

Pharmaceutical Benefits Advisory Committee
PBS Post Market
Department of Health and Ageing
MDP 900
GPO Box 9848
CANBERRA ACT 2601

To the Chairperson,

**Submission to the Review of Pharmaceutical Benefits Scheme Anti-Dementia Drugs
to treat Alzheimer's disease.**

Alzheimer's Australia welcomes the opportunity to contribute to this review of PBS anti-dementia medications available to people with Alzheimer's disease.

Our key message is that the current continuation restriction rule is overly complex and fails to adequately assess the clinical benefits of anti-dementia medications. These benefits have been demonstrated by numerous studies over the past 15 years, and are highly valued by consumers. However, most are not captured by the current continuation rule, and most cannot feasibly be measured using a battery of standardised assessment tools.

The alternative is to delegate responsibility for the assessment of clinical benefit to clinicians.

It is the specialist or GP who knows the individual circumstances of their patient with dementia, who can observe the individual over time and who as a consequence is best placed to determine the extent to which anti-dementia medications are or are not helping to alleviate the cognitive, functional and behavioural symptoms of an individual's condition.

Revising the PBS listing to allow clinicians to use their experience and expertise to determine the most appropriate treatment of their patients with dementia will be an important development that will ensure better patient outcomes, and will bring Australia into line with other jurisdictions around the world.

In our view, such a move will also serve to increase the cost-effectiveness of anti-dementia medications by reducing the administrative burden of the current regime, and ensuring that more of the people with dementia who could potentially benefit from these medications are given the opportunity to do so.

This submission also recommends improving the cost-effectiveness of anti-dementia medications through better medication management, and reducing inappropriate off-label use (and associated costs to the PBS) of antipsychotic medications as a treatment of behavioural and psychological symptoms of dementia.

On behalf of the 280,000 people in Australia with dementia and the 1.2 million people who provide them with support and care, Alzheimer's Australia calls on the PBAC and the Government to ensure that access to the currently available anti-dementia medications is not made more difficult, and that ongoing prescription of the medications is based on judgement of clinical benefit by clinicians.

We would welcome the opportunity to meet with the review panel to discuss these issues in more detail.



Glenn Rees
CEO, Alzheimer's Australia Inc

6 July, 2012.

**Review of the Pharmaceutical Benefits
Scheme
Anti-dementia drugs to treat Alzheimer's
disease**

**Submission from Alzheimer's Australia
National Office**

6 July, 2012

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1. Summary and Recommendations

“It would be tragic for Aricept or other anticholinesterase inhibitors to be cut from the PBS scheme, especially for people diagnosed with early onset Alzheimer’s. In David’s case it has given him some extra years of a good quality life.”

A consumer

There are currently four anti-dementia medications available on the Pharmaceutical Benefits Scheme (PBS) to people with mild-moderate Alzheimer’s disease. Access to the medications requires a diagnosis of probable Alzheimer’s disease by a medical specialist or by a GP in consultation with a specialist, while continued access to the medications beyond six months requires medical evidence of improved cognitive function over the treatment period.

Alzheimer’s Australia believes that the current rules for continued access to anti-dementia medications are overly complex, and fail to account for important clinical benefits that are supported by strong evidence and are valued by people with Alzheimer’s disease and their carers.

This submission recommends that continuation of anti-dementia medications should be based on a clinical judgement of benefit by the treating GP or specialist, as is the case in most other jurisdictions.

The terms of reference for the review cover:

- An assessment of recent data on Australian utilisation of these medications;
- A review of the patient-relevant outcomes used to determine benefit;
- A review of evidence regarding the safety, efficacy and cost-effectiveness of the medications;
- A review of the current continuation restriction rule.

This submission provides details and a summary of relevant evidence on all of these issues, with the following key conclusions.

1. The available data suggest that only a small proportion of people with Alzheimer’s disease in Australia are receiving subsidised prescription of anti-dementia medications.
2. Evidence suggests that anti-dementia medications can deliver clinical benefits in the domains of cognition, functional ability, and behavioural and psychological symptoms of dementia.
3. Evidence supports continued use of medications to maintain function and slow decline.
4. Anti-dementia medications are safe and effective for people with Alzheimer’s disease and some other forms of dementia, from mild to moderately-severe stages.

5. Costs of anti-dementia medications are set to come down as patents expire and generic brands become increasingly available.
6. There is growing evidence that public subsidy of anti-dementia medications is cost-effective for governments in that they can improve patient outcomes, and offset other health-system costs by reducing or delaying the need for high-level formal care, and reducing the burden on informal carers.
7. The current continuation rule is overly complex, and fails to adequately assess the benefits of the medications.
8. Continued treatment with subsidised anti-dementia medication should be based on the clinical judgement of the treating GP or specialist, as is the case in most other jurisdictions.
9. Significant opportunities exist to improve cost-effectiveness of anti-dementia medications by improving management of medications with anticholinergic load.
10. There is longstanding concern about off-label use of antipsychotic medications for people with dementia. These medications carry significant risks, including increased risk of stroke and death, and cost the PBS approximately \$20 million per annum.

1.1 Recommendations

“Medication already costs us \$250 per month. If Aricept is taken off the PBS we will not be able to afford it.”

A consumer

Alzheimer’s Australia believes there are significant opportunities to increase the cost-effectiveness of anti-dementia medications by:

- amending the rules for continued access to subsidised prescriptions;
- implementing strategies to achieve better medication management; and
- tightening regulations around off-label use of antipsychotic medications.

Specifically, Alzheimer’s Australia recommends that:

- | | |
|---|------------------------|
| 1. Assessment of benefit should take account of improvement or stabilisation in the domains of cognition, functional ability, and behavioural and psychological symptoms. | Section 3.2
Page 11 |
| 2. The current rules for continuation of anti-dementia medications beyond six months should be revised to allow the treating clinician (GP or specialist) to exercise their clinical judgement about the extent to which the medications have benefited and will continue to benefit their patient in cognitive, functional, behavioural and psychological domains. The rule should reflect the recommendation in the UK National Institute for Health and Clinical Excellence (NICE) guidelines that anti-dementia medications be continued “only when it is considered by the prescribing clinician (or another appropriately qualified specialist) to be having a worthwhile effect on cognitive, global, functional or behavioural symptoms.” | Section 3.4
Page 18 |
| 3. Strategies should be employed to ensure better medication management amongst people with dementia, with a particular focus on reducing anticholinergic load (a risk factor for cognitive impairment) and reducing concurrent prescription of anti-dementia medications and contraindicated medications. | Section 4.1
Page 20 |
| 4. The PBAC and the Commonwealth Government should take action to ensure appropriate prescribing practices with respect to antipsychotic medications for people with dementia, with a view to reducing off-label prescription and achieving better patient outcomes through non-pharmacological management of behavioural and psychological symptoms of dementia. | Section 4.2
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2. Background

"I always thought of Aricept as my lifeline as it made such a difference to my husband."

A consumer

Dementia is a complex chronic condition caused by one or more of a large number of illnesses affecting the brain. There are 280,000 people living with dementia in Australia now, and there will be almost 1 million by mid-century.¹ It is a terminal and devastating condition that robs people of their abilities and memories.² It is cloaked in stigma and misunderstanding,³ isolates people with dementia and their carers from social networks,⁴ and carries significant societal and economic consequences.⁵ Almost 1.2 million people care for or provide support to people with dementia⁶ (165,000 of these as full-time primary carers⁷) and the total direct cost of dementia to the health and aged care systems exceeds \$6 billion per annum.⁸

Alzheimer's disease is the most common cause of dementia (accounting for 50-70% of cases⁹), and is the only cause of dementia for which there are approved pharmaceutical treatments that are listed on the Pharmaceutical Benefits Scheme (PBS). The four medications currently available (shown in Table 1) are 'authority required', meaning that to be eligible for subsidised prescription, a diagnosis of probable mild to moderate Alzheimer's disease by a medical specialist (psychiatry or any branch of internal medicine) or, since November, 2011, by a GP in consultation with a specialist, is required, along with baseline cognitive and/or functional test results. Following initiation, medications can be prescribed by either specialists or GPs, or by a nurse practitioner in consultation with a GP.

Under this system, specialists have acted as gatekeepers to anti-dementia medications. The revisions to the PBS listing in November 2011 to allow initiation of treatment by a GP in consultation with a specialist was made in part to improve access to these medications, particularly for those in rural and remote areas.¹⁰

Initial approval for subsidised prescription lasts for six months. Continuation of subsidised prescription beyond this time requires a demonstrated improvement in cognitive function on the MMSE (generally administered by specialists or GPs, and requiring a minimum 2 point improvement), the ADAS-cog (usually requiring administration by a neuropsychologist or other specialist, and requiring a minimum 4 point improvement), or an 'improved' rating on the Clinician's Interview-Based Impressions of Severity (CIBIS) scale, depending on the assessment used at baseline. These outcomes were deemed by the PBAC to represent a cost-effective use of public funding at the time of their approval.

Table 1. Listed anti-dementia medications, their manufacturers, market share, and costs

Trade Name	Drug name	Manufacturer	Market Share	MMSE for Initiation	4 week script cost	Annual cost to Govt**
Aricept	Donepezil	Pfizer	62%	10-24*	\$155	\$39.4m
Reminyl	Galantamine	Janssen-Cliag	29%	10-24*	\$95-\$135	\$15.7m
Exelon	Rivastigmine	Novartis	7%	10-24*	\$155-166	\$6.3m
Ebixa	Memantine	Lundbeck	3%	10-14	\$107	\$1.9m
Total						\$63.4m

* MMSE scores >24 require an ADAS-Cog assessment as well. *2010-11 PBS and RPBS costs from Medicare.

The initial listing of the three Cholinesterase Inhibitor (CEI) medications donepezil, galantamine and rivastigmine in 2001, and of memantine in 2008 was made on the basis that an ongoing subsidy could be considered cost-effective if the medications resulted in an improvement in cognitive function, as measured by a 2-point improvement on the Mini-Mental State Examination (MMSE) after 6 months. The committee acknowledged at the time that the medications had been shown to have a beneficial effect on both cognitive and functional abilities, and that there was evidence the medications could delay the rate of decline as well as result in improved function.¹¹

The decision to base eligibility for continuation on improvement on cognitive function was inconsistent with the recommendations of the expert clinical and industry stakeholder group that had proposed maintenance of cognitive function as a sufficient outcome for continuation, and was a compromise reached by the stakeholder group and PBAC after an excessive delay in getting the medications listed on the PBS.

A review of CEI prescription data between 2004 and 2007 by the PBAC Drug Utilisation Sub-Committee (DUSC) indicated that 62.8% of people on the medications were being recorded as having improved cognitive function (as indicated by a 7th prescription), and were therefore receiving on-going subsidisation of the medications beyond 6 months. This was a higher percentage than expected from both the initial clinical trials conducted by the medication sponsors, and from international studies in countries without the continuation rule. This finding led the authors of the review to speculate that the continuation rule might be being misused by some Australian clinicians to prescribe ongoing subsidised anti-dementia medications to some individuals who were not demonstrating improved cognitive function; either to maintain stable functioning, or in response to pressure from carers.

Alzheimer's Australia believes that the current rules governing continued access to anti-dementia medications are out of date and overly restrictive; detracting from the cost-effective utilisation of the medications. The primary focus of this submission is a recommendation that clinicians must be allowed to exercise clinical judgement in determining whether anti-dementia medications are having a sufficiently beneficial effect on their patients' cognitive and functional abilities to warrant continued treatment.

2.1 The consumer experience

We know that many people living with Alzheimer's disease who have used anti-dementia medications value the effect they have had on improving their quality of life, and that of their carers. This is illustrated by the statements provided throughout this submission, and was highlighted by a survey of 1,226 consumers (people with dementia and their carers) undertaken by Associate Professor Susan Kurrle for Alzheimer's Australia in 2005 (included as Attachment A). This survey found that 90% of the individuals with Alzheimer's disease (N = 1,104) had used an anti-dementia medications, and that 70% of these individuals had found them to be effective; improving both memory and functional abilities. As an indication of the consumer demand for these medications, this survey also found that almost 30% of those who had used anti-dementia medications had done so on private prescriptions, including 155 who had used memantine, even though it was not subsidised by the PBS at the time of the survey.

"After your first MMSE, you have to do the following 6 monthly one, to test if the medication is improving you? It has no logic or justice in it. You have to improve by those stupid two points OR obviously the medication is not beneficial to you. (I failed those two points) Then the PBS ceased their financial support. Our dilemma with that diagnostic levelling tool is that for most of us, after such a diagnosis your world is turmoil. Oscar had to retire to stay home with me as I was not safe by myself. In behaviours and lack of mental abilities etc. All these upheavals effect your stress and coping skills. It crippled me for a year. During all this you're expected to sit an "examination" to prove your eligibility for continued financial support from the PBS. Or pay up to \$200 every 4 weeks.

*Carol Cronk,
Person with Alzheimer's disease*

3. Terms of Reference

The following section outlines our main issues on each of the four terms of reference for this review.

3.1 Australian utilisation data

Based on the number of scripts issued (Medicare data), and assuming an average medication course of 13 months¹², an estimated 30,940 people with Alzheimer's disease received subsidised prescription of anti-dementia medications in 2010-11. This number has grown from an estimated 27,554 people in 2007-8; an increase of 12.3% that is slightly less than the increase in Alzheimer's disease prevalence over the same time period¹³ (Figure 1).

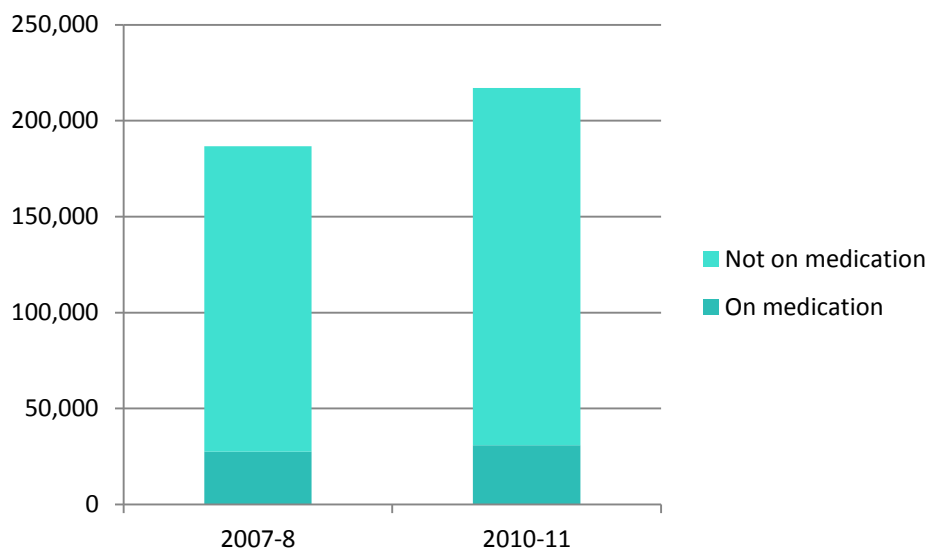


Figure 1. Utilisation of subsidised anti-dementia medications amongst people with Alzheimer's disease in Australia

30,940 is only 16.6% of the estimated 186,200 people in Australia with Alzheimer's disease (not other forms of dementia) in 2011^a. Given a 10 year average course of Alzheimer's disease, and assuming that on average, individuals are in mild-moderate stages of the condition for approximately half of this time¹⁴, these data suggest that only 33% of the people who would potentially have been eligible to receive these medications are receiving them. This is somewhat more than the estimate of 24% in an early report using different methodology¹⁵, and suggests that approximately two-thirds to three-quarters of people with mild-moderate Alzheimer's disease are not taking anti-dementia medications. This low proportion may be due to:

- ineligibility for continuation of subsidised prescription as a result of failure to meet the requirements of the continuation rule;
- contraindication with other medications;
- clinical judgement of GPs or specialists that the medications would not be beneficial;
- discontinuation due to adverse side-effects;

^a There were an estimated 266,000 people with dementia in Australia in 2011, of whom approximately 70% have Alzheimer's disease.

- discontinuation due to lack of beneficial effects within six months;
- low rates of diagnosis of dementia and/or referral to specialists in primary care;
- Individuals with personal preferences to avoid medications.

The Alzheimer's Australia consumer survey described in Section 2.1 found a high rate of private (i.e., unsubsidised) prescriptions amongst that sample, indicating that consumers value access to these medications and in many cases find that they are helpful regardless of whether they meet the criteria required by the PBS. Numerous consumer testimonials received by Alzheimer's Australia in response to this review have also indicated that where resources allow, many consumer access these medications through private prescription either as therapies in addition to a PBS subsidised medication, or to ensure continuation of treatment after failing to meet the PBS continuation criteria. However, it is unknown how many people purchase these medications privately.

3.2 Adequacy of the 2-point improvement on the MMSE as a surrogate for measuring improvement, and whether there are more reliable measures of patient relevant outcomes available.

There are two issues that need to be addressed. The first is whether the continuation rule measures patient relevant outcomes and the second is whether the 2-point improvement on the MMSE is an adequate surrogate for measuring improvement on these outcomes.

3.2.1 Patient Relevant Outcomes

The PBS should, as a minimum, extend the support for people with dementia to at least one full year, replace the MMSE with something relevant and meaningful, then recognise that with the improved scans for diagnosis, many more people are being identified with the symptoms while still being highly functional. This results in the first test score being above 25, probably, as in Carol's case, 27, a two point improvement after six months (while the person is still in trauma over the diagnosis) becomes a near impossibility without a bit of fudging by a compassionate doctor. This is part of the case for replacing the MMSE.

A consumer

The Alzheimer's Australia consumer survey conducted in 2005 indicated a range of patient relevant outcomes of anti-dementia medications. These are summarised in Figure 2.

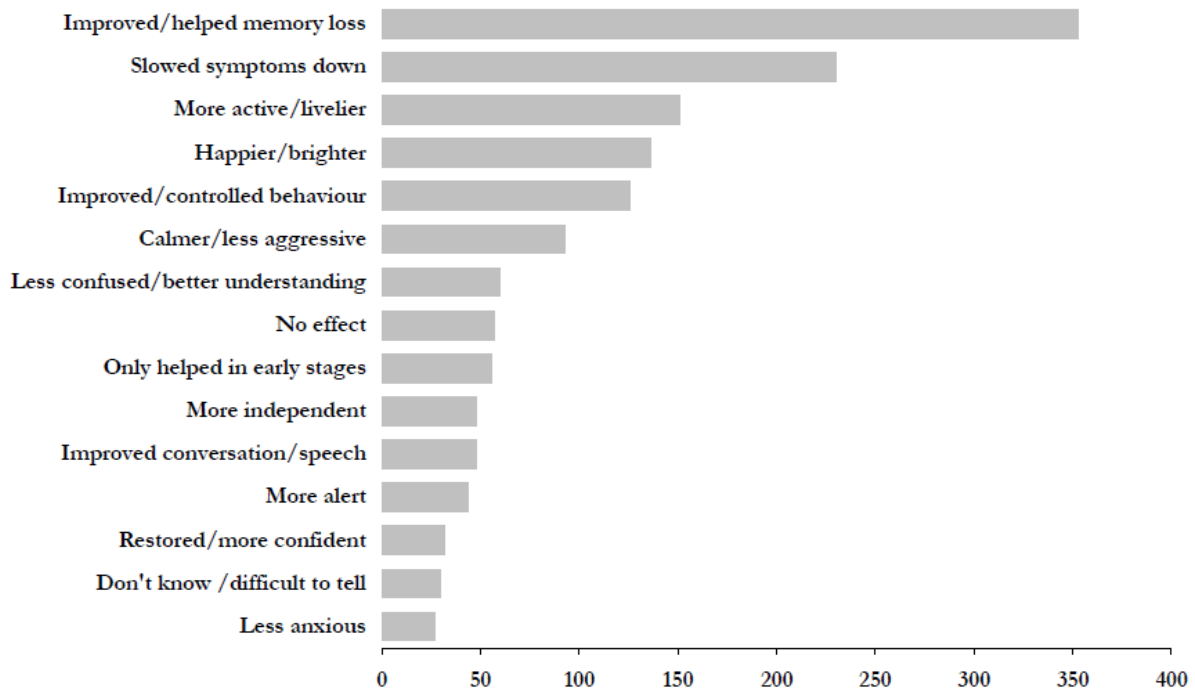


Figure 2. Reported effects of anti-dementia medications (number of respondents)

Improved cognition is clearly the key outcome for consumers. However, this survey also reveals that slowing the progression of symptoms, improving functional abilities, and reducing emotional and behavioural disturbances are highly valued by consumers as outcomes of anti-dementia medications.

In short, outcomes of anti-dementia medications that are relevant to consumers can be categorised into three domains:

1. Cognition (improved or stabilised cognitive function)
2. Functional Ability (improved or stabilised ability to manage activities of daily living, and maintain independence)
3. Psychological and Behavioural Symptoms (increased positive affect, reduced anxiety, apathy and depression, and reduced behavioural disturbance, agitation and aggression)

These patient-relevant clinical outcome domains are supported by a substantial body of empirical evidence that shows the benefits of the medications in:

- Slowing the rate of cognitive decline^{16, 17, 18, 19, 20, 21}
- Improving functional ability and independence, and delayed decline in functional ability,^{22, 23, 24, 25, 26}
- Reduced severity of behavioural and psychological symptoms of dementia.^{27,28,29,30,31}

Recommendation One. Assessment of benefit should take account of improvement or stabilisation in the domains of

cognition, functional ability, and behavioural and psychological symptoms.

3.2.2 Adequacy of a 2-point improvement on the MMSE for measuring improvement

“We changed drugs and after three months he was assessed by a Registrar because the Geriatrician was called away. This gentleman, although very competent and kind and considerate had a very pronounced Indian accent which meant that his questions in the MMSE test were very difficult to understand. Because I had seen this test administered probably ten times by this time I knew all the questions and answers. I did step in to do some interpretation. At the end of the test special permission was obtained to continue the treatment.”

A consumer

My wife said she was more confident on reminyl and felt more in control. Her specialist could see that and massaged the MMSE to show a 2+ score.

A consumer

As discussed in Section 3.2.1 evidence-based and consumer-relevant outcomes of anti-dementia medications have been demonstrated within each of the domains of cognition, functional ability, and behavioural and psychological symptoms of dementia. However, a coarse estimate of improved cognitive function (a single outcome in a single domain) is all that can be determined by a 2-point increase on an MMSE score over time.

The MMSE is a relatively insensitive screening tool that can be used to do a very quick assessment to determine if there may be a cognitive problem that should be investigated further. Also, it does not work well for people with low or high-levels of education, and those from different cultural and linguistic backgrounds. At a group level (such as an intervention or control group in a clinical trial), it can give an indication of average levels of cognitive function, however at the individual level (either as a point estimate or comparing performance at one time against another), there are a number of factors that reduce reliability. These include time of day, test location, physical and emotional state, test administration (including accent of the tester, as illustrated by the testimonial at the beginning of this section), level of encouragement, and practice effects, all of which can all have a major influence on performance.³² Simply having a good or a bad day can have a significant influence on performance on any test; for anyone; irrespective of whether or not they have Alzheimer’s disease.

Given that the MMSE is being used in this context as an indicator of a relatively small change in cognitive performance (2 points) over a relatively long period of time (6 months), test reliability becomes an important consideration. The studies that have examined this question in cognitively intact and impaired populations have generally reported relatively low interrater reliability coefficients and test-retest correlation coefficients in the range 0.8 to 0.95 over periods of 1 week to 2 months, and 0.5 or less over periods of 6-12 months.³³ These

findings suggest that for many individuals, variability of 2 points over six months could be as much an indicator of test artefacts as of real change in cognitive functioning.

For this reason, Alzheimer's Australia has serious reservations about the continued use of the MMSE as an adequate measure of improved cognitive performance as a result of anti-dementia medications.

More broadly, the issue of improvement needs to be examined. A 2 point improvement on the MMSE measures net improvement from baseline performance over a six month period. The course of Alzheimer's disease is highly variable between individuals, and decline in cognition and functional abilities is rarely linear. However, as a broad generalisation, the average expected decline in cognitive function in mild to moderate stages of Alzheimer's disease is roughly equivalent to 2 points on the MMSE per year.³⁴ The continuation rule requires reassessment of cognitive function after six months during which time the average expected decline would be 1 point on the MMSE).

An increase of two points or more relative to baseline performance six months earlier is clearly a significant improvement, and presuming the MMSE is providing an accurate measurement of cognitive ability, those who do achieve this level are clearly likely to be benefiting from the medications with respect to cognitive function. However, given the progressive nature of Alzheimer's disease, the assessment of benefit to the individual should consider maintenance of abilities that would otherwise be expected to decline over time as a clinically meaningful outcome. The current continuation rule requiring improvement of 2 points on the MMSE (or equivalent change on the ADAS-Cog) relative to baseline performance is clearly ignores the benefit experienced by those who are able to maintain baseline performance as a result of taking the anti-dementia medications..

3.2.3 Assessment of benefit to patients

“The distress of carers when their loved one fails the 2 point test and is no longer eligible for the medication is profound – especially if the medication has been assisting in maintaining a good quality of life.”

A consumer

The two critical questions that the review will need to consider in terms of assessment of benefit to patients are therefore:

1. How benefit should be defined? and
2. Benefit on which outcomes?

The weight of evidence over the past decade suggests that benefit should be defined as improvement or maintenance of abilities and symptoms that would otherwise be expected to decline or worsen over time, and that this benefit should be assessed within the evidence-based patient relevant outcome domains of cognition, functional ability and psychological and behavioural symptoms of dementia.

The next question to be addressed is how such assessment should be undertaken.

The Commonwealth Government funded Dementia Outcomes Measurement Suite (DOMS) project undertook a comprehensive review of published dementia assessment instruments, and showed that there are a large number of validated measures available for use in assessing cognitive, functional and behavioural outcomes in people with dementia.³⁵ Many of these measures could in theory be used to provide reliable quantitative measures of change on patient relevant outcomes in assessing the effectiveness of anti-dementia medications and determining eligibility for continuation of subsidised prescription. However, such tests are not widely available, require significant training to use and in many cases require an expensive kit for administration (the ADAS-cog is an example). However, the specialist nature of most of these tests means that administration by a neuropsychologist or other qualified specialist is required. Referral to and appointments with specialists are costly to both consumers and the health system, and access to specialists is limited in many areas, particularly in regional and remote settings.

For this reason, Alzheimer's Australia holds that standardised quantitative assessment of benefit from anti-dementia medications using a battery of instruments to assess change across all of the patient-relevant outcome domains will not be a feasible or cost-effective option for consumers or for the health system.

The alternative to standardised quantitative assessment based on validated instruments is qualitative clinical judgement based on clinical training and expertise, and supported where appropriate by quantitative measures and clinical tools. This is the approach to these medications that has been taken by most other jurisdictions around the world.

3.3 Evidence regarding efficacy, safety and cost-effectiveness

3.3.1 Efficacy and Safety

“Everyone who has used the drugs available has acknowledged that their best improvement has been in better ability to manage activities of daily living, rather than the improvement in memory functioning. All of these facts have also been noted by the carers' groups with whom I have interacted. It is about time that more realistic guidelines for the prescription of these drugs were formulated by the Advisory Committee, so that people with a diagnosis of dementia can be enabled to function at their best for as long as possible.”

A consumer

While the medications may not work for everyone, and they do carry risks of side effects, a growing body of empirical evidence has established their safety and efficacy for people with mild to moderate Alzheimer's disease, and for certain other types of dementia.³⁶ The UK's NICE recently reviewed this evidence in updating its guidelines for use of anti-dementia

medications in 2011. The conclusion of the review panel was that sufficient evidence had emerged since the previous guidelines in 2007 to extend availability of the three CEI medications to people with mild as well as moderate Alzheimer's disease.³⁷

In terms of cognitive function, the three CEIs and memantine have been shown to maintain or improve cognitive abilities for some people for average periods of 6-18 months.^{38, 39, 40} Other reported benefits include improvements in functional abilities,⁴¹ reduced behavioural and psychological symptoms of dementia,^{42,43} and reduced caregiver stress and burden.⁴⁴

Donepezil was listed on the PBS on the basis of clinical trials showing that on average, benefits to consumers were evident for 38 weeks (8.75 months), after which cognitive performance returned to baseline levels. After this time, intervention participants (still taking the medications) declined in parallel with placebo participants, but with a 9 month delay.^{45, 46} These findings are very similar to the results of the clinical trials conducted by the sponsors of the other anti-dementia drugs prior to their approval^{47, 48}

This means that while anybody diagnosed with probable mild to moderate Alzheimer's disease may be eligible for initiation of treatment with anti-dementia medications, the benchmark for improvement set by the continuation rule requires a much higher level of benefit to cognitive function to the patient than the average cognitive benefit observed in clinical trials.

More recent studies have also shown that patients with moderate to severe Alzheimer's disease who discontinue drugs may be at greater risk of cognitive decline. For example, a randomised control trial of donepezil discontinuation showed significantly poorer cognitive performance after 12 months amongst participants who discontinued treatment than those who remained on the medication, although both groups had declined from baseline.⁴⁹

Finally, studies over the past decade have shown that anti-dementia drugs can be of significant benefit on cognitive, functional and behavioural outcomes to people with:

- Advanced Alzheimer's disease (MMSE scores of 10 or below, for which the medications are not currently approved for subsidy in Australia);⁵⁰
- To people with other forms of dementia, such as vascular dementia(ref), dementia with Lewy bodies⁵¹, or mixed dementias such as Alzheimer's disease with vascular dementia.^{52, 53}

There is also emerging evidence in support of the efficacy of anti-dementia medications as combination therapies as opposed to monotherapies.⁵⁴

Results such as these indicate that while cognitive ability may improve over the short term as a result of anti-dementia medications, their most significant benefit in terms of cognitive function might simply be maintaining cognitive ability, and slowing the rate of cognitive decline.⁵⁵

3.3.2 Costs

Increased costs to consumers will in many cases increase the burden on carers and lead to crises which may well lead to earlier institutionalisation and or Carers needing medical assistance / support. What they save is likely to be swallowed up by extra expenses and then some, elsewhere.

A consumer

The total cost of anti-dementia medications to the government through the PBS and RPBS in 2010-11 (the most recent publicly available data) was \$63.4 million. These costs increased 3-4-fold between 2001 and 2007, but have increased only moderately since then: a 17.8% increase in the four years from 2007-8 to 2010-11 (slightly more than the approximately 14% increase in dementia prevalence over the same period).

Moreover the price of the existing medications is set to come down significantly in the next 12-24 months as their patents expire and generic brands become available. Galantamine and memantine are currently available in generic forms in Australia, and donepezil (the most commonly prescribed drug in this class at present) will become available in generic forms from 2013. With increased competition, it is possible that the cost per prescription will fall by 30% or more.

3.3.3 Cost effectiveness

Even if I could not get Exelon on the PBS, I would pay for it, as it is worth every penny. It definitely works for most types of dementia as it simply increases the amount of acetylcholine in the brain. This is a chemical messenger, keeping the brain cells more active and talking to each other. If I could not afford it, then I am sure each of my three girls would contribute a bit each month to help out, so as to keep their mother more functional.

*Christine Bryden
Person with Alzheimer's disease.*

There is growing evidence that public subsidy of anti-dementia medications is cost-effective for governments in terms of both improving patient outcomes, and offsetting other health-system costs by reducing or delaying the need for high-level formal care, and reducing the burden on informal carers.

A large observational study in the UK followed people with Alzheimer's disease who had or had not been prescribed with an anti-dementia medication. After 2.5 years, those who were taking medications were significantly less likely to be in a residential care facility, with aged care placement delayed by an average of 12 months. At the conclusion of the follow-up period (4 years), there was no longer any difference in likelihood of being in aged care.⁵⁶ Another study found that use of donepezil in patients with Alzheimer's disease living in the

community delayed entry into residential care by at least 21.4 months compared to patients receiving no or minimal doses of the drug.⁵⁷

In terms of direct costs, a Canadian clinical trial examining healthcare resource utilisation in donepezil intervention and control groups found a net saving of US\$224 (2004 dollars) over six months; or total care costs that were 3.5% lower in the treatment group than the control.⁵⁸ Similar results of small or neutral cost benefits have been demonstrated in more recent studies^{59,60,61}, while cost-benefit analyses of the impact of timely diagnosis of dementia more generally (including early treatment with anti-dementia medications) indicates potential cost savings of approximately \$10,000 per patient.⁶²

The average annual cost to Government of a residential aged care place is approximately \$40,000 per annum⁶³, and although other factors must be considered, there is a strong economic case for continuing to subsidise existing medications at approximately \$1,500 per annum per patient given the opportunity to save months or years of residential care expenditure.

3.4 Review the current PBS restriction continuation rule and the likely effect it has on cost-effective utilisation of these medicines.

“Mum says she feels “like the fog has lifted”, so should we really be caring what her MMSE score is? We know the drugs don’t work for everyone, but everyone should have the opportunity to try them and to stay on them as long as they and their doctor feel they help.”

A consumer

Section 3.3 of this submission summarised the growing body of evidence supporting the efficacy and the cost effectiveness of anti-dementia medications in terms of delayed institutionalisation and reduced healthcare resource usage. It also discussed the fact that the unit cost of the medications will come down over the next 12-24 months as generic brands become more widely available. Together, these factors argue in support of continued provision of publicly-subsidised anti-dementia medications as a treatment option for people with mild to moderate Alzheimer’s disease, and for continuation of subsidised access to those individuals who derive a clinical benefit in cognitive, functional, behavioural or psychological domains based on the clinical judgement of the treating doctor or specialist.

However, the case was made in Section 3.2 that the continuation rule in its current form does not provide an adequate measure of benefit on patient-relevant outcomes. As such, the continuation rule may undermine cost-effective utilisation of anti-dementia medications in some cases by restricting access to individuals who could potentially derive a clinical benefit from the medications that is not covered by the current continuation rule (for example, improved or stabilised functional ability, or reduced behavioural symptoms).

The cost of the continuation rule in its current form must be considered. This includes:

- The cost to consumers of repeat appointments with GPs and specialists for reassessment of cognitive function;
- The cost to Medicare of repeat appointments reassessment of cognitive function;
- The cost to the PBS of administering the restriction continuation rule.

These costs must also be factored in to a consideration of cost effectiveness of the medications.

Recommendation Two: Alzheimer’s Australia recommends that the current rules for continuation of anti-dementia medications beyond six months should be revised to allow the treating clinician (GP or specialist) to exercise their clinical judgement about the extent to which the medications have benefited and will continue to benefit their patient in cognitive, functional, behavioural and psychological domains. The rule should reflect the recommendation in the UK National Institute for Health and Clinical Excellence (NICE) guidelines that anti-dementia medications be continued “only when it is considered by the prescribing clinician (or another appropriately qualified specialist) to be having a worthwhile effect on cognitive, global, functional or behavioural symptoms.”⁶⁴

4. Alternative opportunities for cost-saving

The initial response to the medication was an overall improvement to a level of functioning that he had been at about 6 months previous. This caused some initial problems for the family as he got quite angry about the fact that my husband was handling his financial affairs because he had no recollection of being unable to manage himself. Once that issue was worked through, his overall condition improved and enabled him to remain at home for longer. I think the medication slowed his rate of decline and it was about 12 months before he was back to the level he had been when he started on the medication.

A consumer

Alzheimer's Australia recognises that there is a need to ensure appropriate prescribing of medications to individuals with dementia. This section of the submission recommends options that could be explored by the PBAC or the Commonwealth Government as alternatives to further restricting access to anti-dementia medications through the PBS.

4.1 Improving management of CElS and anticholinergic medications

"I believe that if he had started on medication when first diagnosed his decline would have been considerably slower and he would have retained basic living skills for longer."

A consumer

The 2009 review undertaken for the PBAC⁶⁵ identified that 32% of people with dementia receiving CElS were concurrently being prescribed medications with anticholinergic effects (primarily antipsychotics and some antihistamines, antidepressants, muscle relaxants and incontinence medications). The effect of concurrently taking cholinergic and anticholinergic medications is to reduce or nullify the effectiveness of both medications. Anticholinergic load in older people has also been found to be a significant but reversible risk factor for cognitive decline and incident dementia.⁶⁶ Improving management of contra-indicated medications through guidelines, regulation and training (for example, through the National Prescribing Service), would deliver both cost savings and improvements in efficacy: a distinct improvement in cost-effectiveness without reducing consumer access to anti-dementia medications.

Recommendation Three: Alzheimer’s Australia recommends that strategies should be employed to ensure better medication management amongst people with dementia, with a particular focus on reducing anticholinergic load (a risk factor for cognitive impairment) and reducing concurrent prescription of anti-dementia medications and contraindicated medications.

4.2 Addressing overuse of antipsychotic and antidepressant medications in people with dementia

“My husband was turned into a zombie within a couple of weeks. He wandered into ladies rooms and was put on an antipsychotic. They increased the dose against my wishes. He has been put on four antipsychotics that should not have been put on together. He started falling. This is a serious concern because it has ended with my husband losing his mobility.”

A consumer

Medicare data indicates that PBS subsidies for antipsychotic medications for people with dementia are approximately \$20 million/annum. There is good evidence to show that in many cases, these medications are prescribed and used off-label as a first-line of treatment to control behavioural and psychological symptoms of dementia.⁶⁷ This is in contrast to their approved use as a treatment of last resort, after non-pharmacological approaches have been tried. While some people with dementia benefit from these medications, they carry very significant side-effects, including increased risk of stroke and death.

Implementing strategies through the National Prescribing Service and other agencies to reduce the use of antipsychotics in dementia through regulation and training would result in a substantial cost-saving to the government, and better clinical outcomes for people with dementia.

Recommendation Four: Alzheimer’s Australia recommends that the PBAC and the Commonwealth Government should take action to ensure appropriate prescribing practices with respect to antipsychotic medications for people with dementia, with a view to reducing off-label prescription and achieving better patient outcomes through non-pharmacological management of behavioural and psychological symptoms of dementia.

5. Conclusions

This submission has made the case that the current rules governing continued access to anti-dementia medications through the PBS are overly complex, and fail to account for important clinical benefits in the domains of cognition, functional abilities and behavioural and psychological symptoms that are supported by strong evidence and are valued by people with Alzheimer's disease and their carers.

Since the listing of the cholinesterase inhibitors in 2001 and of memantine in 2008, there has been a significant amount of research that provides further evidence in support of the safety of antidementia medications, of their efficacy in multiple clinical domains, and their efficacy for Alzheimer's disease as well as other forms of dementia, from mild to severe stages. A recent but growing body of evidence is also emerging in support of the cost-benefit of anti-dementia medications in relation to other health and aged care system costs.

This submission has summarised the evidence in support of its core recommendation: that continuation of anti-dementia medications should be based on a clinical judgement of benefit by the treating GP or specialist. This would serve to increase the cost-effectiveness of anti-dementia medications by reducing the costs of administration of the current continuation rule, and ensuring that those who are benefiting from the medications in one or more of a number of clinical domains can continue to receive them.

It is important to note that while the current anti-dementia medications don't work for everyone, even a marginal clinical difference can have an enormous impact on the lives of the person with dementia and their carers. Chris and Judy's example below shows how this can happen.

My partner Chris was diagnosed with Alzheimer's disease in December 2007. He commenced Aricept in March 2008. Over a period of the three months following the commencement of the medication I noticed an improvement in both functioning and memory. This improvement was maintained for a couple of years after which he started to decline. He was then prescribed Ebixa as a supplement to Aricept via a private prescription. This helped with his functioning in particular.

I believe having these drugs have stabilised his condition for over three years and have continued to slow down his decline.

Chris was devastated by his diagnosis and thought he was near the end of his life. He found everything difficult. Having had the improvement enabled him to have a quality of life and he was able to participate in activities such as a men's group, art group and coffee and walking groups. In addition he was able to maintain his independence for quite a while, living on his own for the first six months and being able to catch buses to activities for a couple of years. He was also able to see that it wasn't the end and there

was value to his life and plenty he could do.

Chris was just 56 when diagnosed and had been working. Although he had comprehensive neurological testing which showed major deficiencies and a SPECT test showing Alzheimer's disease, his MMSE at the time was within normal range. As the Doctor felt he could not show a two point improvement via the MMSE, he was given an ADAS-Cog test and was able to show the necessary improvement. However this test was expensive and time consuming and there was no Medicare rebate.

*Judy Woolstencroft
June, 2012*

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