse outcomes associated with prescribing cascades can result when the added drug increases the severity of the initial ADR or places the older person at risk of additional adverse reactions. For example, cholinesterase inhibitors can result in incontinence, leading to treatment with an anticholinergic like oxybutynin. Sometimes there may be different specialist involvement with doctors treating different conditions in the same patient, and this can lead to the co-prescribing of two conflicting classes of drugs in patients who are particularly susceptible to their side effects. This practice, together with the use of psychoactive drugs, raises the likelihood of additional unintended adverse effects.

Our work with health professionals suggests there is mixed understanding of what constitutes a prescribing cascade and how to avoid this, and the importance of carefully considering the decision to prescribe a second medicine to counteract an ADR from a first medicine where the benefits of continuing therapy outweigh the risks of additional adverse reactions from the second medicine. It is important that clinicians recognise prescribing cascades and are aware of strategies to prevent these.

We view ongoing education to health professionals as key to optimising use of these therapies in the treatment of Alzheimer's disease, along with strengthened enforcement and compliance monitoring of PBS restrictions. We are happy to provide additional information on any of the comments within this submission if required. Please contact Kerren Hosking, Manager Corporate Affairs on (02) 8217 8796 or email khosking@nps.org.au.

Yours sincerely



Dr Lynn Weekes
Chief Executive