# Response to review of Pharmaceutical Benefits Scheme anti-dementia drugs to treat Alzheimer's disease

## Aricept®
## (donepezil)

**6 July 2012**

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## Introduction

Dementia is a progressive condition with multiple causes, for which there is presently no cure. Alzheimer's disease (AD) and other causes of dementia result in impaired memory, thinking and behaviour. Alzheimer's disease accounts for approximately 70% of dementia cases. Dementia, and therefore Alzheimer's disease, is recognised as a national epidemic (Commonwealth of Australia, 2012).

In 2011 it was estimated that 266,574 Australians had dementia, with this figure expected to double by 2030 (553,285), increasing to 942,624 affected individuals by 2050 (Deloitte Access Economics, 2011). This is consistent with international estimates with dementia recognised as a global public heath challenge as populations age (WHO and Alzheimer's disease International, 2012).

The Government in their 2012 report entitled "Living Longer. Living Better" recognise the challenges facing the aged care system and the ageing population, the complex management arrangements for dementia and the increasing prevalence of the disease (Commonwealth Australia, 2012). A number of key initiatives to improve the lives not only of those individuals with dementia, but also their carers, are included in the report. We commend the Government for their report and the recognition that dementia should be considered as a National Health Priority (Standing Council on Health, 2012).

Dementia is often overwhelming not just for individuals but their families and caregivers; it is estimated that there are over 1.2 million caregivers for the 260,000 Australians with dementia. In 2009, about 1 in 5 people with dementia who lived in the community received assistance from informal sources (family and friends) only, while about 3 in 4 received assistance from both informal and formal (organisations or paid help) sources. Very few relied solely on formal support (AIHW 2012). This represents a significant health and medical burden and also an increasing social and economic challenge for communities and governments. The current cost of dementia care in Australia is $6 billion per annum and as more people develop dementia, the cost to Australia is estimated to grow to $83 billion by the 2060 (Alzheimer's Australia, 4 April 2012).

There has been considerable debate in the literature about the effectiveness of Alzheimer's treatments. Benefits have generally been described as modest but consistent. However, patients should not be denied access to the only available treatments for their condition.

The consequence of these treatments in patients who respond can have a huge impact. Improved communication and being recognised is extremely valuable to relatives and carers as is small improvements in activities of daily living and/or behaviour that can save time for carers. Finally a delay in nursing home placements by keeping the patients in the community can result in significant cost savings.

Donepezil was listed on the Pharmaceutical Benefits Schedule in 2001 following four submissions to the Pharmaceutical Benefits Advisory Committee (PBAC) and two stakeholder meetings. The choice of the current initiation and continuation criteria was a pragmatic one which was agreed by clinicians committed to obtaining access to pharmacotherapy for their patients.

However, 11 years have passed since the listing of donepezil and it is therefore necessary to consider whether the restrictions, with particular reference to continuation of treatment at 6 months, are still relevant.

The PBAC submissions were generated from 1997 to 2000. Health Technology Assessment in Australia was in its relative infancy and there have been two subsequent iterations of the "Guidelines for preparation of submissions to the Pharmaceutical Industry" since then. In addition, Deloitte Access Economics has invested significant effort into establishing the prevalence of Alzheimer's disease as well as providing forecasts for its growth. In addition, diagnosis of Alzheimer's disease has improved with patients being diagnosed earlier in the course of their illness. The consequence of this could have improved response rates at 6 months.

It is not surprising, when one considers this history, that usage is considered to have outstripped estimates provided in 2000. However, there are divided opinions on whether the continuation criteria has been effective with a publication by Veteran's Affairs (Gadzhanova et al, 2010) contradicting the findings of the Drug Utilisation Subcommittee (DUSC). Additionally, a publication by Hollingworth and Byrne (2011) expressed concern that insufficient patients with AD are being treated with these agents, with figures suggesting less than a quarter of those with AD are receiving cognition enhancing drugs (CEDs).

Even if these drugs are being used by a larger number of patients than estimated it does not mean that this usage is inappropriate and that their use is not cost effective. It is also possible that patients do respond better in clinical practice than they did in clinical trials

although it is important to note that the current PBS continuation criteria do not reflect improvements in MMSE scores achieved in the pivotal trials.

With regard to cost effectiveness, it is important to note that donepezil will face loss of exclusivity in April 2013 and will therefore be subject to a 16% price reduction and enter the price disclosure cycle.

It is also important to note that on 20 March 2012 the Minister for Mental Health, the Hon. Mark Butler MP, requested that the House of Representatives Standing Committee on Health and Aging to inquire into and report to the Parliament on Dementia: Early Diagnosis and Intervention (Dementia review) (House of Representatives Committees, 2012). Submissions were requested by 2 May 2012 and public hearings were completed by 22 June 2012. As the sponsor of the PBS listed anti-dementia medicine donepezil (Aricept®) and with our ongoing commitment to the development of novel and innovative medicines and vaccines for Alzheimer's disease Pfizer provided a submission which responded to the Terms of Reference.[1] This Submission is included as **Appendix 1**. It would seem that the timelines for reporting of these two parallel reviews, whilst under the review by different committees, are similar however the key concerns which have prompted these reviews diverge substantially, as demonstrated through the terms of reference for each review.

Our submission to the Dementia review highlighted the fact that currently in Australia the number of people treated with PBS-listed anti-dementia medicines represents approximately 24% of the population currently diagnosed with Alzheimer's disease. The number of people treated with the anti-dementia drugs from the Australian study is similar to the number determined by the DUSC in their review (DUSC Review, Table 1). However, there is information that the rate of treatment for Alzheimer's is lower than 24%, with some estimates indicating the rate of treatment could be as low as 16.5%. The belief is that insufficient access to diagnostic and treatment services, complex prescribing rules for anti-dementia medications and negative perceptions about the efficacy of these medicines contribute to a low treatment rate in this population (Hollingworth and Byrne, 2011).

The submission from Minister Butler's Dementia Advisory Group (MDAG) clearly shows that dementia and Alzheimer's disease are currently under-diagnosed in Australia for a variety of reasons. The MDAG also highlights the need to optimise currently available services and

[1] Pfizer's pipeline includes several molecules in Phase 1, a vaccine in Phase 2 and a beta amyloid inhibitor in Phase 3 testing, representing the range of research into a complex and complicated disease area (Pfizer, 2012).

management options, from healthcare professionals to infrastructure such as Medicare Locals, to maximise benefits to individuals with dementia and their carers. One of the benefits of early diagnosis put forward by the MDAG to improve the quality of life and providing assistance to people with dementia to remain independent for as long as possible, is:

> *As diagnosis is essential before commencing anti-Alzheimer's drug treatment, by enabling such medications to be commenced earlier which may have greater benefit in helping people with dementia stay independent longer.*

One of our, and it appears many of the key stakeholder groups, hopes from the Dementia review is for recognition of the need for a roadmap to facilitate timely diagnosis which in turn ensures individuals and caregivers have access to appropriate support programs, respite care and financial support. It is essential to ensure there is reasonable and equitable access to diagnostic services, the best treatment management options, the appropriate healthcare professionals, respite care, home assistance and nursing homes, for example. The ability to provide an early diagnosis and appropriate disease management is clearly changing with the advances in care, the recognition of the value of a multi-disciplinary team approach will need to be balanced in view of the increasing prevalence of dementia in Australia. Any roadmap for the management of aged care, and more specifically dementia, must include recognition of the need for the appropriate infrastructure to support access to existing and innovative management options.

# Term of Reference a: Recent Australian utilisation data on patient initiation and continuation rates to cholinesterase inhibitors and memantine

## 1. DUSC review of PBS-subsidised dementia drugs

Pfizer Australia provided a response to this review in December 2011. However, a couple of points will be addressed.

This report used the AD2000 study as evidence of the uncertainty with regard to the clinical effectiveness of these drugs. In contrast, Birk (2012) excluded this trial from the Cochrane Review of Cholinesterase inhibitors for Alzheimer's disease due to problems with the design and execution of this trial and concluded: "It would be unwise to base important decisions on the provision and use of donepezil on the results of this trial."

Additionally, as mentioned in the introduction, Gadzhanova et al (2010) studied use of acetylcholinesterase inhibitors in the Australian veteran population. They performed a retrospective cohort study of the Department of Veterans' Affairs pharmacy claims data. Patients were included in the cohort if they had been dispensed at least one acetylcholinesterase inhibitor prescription between 2003 and 2006, were aged 65 years or over and had not been dispensed any acetylcholinesterase inhibitors in the previous 12 months. Patients were followed until discontinuation (ceased or switched), death or 1 year of follow up. They found a median duration of 199 days for donepezil patients and that the discontinuation rate of donepezil at 6 months is 47%. The authors indicated that the discontinuation rates were similar to a study performed by Woodward et al (2006) which found cumulative discontinuation rates of 52% for donepezil. They also found that 70% of patients who ceased therapy did not reinitiate it during the study period, which lead them to state that this: "may indicate that the PBS criteria do facilitate cessation where therapeutic failure occurs." Interestingly, Woodward et al (2006) described the discontinuation rates at 6 months as being high.

Hollingworth and Byrne (2011) performed a study to examine the trends in prescribing of cholinesterase inhibitors and memantine which they described as cognition enhancing drugs (CEDs). They analysed Medicare Australia and DUSC databases for CED prescription data, 2002-2007, by gender, age and prescriber class. Aggregated prescription data for each medication was converted to defined daily doses (DDD) per 1000 persons per day using national census data. They found that CEDs were only used by 0.16% of the total population or no more than 24% of those with AD. They concluded that "despite subsidized access to

CEDs in Australia, only a minority of people with AD was prescribed these drugs during the period of the study. It is likely that the combination of complex prescribing rules and negative perceptions about efficacy and cost-effectiveness might have contributed to these findings."

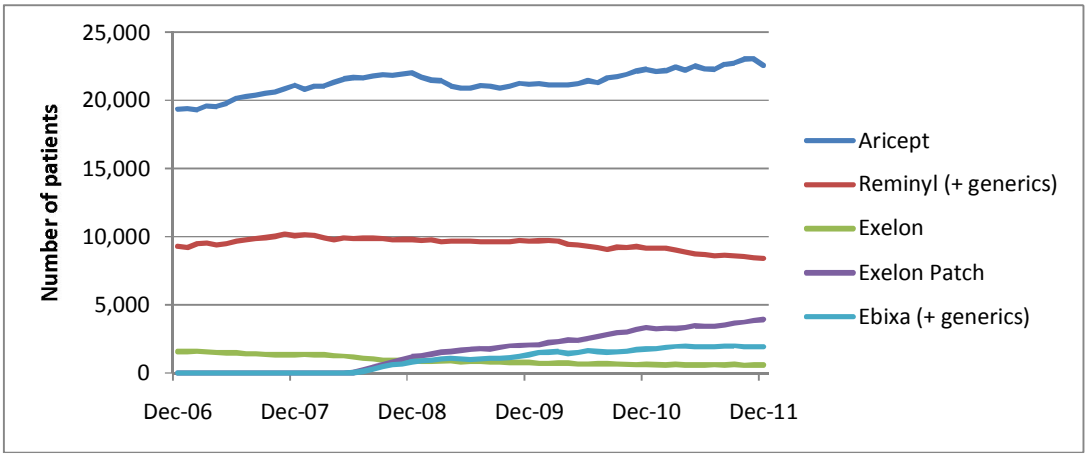
## 2. Current usage of Alzheimer's disease treatments[2]

The number of patients currently treated with Alzheimer's disease treatments is shown in **Table 1** and **Figure 1**. In 2011, donepezil was prescribed for 60% of patients on AD treatments the growth of donepezil prescribing from 2010 to 2011 was 1.2%.

**Table 1: Number of patients treated with AD treatments**

| | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 |
|---|---|---|---|---|---|---|
| Aricept | 19,354 | 21,100 | 22,017 | 21,170 | 22,261 | 22,534 |
| Reminyl (+ generics) | 9,284 | 10,055 | 9,774 | 9,675 | 9,157 | 8,401 |
| Exelon | 1,564 | 1,345 | 914 | 782 | 634 | 590 |
| Exelon Patch | 0 | 0 | 1,200 | 2,070 | 3,326 | 3,932 |
| Ebixa (+ generics) | 0 | 0 | 812 | 1,348 | 1,768 | 1,931 |
| **Total** | **30,202** | **32,500** | **34,717** | **35,044** | **37,145** | **37,388** |

**Figure 1: Patients on AD treatment**




Initiations on Alzheimer's disease treatments are shown in **Table 2.** It is interesting to compare this to the estimates in the October 2000 PBAC submission which resulted in the listing of donepezil. This submission estimated that 16,827 patients would be initiated on

[2] PBS data purchased by Pfizer Australia. Report available on request.

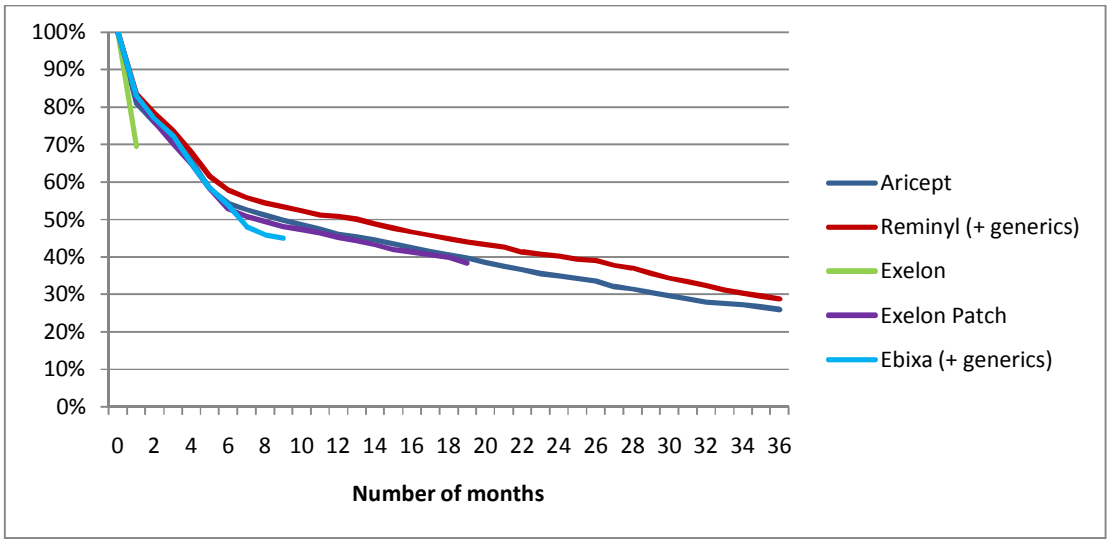
treatment in 2001 increasing to 30,810 in 2003. The initiations on all treatments in 2011 were similar to the estimate for donepezil in 2001.

**Table 2: Initiations on Alzheimer's disease treatments**

| | 2007 | 2008 | 2009 | 2010 | 2011 |
|---|---|---|---|---|---|
| Aricept | 10,592 | 11,438 | 10,402 | 10,995 | 10,794 |
| Reminyl (+ generics) | 4,227 | 3,629 | 3,844 | 3,326 | 2,443 |
| Exelon | 339 | 250 | 210 | 204 | 91 |
| Exelon Patch | 0 | 879 | 1,505 | 2,531 | 2,597 |
| Ebixa (+ generics) | 0 | 585 | 985 | 992 | 892 |
| **Total** | **15,157** | **16,781** | **16,945** | **18,049** | **16,817** |

Persistence with Alzheimer's disease treatments is shown in **Figure 2**. With donepezil, by month 6, 51.3% of patients remain on therapy. This decreases to 43% by month 12.

**Figure 2: Persistence with Alzheimer's disease treatments**




The Commonwealth payment for donepezil in 2011 was $36,295,677. Deloitte Access Economics dementia statistics for (Deloitte Access Economics, 2011) were inserted into the spreadsheet for the patient and financial estimates for the October 2000 submission and a Commonwealth payment of $40,573,601 was calculated. This means that the PBAC actually recommended expenditure for donepezil which is higher than current payments.[3]

[3] Data available on request.

## Term of reference b: Whether the two point improvement in Mini-Mental State Examination continues to be an adequate surrogate for measuring improvement in patients with dementia treated with these medicines and whether there are other more reliable measures of patient relevant outcomes

Please refer to an extract of the minutes of the PBAC meeting of December 2000 which is included in **Figure 3**.

**Figure 3: Extract from minutes of December 2000 PBAC meeting**

In October 2000 stakeholders met to develop guidelines (stopping rules) that would target PBS subsidy of cholinesterase inhibitors to those Alzheimers disease patients who demonstrate an unambiguous clinical improvement after six months' treatment.

The clinicians noted that cognitive scales are easy to use and are widely available. They suggested that an increase of 2 points or more on the MMSE scale, or in patients with a baseline MMSE score ≥25, a decrease of 4 points or more on the ADAS-cog scale would be indicative of a substantial clinically meaningful improvement. However, functional measurements are more complicated to use and open to bias. Assessing treatment impact on both cognitive and functional scales could be impractical in the clinical setting, thus testing only for cognition was recommended.

As can be seen from the above, the choice of MMSE was a pragmatic one. It was a compromise between stakeholders and the Department of Health in order to provide access to treatments for Alzheimer's disease patients.

Alzheimer's disease is a neurodegenerative disease. It is acknowledged that in clinical studies patients may have had an early modest improvement in MMSE, however, typically this is followed by continued decline. The value of acetylcholinesterase inhibitors is that they slow the decline of the disease. It is illogical to expect that symptomatic treatment would result in improvement in this patient population.

Additionally the MMSE does not reflect changes in the other domains. It selectively examines cognition and therefore, patients who show a benefit in other domains would be denied continuation of treatment after 6 months.

In 2011, the NICE guidance was revised and recommendations for continuation are included **in Figure 4**.

**Figure 4: NICE guidance on continuation of acetylcholinesterase inhibitors**

- Treatment should be continued only when it is considered to be having a worthwhile effect on cognitive, global, functional or behavioural symptoms.
- Patients who continue on treatment should be reviewed regularly using cognitive, global, functional or behavioural assessment. Treatment should be reviewed by an appropriate specialist team, unless there are locally agreed protocols for shared care. Carers' view on the patient's condition at follow-up should be sought."

As can be seen, the NICE guidance refers to a worthwhile effect on all domains (cognitive, global, functional or behavioural symptoms). It allows continuation to be at the discretion of the treating clinician(s) and it allows for the carer's opinion to be considered.

Canada, like Australia, typically allows continuation based on response. However response is generally defined as a **reduction** of no more than 2-3 points on MMSE. Therefore, Canadian Alzheimer's disease patients are not required to show an improvement in their condition for continuation of treatment.

The Authority Criteria currently in place are a huge administrative burden for both clinicians and Medicare Australia. Indeed the administration of the system is costly to the Government.

Additionally, there are logistical issues. For example, if a patient is initiated on treatment in hospital or by another clinician, the clinician seeing the patient at 6 months may not have access to the baseline MMSE. Additionally, should the clinician wish to try an alternative acetylcholinesterase inhibitor, a washout period is required to obtain a baseline MMSE prior to the alternative treatment.

In Australia, symptoms of dementia were noticed by families an average of 1.9 years prior to the first health professional consultation and there was an average of 3.1 years before a firm diagnosis was made – a finding consistent with overseas studies (Philips et al, 2011). After diagnosis, the difficult and time-consuming prescribing rules are a deterrent to prescribers, meaning that patients face additional delays to treatment.

It is important to note that Brodaty et al (2009) found that Australian AD patients were institutionalised earlier than their US and UK counterparts. This could be due to the treatment practices in this country.

## Term of reference c: Recent evidence on the safety and efficacy of donepezil that would inform the PBAC about its cost-effectiveness

A literature search was performed to identify new evidence for donepezil. The search strategy is included in **Figure 5.**

**Figure 5: Search strategy for donepezil evidence**

| | |
|---|---|
| 1 | *donepezil/ (1925) |
| 2 | (donepezil or aricept).mp. [mp=ti, ab, ot, nm, hw, ps, rs, ui, sh, tn, dm, mf, dv, kw] (9815) |
| 3 | 1 or 2 (9815) |
| 4 | exp Alzheimer disease/ (162612) |
| 5 | 1 and 4 (1259) |
| 6 | limit 5 to yr="2000 -Current" (1051) |
| 7 | limit 6 to ("reviews (maximizes specificity)" or "therapy (maximizes specificity)") [Limit not valid in Embase Weekly Alerts; records were retained] (276) |
| 8 | limit 6 to randomized controlled trial (150) |
| 9 | 7 or 8 (308) |
| 10 | 2 and 4 (5989) |
| 11 | limit 10 to yr="2000 -Current" (5310) |
| 12 | limit 11 to ("reviews (maximizes specificity)" or "therapy (maximizes specificity)") [Limit not valid in Embase Weekly Alerts; records were retained] (827) |
| 13 | limit 11 to randomized controlled trial (489) |
| 14 | 12 or 13 (936) |
| 15 | from 14 keep 1-198 (198) |
| 16 | ((donepezil or aricept) and alzheimer*).mp. [mp=ti, ab, ot, nm, hw, ps, rs, ui, sh, tn, dm, mf, dv, kw] (6775) |
| 17 | from 16 keep 1437-1575 (139) |
| 18 | 17 and (placebo* or random*).mp. [mp=ti, ab, ot, nm, hw, ps, rs, ui, an, sh, tn, dm, mf, dv, kw] (47) |
| 19 | 9 or 15 or 18 (553) |
| 20 | remove duplicates from 19 (424) |

The objective of the search was to identify new evidence which could confirm the effectiveness of donepezil. Additionally, reviews that showed that donepezil has acceptable tolerability were also included.

It was not possible within the timeframe provided to perform a cost-effectiveness analysis to demonstrate that donepezil is and will remain cost-effective when used to treat Australian Alzheimer's disease patients. It is proposed that the sponsor be provided an opportunity to submit such a cost-effectiveness analysis.

In the absence of a cost-effectiveness analysis in Australian patients, abstracts of international cost-effectiveness analyses have been provided.

It is noted that a systematic review has been commissioned by the Department, however, the Sponsor sought to provide a comprehensive review as part of this submission.

Exclusions from presentation in this submission and reasons for exclusion are provided in **Table 3.**

**Table 3: Exclusions and reasons for exclusion**

| Exclusions | Reasons for exclusion |
|---|---|
| Clinical studies comparing donepezil to other acetylcholinesterase inhibitors or memantine | Comparative data was not included as this submission sought to demonstrate donepezil's efficacy not comparative efficacy vs other agents |
| Studies which included fewer than 50 patients | Considered too few to provide meaningful data |
| Studies which were restricted to severe AD | Donepezil is not PBS-listed for severe disease |
| Studies which included outcomes outside of the usual domains considered in AD studies for example sleep apnoea or only one symptom for example agitation | Not relevant to consideration of efficacy |
| Individual study which only considered safety | In the time frame provided it was not possible to review all safety data |

The following were included in this Submission:

- Summaries of clinical studies with donepezil not excluded above (**Table 4**);
- Summary of clinical studies with acetylcholinesterase inhibitors (**Table 5**)
- Summaries of reviews and meta-analyses of donepezil (**Table 6**)
- Summaries of reviews and meta-analyses of AD treatments (**Table 7**);
- Summaries of safety and tolerability reviews of donepezil or AChEIs (**Table 8**), and
- Summaries of international cost-effectiveness analysis (**Table 9**).

The studies included in this review were considered to ensure that all relevant clinical evidence has been included in this submission. Publications of these studies were sourced and included as relevant

## Table 4: Summary of clinical studies: donepezil

| First Author[4] | Design | Centres, Countries | Population | N | Dose | Duration | Outcome measures | Results |
|---|---|---|---|---|---|---|---|---|
| AD2000 | Double-blind design with a run-in treatment period of 12 weeks, in which patients were randomly allocated to donepezil (5 mg/day) or placebo, followed by a 2nd randomisation to long-term donepezil (sub-randomised between 5 and 10 mg/day) or placebo. | US | Mild to moderate AD | 565 | Donepezil 5 mg or 10 mg | 60 weeks to indefinitely | Primary endpoints were entry to institutional care and progression of disability, defined by loss of either two of four basic, or six of 11 instrumental, activities on the BADLS | Findings<br>Cognition averaged 0·8 MMSE (mini-mental state examination) points better (95% CI 0·5–1·2; p<0·0001) and functionality 1·0 BADLS points better (0·5–1·6; p<0·0001) with donepezil over the first 2 years.<br>No significant benefits were seen with donepezil compared with placebo in institutionalisation (42% *vs* 44% at 3 years; p=0·4) or progression of disability (58% *vs* 59% at 3 years; p=0·4). The relative risk of entering institutional care in the donepezil group compared with placebo was 0·97 (95% CI 0·72–1·30; p=0·8); the relative risk of progression of disability or entering institutional care was 0·96 (95% CI 0·74–1·24; p=0·7).<br>Similarly, no significant differences were seen between donepezil and placebo in behavioural and psychological symptoms, carer psychopathology, formal care costs, unpaid caregiver time, adverse events or deaths, or between 5mg and 10 mg donepezil.<br>Authors' conclusion<br>Donepezil is not cost effective, with benefits below minimally relevant thresholds. More effective treatments than cholinesterase inhibitors are needed for Alzheimer's disease.<br>Please note:<br>As discussed above, Birk (2012) excluded this trial from the Cochrane Review of Cholinesterase inhibitors for Alzheimer's disease due to problems with the design and execution of this trial and concluded: "It would be unwise to base important decisions on the provision and use of |

[4] Plus publication year if author has numerous publications included in this submission

| First Author[4] | Design | Centres, Countries | Population | N | Dose | Duration | Outcome measures | Results |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | donepezil on the results of this trial." |
| Boada-Rovira | Open label, multicentre | 246 study centres in 18 countries including Australia | Mild to moderate AD | 1,113 | 5 mg for 28 days increasing to 10 mg at discretion of clinician | 12 weeks | MMSE, Patient activity and social interaction as assessed by carer | Efficacy<br>Donepezil significantly improved cognition compared with baseline at weeks 4 and 12, and at week 12 using a LOCF analysis (all $p < 0.0001$). Mean change from baseline MMSE score (±SE) at week 12-LOCF was +1.73 ± 0.10. Donepezil was also associated with significant improvements in patient social interaction, engagement and interest, and initiation of pleasurable activities at all weekly assessments and week 12-LOCF (all $p < 0.0001$).<br>Safety<br>59 (5%) patients discontinued because of adverse events. Donepezil was generally well tolerated; adverse events were consistent with the known safety profile of donepezil.<br>Authors' conclusion<br>Donepezil treatment resulted in statistically significant improvements in cognition and patient activity and social behaviour, and was generally well tolerated despite high levels of comorbid illness and concomitant medication use. The results of this open-label study in a large patient population are consistent with those from controlled trials and support that donepezil is effective in the treatment of mild-to-moderate Alzheimer's disease in everyday practice. |
| Burns (2007) | Open-label, multicentre (continuation of Burns, 1999 after 6-week placebo | UK, Canada, US | Mild to moderate AD | 579 | 5 mg per day for 6 weeks, optional increase to 10 mg per day | 132 weeks | ADAS-cog, CDR-SB | Efficacy<br>After 6 weeks of open-label treatment with donepezil 5 mg/day, mean ADAS-cog improved by approximately two points, while after 12 weeks of open-label treatment (with a majority of patients receiving 10 mg/day), the mean ADAS- |

| First Author[4] | Design | Centres, Countries | Population | N | Dose | Duration | Outcome measures | Results |
|---|---|---|---|---|---|---|---|---|
| | washout period)[5] | | | | | | | cog score was 1 point better than the score at the end of the placebo washout period. Scores then declined gradually over the remainder of the study.<br>Mean changes in CDR-SB scores showed slight improvement over the first 12 weeks of open-label treatment and then slowly declined for the remainder of the study period.<br>Safety<br>Donepezil was well tolerated over the entire 162-week study period. Overall, 85% of patients experienced at least one adverse event (AE). The most common included diarrhoea (12%), nausea (11%), infection (11%) and accidental injury (10%). Some patients discontinued the study due to AEs (15%).<br>Authors' conclusion<br>These results support the conclusion that donepezil is safe and effective for the long-term treatment of patients with mild to moderate AD. |
| Carrasco | Naturalistic | Spain | AD with behavioural symptoms | 529 | 5 to10 mg per day | 6 months | Primary adverse events, NPI, MMSE, caregiver burden | Sixty-five patients (12.3%) experienced an adverse event. The most frequent adverse events were diarrhoea and agitation (<2%).<br>Seventeen patients (3%) presented with a neuropsychiatric adverse event and 11 (2%) patients presented with a neurologic adverse event over the course of the study. NPI scores improved by 34.4% over the course of the study, with all items showing a statistically significant improvement.<br>Mini-Mental State Evaluation scores and Zarit caregiver burden scores also improved by 1.27 points and 5.9 points, respectively.<br>Authors' conclusion<br>This study showed a low incidence of adverse |

[5] Not presented in this document as would have been presented in PBAC submissions for donepezil

| First Author[4] | Design | Centres, Countries | Population | N | Dose | Duration | Outcome measures | Results |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | events accompanied by an improvement in the neuropsychiatric and cognitive functions in patients with mild to moderately severe Alzheimer disease treated with donepezil in a community setting in Spain. Donepezil also reduced caregiver burden. |
| Cummings (derived from Finkel 2004)[6] | Open-label for 8 weeks then double-blind treatment of donepezil + sertraline vs donepezil + placebo for 12 weeks[7] | NR | Patients with probable or possible AD, and a NPI total score >5 (with a severity score ≥2 in at least one domain) | 120[8] | 5 mg for 28 days increasing to 10 mg in absence of dose-limiting side-effects | 20 weeks | NPI | The total score of the NPI was significantly reduced over the 20 weeks of therapy with donepezil. Sixty-two percent of patients had at least a 30% reduction in the total NPI score (significantly greater than the number with no meaningful response). Likewise, more patients had total or partial resolution of depression and delusions than those who had no meaningful change. Factor analysis of baseline NPI data revealed five factors, including a psychosis factor, an agitation factor, mood factor, frontal lobe function factor, and appetite and eating disorders factor. Clinically meaningful treatment effect sizes were notable for the delusion factor (0.340) and the mood factor (0.39).<br>Authors' conclusion<br>The results of these analyses suggest that donepezil reduces behavioural symptoms, particularly mood disturbances and delusions, in patients with AD with relatively severe psychopathology. |
| Doody | Multicentre, open-label, 144 week extension study of 2 US | NR | Mild to moderate AD | 763 | 5 mg for 6 weeks and encouraged to increase to 10 mg | 144 weeks | ADAS-cog, CDR-SB | Efficacy<br>After the shorter 3-week placebo washout, donepezil associated benefits remained above original baseline values for 24 weeks of open-label treatments. In contrast, donepezil- |

[6] Not presented in this submission as the objective was to consider sertraline augmentation therapy
[7] Hypothesis-driven secondary analysis of a three-phase study involving donepezil and sertraline. In phase 1, psychotropic agents were withdrawn; in phase 2, patients were treated in an open-label fashion with donepezil for 8 weeks; and in phase 3, patients on donepezil were randomised to receive placebo or sertraline for an additional 12 weeks.
[8] The data set analysed is comprised of the patient population treated with donepezil (without sertraline) for 20 weeks.

| First Author[4] | Design | Centres, Countries | Population | N | Dose | Duration | Outcome measures | Results |
|---|---|---|---|---|---|---|---|---|
| | phase 3 studies[9] | | | | | | | associated benefits were lost after the 6-week placebo washout and scores decreased below original baseline values. Although scores improved relative to the open-label study baseline after drug use was restarted, patients remained below original baseline values.<br>Safety<br>The most common adverse events were associated with the nervous and digestive systems and were generally mild and transient. 17% of patients discontinuations were associated with adverse events.<br>Authors' conclusion<br>Donepezil is an effective and safe drug for the long-term symptomatic treatment of mild to moderately severe AD for up to 144 weeks (2.8 years), and sustained treatment may confer some advantages. |
| Feldman 2001 | Double-blind, placebo-controlled | 32 sites - Canada: 22 Australia: 6 and France: 4 | Moderate to severe AD | 290[10] | 5 mg for 28 days increasing to 10 mg at discretion of clinician | 24 weeks | CIBIC-plus, sMMSE, SIB, DAD, FRS, NPI | Efficacy<br>Patients receiving donepezil showed benefits on the CIBIC-plus, compared with placebo, at all visits up to week 24 ($p < 0.001$) and at week 24 last observation carried forward (LOCF) ($p < 0.0001$). All other secondary measures (including sMMSE, SIB, DAD, FRS and NPI) showed significant differences between the groups in favour of donepezil at week 24 LOCF.<br>Safety<br>AEs were experienced by 83% of donepezil- and 80% of placebo-treated patients, the majority of which were rated mild in severity; 8% of donepezil- and 6% of placebo-treated patients discontinued because of an AE. Laboratory and |

[9] A 15 weeks study (12 weeks of treatment followed by a 3-week placebo washout) (Rogers, 1998a) and a 30 week study (24 weeks of treatment followed by a 6-week placebo washout) (Rogers, 1998b)

[10] The data set analysed is comprised of the patient population treated with donepezil (without sertraline) for 20 weeks.

| First Author[4] | Design | Centres, Countries | Population | N | Dose | Duration | Outcome measures | Results |
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| | | | | | | | | vital sign abnormalities were similar between the treatment groups.<br>Authors' conclusion<br>These data suggest that donepezil's benefits extend into more advanced stages of AD than those previously investigated, with very good tolerability. |
| Feldman 2003 (ADL and effect on caregivers from Feldman 2001) | Double-blind, placebo-controlled | 32 sites - Canada: 22 Australia: 6 and France: 4 | Moderate to severe AD | 290 | 5 mg for 28 days increasing to 10 mg at discretion of clinician | 24 weeks | DAD<br>IADL+<br>PSMS+ | IADL+ and PSMS+ mean change from baseline scores for donepezil-treated patients showed a significantly slower decline during the study than placebo-treated patients (Week 24 LOCF mean treatment differences).<br>Significant differences between the groups in favour of donepezil were observed on the DAD for instrumental and basic ADLs and on the three components required for the completion of each ADL: initiation, planning and organisation, and effective performance.<br>At Week 24 LOCF, the overall distribution of caregiver ratings on each of the three caregiver diary items favoured donepezil-treated patients over placebo-treated patients. At Week 24 LOCF, mean change from baseline scores for CSS total and individual domain scores (all domains except caregiving competence, personal gain, and management of distress) were better for caregivers of donepezil-treated patients than for those of placebo-treated patients. Caregivers of donepezil-treated patients reported spending less time assisting with ADLs than caregivers of placebo-treated patients.<br>Authors' conclusion<br>Donepezil demonstrated a significantly slower decline than placebo in instrumental and basic ADLs in these patients with moderate to severe AD. The ADL benefits in AD patients treated with donepezil were associated with less caregiving |

| First Author[4] | Design | Centres, Countries | Population | N | Dose | Duration | Outcome measures | Results |
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| | | | | | | | | time and lower levels of caregiver stress. |
| Feldman 2005 (more severe sub-population of Feldman 2001) | Double-blind, placebo-controlled | 32 sites - Canada: 22 Australia: 6 and France: 4 | More severe population | 145 | 5 mg for 28 days increasing to 10 mg at discretion of clinician | 24 weeks | CIBIC-plus, sMMSE, SIB, DAD, FRS, NPI | Efficacy<br>CIBIC-plus scores for donepezil patients were significantly improved compared with placebo for each time-point, with a 0.70 mean treatment difference at Week 24 last observation carried forward (LOCF; p=0.0002). Significant differences favouring donepezil were noted at Week 24 LOCF for all secondary measures. There were no treatment-severity interactions for any of the efficacy measures.<br>Safety<br>In this more severe AD subgroup, 82% of donepezil- and 78% of placebo-treated patients experienced at least one AE during the course of the trial, with 7% of donepezil-treated and 5% of placebo-treated patients withdrawing due to AEs. Thirteen percent of donepezil- and 16% of placebo-treated patients experienced severe AEs. Overall, the majority of AEs (95%) were rated as mild or moderate in severity.<br>Authors' conclusion<br>In this analysis, donepezil had significant benefits over placebo on global, cognitive, functional, and behavioural measures in a subgroup of patients with more severe AD. Furthermore, the treatment effects of donepezil were not driven by a particular stratum within the moderate to severe dementia range. |
| Fillit | Survey | New Jersey | Carers of AD patients | 274 carers of patients receiving donepezil, 274 carers of patients not receiving donepezil | N/A | N/A | Caregiver Burden Scale which measured time demands and distress linked to commonly performed | Results demonstrated that donepezil caregivers reported significantly lower scores on difficulty of caregiving. This difference remained when statistical controls for multiple patient and caregiver variables were imposed. However, selection factors must be recognised as a possible explanation for differences. The groups reported no difference on the time-demand subscale. |

| First Author[4] | Design | Centres, Countries | Population | N | Dose | Duration | Outcome measures | Results |
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| | | | | | | | caregiving tasks | Authors' conclusion<br>Better management of AD symptoms through donepezil treatment may reduce the burden of caregiving, providing physicians with a pharmacologic approach to improving quality of life for AD patients and their families. |
| Froelich | Multicentre, open-label (routine clinical practice) | Germany | Mild to moderately-severe AD | 237 | 5 mg/day for 28 days.<br>Thereafter, a dose increase to 10 mg/day was allowed according to the investigator's clinical judgement | 24 weeks | MMSE | A total of 237 patients with mild-to-moderate AD were treated with donepezil for 24 weeks, 186 completed the study according to the protocol. In the completer group, mean MMSE score for efficacy showed an improvement from baseline of +1.6 points at week 12 (95% CI +1.1 to +2.1) and of +1.1 points at week 24 (95% CI +0.5 to +1.7).<br>In more than 80% of the patients, global tolerability was rated to be very good or good. There were only insignificant effects on ECG parameters.<br>Authors' conclusion<br>This study confirms the results obtained in previous double-blind trials, which showed that donepezil is effective and well tolerated in patients with mild-to-moderately severe AD. |
| Frolich | Post-marketing surveillance study | Germany | AD with and without cerebro-vascular disease | 913 | 5 mg per day increased to 10 mg if appropriate | 3 months | Efficacy parameters were changes in MMSE, global clinical (invest-tigators) judgment of efficacy, and a clinical judgment about the patients' quality of life | In a post-marketing surveillance (PMS) study in Germany, patients under routine treatment conditions were observed while treatment was switched from other antidementia drugs (i.e., nootropics) to donepezil. In 29.6% of patients, investigators documented concomitant cerebrovascular disease (CVD+) according to their clinical judgment.<br>After 3 months, patients had improved by a mean MMSE change from baseline of 2.2 points (CVD+: 2.4 pts, CVD-: 2.1 pts). QoL was judged "improved" in 70.0% of patients (CVD+: 72.5%, CVD-: 69.6%).<br>Adverse events were reported in 85/913 (9.3%) of patients (CVD+: 11.2%, CVD-: 7.9%). |

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| | | | | | | | (QoL) | Reported adverse events were substantially less than reported previously in controlled clinical trials.<br>Authors' conclusion<br>This suggests that donepezil therapy is effective and well tolerated in AD patients, both with and without concomitant cerebrovascular disease. |
| Gasper | Retro-spective matched cohort | US | AD | 5423 patients on donepezil and 5423 patients not on donepezil | 5 mg and 10 mg | Between 1998 and 2000 | Mortality in nursing home patients | Methods<br>Retrospective matched cohort study using the Systematic Assessment of Geriatric Drug Use via Epidemiology database, which contains data collected with the Minimum Data Set on a cross section of 915,469 nursing home residents aged >65 years between 1998 and 2000 in 6 US states.<br>The authors identified users of donepezil (5 and 10 mg) and an equal number of matched nonusers in the same facility, date of donepezil use, level of cognitive function, and dementia diagnosis.<br>Comparisons of the 2 groups were made for sociodemographic variables, dementia severity, number of medications, and major comorbid illnesses (heart disease, cancer, diabetes mellitus, chronic obstructive pulmonary disease, and malnutrition), as well as survival over the 2-year study period.<br>Results<br>A total of 5423 users and 5423 nonusers of donepezil were identified. Based on Cox proportional hazards models, donepezil users showed a lower mortality rate than nonusers. The hazard rate ratio was 0.89 (95% CI, 0.83-0.95). After adjusting for the confounding variables, sociodemographic factors, other psychotropic drugs, and comorbid conditions, this survival advantage remained (hazard rate ratio, 0.90; 95% CI, 0.84-0.96). |

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| | | | | | | | | Authors' conclusion<br>A relationship was observed between treatment of nursing home residents with donepezil and lower mortality. If the relationship was due to a direct effect of donepezil use, then this observation has implications for the socioeconomic impact of CEI therapy in those with advanced dementia in the nursing home. These implications deserve future investigation. |
| Gauthier (subgroup of Feldman) | Double-blind, placebo-controlled | 32 sites - Canada: 22 Australia: 6 and France: 4 | Moderate AD | 207 | 5 mg for 28 days increasing to 10 mg at discretion of clinician | 24 weeks | CIBIC-plus, sMMSE, SIB, DAD, FRS, NPI | Efficacy<br>CIBIC-plus scores for donepezil-treated patients were improved from, or close to, baseline severity at all visits, and were significantly different from placebo at weeks 8, 12, 18, and 24.<br>LS mean change from baseline scores on the sMMSE and SIB for the donepezil group improved throughout the study, and were significantly different from placebo at each visit for the sMMSE and from week 8 for the SIB.<br>LS mean change scores on the DAD remained at or above baseline levels throughout the study for the donepezil group, while the placebo group showed a steady decline; treatment differences were significant at each visit.<br>LS mean change scores on the NPI 12-item total improved throughout the study for the donepezil group and were significantly different from placebo at weeks 4 and 24.<br>Safety<br>Eighty-one per cent of donepezil-treated and 89% of placebo-treated patients completed the trial, with 9% and 5%, respectively, discontinuing due to adverse events (AEs). Eighty-two per cent of donepezil-treated and 80% of placebo-treated patients experienced AEs, the majority of which were rated mild in severity and, in general, were similar between treatment groups. |

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| | | | | | | | | Authors' conclusion<br>The significant treatment responses observed with donepezil in these patients reinforce the findings from earlier studies that show donepezil to have important benefits, compared with placebo, across functional, cognitive, and behavioural symptoms, with good tolerability, in patients with AD of moderate severity. |
| Gauthier (b) (behavioural symptoms out of Feldman) | Double-blind, placebo-controlled | 32 sites - Canada: 22 Australia: 6 and<br>France: 4 | Moderate to severe AD | 290 | 5 mg for 28 days increasing to 10 mg at discretion of clinician | 24 weeks | NPI | Efficacy<br>NPI individual item change from baseline scores at Week 24 using a last observation carried forward (LOCF) analysis showed benefits with donepezil treatment compared with placebo for all items, with significant treatment differences for depression/dysphoria, anxiety, and apathy/ indifference ($p < .05$). Symptoms present at baseline that improved significantly for donepezil- compared with placebo-treated patients at Week 24 LOCF included anxiety, apathy/indifference, and irritability/lability $p < .05$). When patients who were not receiving psychoactive medications at baseline were analysed separately, significant improvements in NPI12-item total score were observed with donepezil compared with placebo at most visits and at Week 24 LOCF ($p < .05$).<br>Safety<br>Eighty-three percent of donepezil- and 80% of placebo-treated patients experienced at least one AE during the course of the trial, of whom 8% of donepezil- and 6% of placebo-treated patients withdrew due to AEs. Most AEs (94%) were rated as mild or moderate in severity and, in general, were similar between treatment groups.<br>Authors' conclusion<br>Behavioural symptoms of the magnitude observed in this moderate to severe AD population improved with donepezil. |

| First Author[4] | Design | Centres, Countries | Population | N | Dose | Duration | Outcome measures | Results |
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| Geldmacher | Observational follow-up (double-blind studies: Rogers, 1996; Rogers, 1998a; Rogers 1998b[11] and extension studies: Rogers, 2000 and Doody, 2001 ) | NR | Mild to moderately severe AD | 671 patients provided data for analysis | 5 mg increased to 10 mg if appropriate | Up to 240 weeks | NHP | Use of donepezil of 5 mg per day or more was associated with significant delays in NHP. A cumulative dose-response relationship was observed between longer-term sustained donepezil use and delay of NHP. When donepezil was taken at an effective dose for at least 9 to 12 months, conservative estimates of the time gained before NHP were 21.4 months for first dementia-related NHP and 17.5 months for permanent NHP.<br>Authors' conclusion<br>Use of donepezil by AD patients resulted in significant delays in NHP. Long-term use of donepezil may help AD patients live longer in community settings, with consequent personal, social, and economic benefits. |
| Greenberg | Two-centre, randomised, placebo-controlled, crossover | Memory disorders unit at Massa-chusetts General and Brigham Hospitals Boston | Probable AD | 60 | 6 week single-blind placebo wash-in then equally randomised to double-masked therapy with donepezil (5 mg/d) or placebo in either of 2 sequences: (1) 6 weeks each of placebo treatment, donepezil therapy and placebo washout, (2) 6 weeks each of donepezil therapy, placebo washout and placebo treatment | | ADAS-cog | Efficacy<br>Among patients completing treatment and testing for both periods, subscale scores improved during donepezil therapy relative to donepezil therapy (p=0.04). Scores returned toward baseline within 3 weeks of drug washout.<br>There was no associated change in caregiver-rated global impression (donepezil vs placebo: p=0.34) or on specific tests of explicit memory or verbal fluency.<br>Safety<br>Most common adverse events related to donepezil therapy were nausea (5 patients), diarrhoea (3 patients) and agitation (3 patients). Serious events possibly related to drug were seizure, pancreatitis and syncope (1 patient each).<br>Authors' conclusion<br>This independent confirmation of data from |

[11] The double-blind studies are not presented as they would have been part of the PBAC submissions for Aricept

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| | | | | | | | | phase 3 trials suggests that donepezil therapy modestly improves cognition in patients with Alzheimer disease who are encountered in clinical practice. |
| Hager | Observational | Germany | AD | 2,092 | 5 mg or 10 mg | 3 months | MMSE NOSGER | MMSE and NOSGER scores showed statistically significant improvements in the total patient population and in the subpopulations with severe AD or ADPS<br>AEs were reported in a total of 12% of patients and were mostly due to peripheral cholinergic effects.<br>Authors' conclusion<br>In this observational PMS study, donepezil was shown to be an effective and well-tolerated therapy in the overall patient population, in patients with severe AD, and in the ADPS cohort. |
| Holmes | Open-label then double-blind, randomised, placebo-controlled, withdrawal study[12] | 16 sites in the UK | Mild to moderate AD with marked neuro-psychiatric symptoms | 134 patients | 5 mg daily for 6 weeks followed by 10 mg daily for a further 6 weeks | 24 weeks | NPI and carer distress | During the open-label phase the total NPI and NPI-Distress scores were lower after 12 weeks treatment with open-label donepezil compared with baseline. In the open-label phase all domains of the NPI (with the exception of elation) were significantly improved.<br>Following randomisation patients who continued on donepezil 10 mg for 12 weeks had significant improvements in NPI compared with the placebo group and in NPI-Distress scores.<br>Authors' conclusion<br>Donepezil has significant efficacy in the treatment of neuropsychiatric symptoms in patients with mild to moderate AD. |
| Homma | Double-blind, placebo-controlled | 54 centres in Japan | Mild to moderately severe AD | 268 | Donepezil 5 mg/day | 24 weeks | ADAS-J-cog, J-CGIC, CDR-SB, | Efficacy<br>Donepezil was superior to placebo on the ADAS-J cog ($p = 0.003$) and the J-CGIC ($p = 0.000$). |

[12] 12 weeks donepezil treatment (6 weeks on 5 mg then 6 weeks on 10 mg) then patients were randomised (60:40) to either placebo or 10 mg donepezil daily . All patients were assessed at 6 weeks and provided there was no marked cognitive deterioration their blinded treatment was continued for a further 6 weeks.

| First Author[4] | Design | Centres, Countries | Population | N | Dose | Duration | Outcome measures | Results |
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| | | | | | | | MENFIS, CMSC | The superiority of donepezil was also shown by secondary measures: the CDR-SB, the MENFIS and the CMCS.<br>Safety<br>The incidence of drug-related adverse events was 10% (14/136) in the donepezil and 8% (10/131) in the placebo group; no significant difference was seen between the two groups. The main AEs were gastrointestinal symptoms, and these were mild, and they all disappeared with continued administration or temporary discontinuation of donepezil.<br>Authors' conclusion<br>These results indicate that the donepezil appears to be effective and well tolerated in patients with mild to moderately severe Alzheimer's disease. |
| Howard[13] | Multicenter, double-blind, placebo-controlled, clinical trial with a two-by-two factorial design<br>Arms:<br>1. Donepezil<br>2. Donepezil + memantine<br>3. Memantine<br>4. Placebo | UK | Moderate or severe AD<br>Patients had received donepezil for at least 3 months at<br>a dose of 10 mg for at least 6 weeks | | Donepezil 10 mg per day<br>(Memantine 5 mg increasing to 20 mg) | 52 weeks | sMMSE, BADLS | Efficacy<br>Patients assigned to continue donepezil, as compared with those assigned to discontinue donepezil, had a score on the sMMSE that was higher by an average of 1.9 points (95% confidence interval [CI], 1.3 to 2.5) and a score on the BADLS that was lower (indicating less impairment) by 3.0 points (95% CI, 1.8 to 4.3) (P<0.001 for both comparisons).<br>Patients assigned to receive memantine, as compared with those assigned to receive memantine placebo, had a score on the sMMSE that was an average of 1.2 points higher (95% CI, 0.6 to 1.8; P<0.001) and a score on the BADLS that was 1.5 points lower (95% CI, 0.3 to 2.8; P = 0.02).<br>The efficacy of donepezil and of memantine did not differ significantly in the presence or absence of the other. There were no significant benefits of |

[13] The Donepezil and Memantine in Moderate to Severe Alzheimer's Disease (DOMINO) study

| First Author[4] | Design | Centres, Countries | Population | N | Dose | Duration | Outcome measures | Results |
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| | | | | | | | | the combination of donepezil and memantine over donepezil alone.<br>Safety<br>A total of 188 serious adverse events were reported, of which 6 (2 in the group receiving placebo donepezil and placebo memantine, 2 in the group receiving memantine and placebo donepezil, and 2 in the group receiving donepezil and memantine) were considered to be possibly related to the study drugs. None were considered to be unexpected serious adverse reactions. There was no evidence that the incidence of serious adverse events or death differed according to treatment group (P = 0.77).<br>Authors' conclusion<br>In patients with moderate or severe Alzheimer's disease, continued treatment with donepezil was associated with cognitive benefits that exceeded the minimum clinically important difference and with significant functional benefits over the course of 12 months. |
| Johanssen[14] | Open-label donepezil phase; double-blind, placebo-controlled, phase; single-blind donepezil treatment phase. | 57 sites in Belgium, Denmark, Germany, Greece, Hungary, Iceland, The Neth-erlands, Poland and the US | Mild to moderate AD | 812 | Three phases: (i) a 12- to 24-week, pre-randomisation, open-label donepezil-treatment phase; (ii) a 12-week, randomised, double-blind, placebo-controlled phase; and (iii) a 12-week, single-blind (i.e. patient-blind) donepezil-treatment phase.<br>Donepezil treatment was 5 mg per day for 4 weeks then 10 mg per day for the remainder of the phase | | MMSE, ADL | Efficacy<br>Six hundred and nineteen patients completed the open-label phase; 69% showed clear clinical benefit and 31% showed uncertain benefit. 202 patients were randomised to continued donepezil treatment (n = 99) or placebo (n = 103). Differences in favour of continued donepezil versus placebo were observed in cognition and behaviour. In addition, there was a non-significant trend favouring donepezil in activities of daily living (ADL) [week 12 observed case mean treatment differences: MMSE, 1.13 (p = 0.02); Alzheimer's Disease Assessment Scale – cognitive subscale, 0.57 (p = 0.5); the |

[14] Objective was to determine the value of continued donepezil treatment in patients with AD for whom clinical benefit was initially judged as uncertain

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| | | | | | | | | Neuropsychiatric Inventory, –3.16 (p = 0.02); Disability Assessment for Dementia scale, 3.67 (p = 0.1)].<br>Safety<br>The overall frequency of adverse events was low and decreased throughout the study. During the open-label phase, 75 patients (9.2%) experienced serious treatment-emergent adverse events. None were reported during the double-blind phase, and only five during the single-blind phase (two patients in the continued donepezil treatment group and three patients in the placebo/donepezil group. The overall incidence of adverse events, serious adverse events and treatment-related adverse events were similar between groups. The majority of adverse events affected the digestive or nervous systems, and were transient and mild to moderate in severity. Six deaths occurred during the study; none was considered by the investigator to be related to study medication.<br>Authors' conclusion<br>Most patients showed clear clinical benefit during initial donepezil treatment. Among patients for whom clinical benefit was uncertain, improvement in cognition and behaviour were observed for those who continued donepezil treatment compared with the group switched to placebo. Initial decline or stabilisation does not necessarily indicate a lack of efficacy in Alzheimer's disease, and the decision to discontinue treatment should be based on an evaluation of all domains (cognition, behaviour and ADL) and performed at several timepoints. |
| Mohs | Prospective, double-blind, placebo-controlled, survival to | 31 sites in the US | Probable AD | 431 | Donepezil (5 mg/day for 28 days, 10 mg/day there-after) | 54 weeks | ADFACS, CDR, MMSE | Efficacy<br>Donepezil extended the median time to clinically evident functional decline by 5 months versus placebo. The probability of patients treated with donepezil remaining in the study with no clinically |

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| | endpoint study | | | | | | | evident functional loss was 51% at 48 weeks, compared with 35% for placebo. The Kaplan–Meier survival curves for the two treatment groups were different ($p$ = 0.002, log-rank test).<br>Safety<br>Donepezil was well tolerated in this study. The AEs that were reported significantly more frequently with donepezil compared with placebo were headache and those associated with the digestive system (anorexia, diarrhoea, dyspepsia, and nausea). The majority of adverse events were mild to moderate in intensity and unrelated or possibly related to study medication.<br>Authors' conclusion<br>Patients with AD continue to show detectable disease progression over time, but treatment with donepezil for 1 year was associated with a 38% reduction in the risk of functional decline compared with placebo |
| Relkin[15] | Multicentre, open-label | 255 sites in the US | Mild to moderate probable of possible AD | 1,035 | Donepezil (5 mg/day for 28 days, 10 mg/day there-after) | 12 weeks | sMMSE | Efficacy<br>Mean sMMSE score increased by 1.54 points over baseline ($p < 0.0001$) in donepezil-treated patients.<br>Safety<br>Most AEs (64%) were mild, and the occurrence of cholinergic-induced AEs was significantly lower after a dose increase at 4 weeks than that seen with a dose increase after 1 week in previous trials. Risk ratios for gastrointestinal side effects were not significantly increased by the use of aspirin or nonsteroidal anti-inflammatory drugs. Risk ratios for bradycardia were not significantly increased by the use of beta-blockers, nondihydropyridine calcium channel blockers or digoxin. |

[15] To evaluate the safety and efficacy of donepezil in Alzheimer's disease (AD) patients with a greater range of comorbid conditions and concomitant medication use than those previously evaluated in placebo-controlled trials

| First Author[4] | Design | Centres, Countries | Population | N | Dose | Duration | Outcome measures | Results |
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| | | | | | | | | Authors' conclusion<br>Therefore, donepezil improved cognition, as measured by the sMMSE, and was well tolerated despite high concomitant medication use and extensive comorbidity. These results highlight donepezil as a safe and effective treatment for AD patients typically seen by community-based physicians. |
| Rockwood 2007 | Multicentre, open-label | Canada | Mild to moderate AD | 101 | Donepezil 5 mg increasing to 10 mg if possible | 6 months | TOPS checklist (covering cognition, ADL, behaviour and caregiver burden) | Efficacy<br>Clinicians reported that symptoms did not improve in 38 patients, whereas there was some improvement in 43, and improvement in most symptoms in 20.<br>Caregivers reported that symptoms did not improve in 55 patients, whereas 27 and 19 patients showed some and most symptoms improving respectively.<br>Patients with the greatest symptomatic improvement also improved most on the ADAS-cog and the other standardised measures, whereas no improvement (or decline) in each standardised measure was observed in people whose symptoms worsened or did not improve.<br>Safety<br>A total of 83 patients experienced 260 adverse events of any cause, with any intensity. Forty-seven experienced 116 adverse events that were considered as treatment-related, including the 5 patients who discontinued. Nine patients had serious adverse events, of which one (worsening gait) was felt to be treatment-related. Symptoms that occurred in more than 5% of patients chiefly included gastrointestinal and related cholinergic effects.<br>Authors' conclusion<br>A symptom checklist allowed clinically meaningful profiles to be identified, but revealed different estimates of response between |

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| | | | | | | | | clinicians and caregivers. Both agreed that improved executive function was the most common response. A symptom checklist can help translate between standard measures and everyday practice. |
| Rogers 2000 | Multicentre, open-label (extension of double-blind study) | NR | Mild to moderately severe AD | 133 | Donepezil 3 mg per day increased to 5, 7 and 10 mg per day in a step-wise fashion | Up to 240 weeks | ADAS-cog, CDR-SB | Efficacy<br>During the first 6–9 months of the study, mean ADAS-cog and CDR-SB scores showed evidence of clinical improvement from baseline. After this time scores gradually deteriorated. Overall the decline was less than that estimated if this cohort of patients had not been treated.<br>Safety<br>The most common adverse events were related to the nervous and digestive systems, and were generally mild and transient, resolving without the need for dose modifications. There was no evidence of hepatotoxicity.<br>Authors' conclusion<br>These data demonstrate that donepezil is a well-tolerated, realistic symptomatic treatment for AD over a period of up to 4.9 years. |
| Santens | Multicentre, open-label | 25 centres in Belgium | Mild to moderate probable or possible AD | 200 | Donepezil 5 mg for the first 8 weeks after which dose could be increased to 10 mg | 24 weeks | MMSE, ADL, IADL, NPI | Efficacy<br>No significant changes could be found in cognition and behaviour over this 6-month period. Changes in daily functioning were small.<br>Safety<br>Sixteen (8.1%) patients discontinued the study due to an AE, while one patient died during the study after shock and skin ulcer.<br>Of all the included patients, 136 subjects (69%) suffered at least one AE. The most frequent were: nausea, depression, headache, abdominal pain, accidental injury and bronchitis. From all of these AE, 18 patients (9.1%) were considered as experiencing serious adverse events (SAE), many of those being accidental. Of those SAE, 5 were considered related to the |

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| | | | | | | | | disease under study, one to concomitant treatment, and none to the investigated drug.<br>Authors' conclusion<br>These results suggest that the findings of more robust double-blind, placebo-controlled studies can be confirmed in real life situations. |
| Seltzer (2004) | Multicentre, randomised, double-blind, placebo-controlled | 17 sites in the US | Early stage AD | 153 | Donepezil 5 mg/day for the first 6 weeks then 10 mg/day. Patients unable to tolerate 10mg were dis-continued from the study. | 24 weeks | ADAS-cog, MMSE, CMBT tasks, CDR-SB, Patients global assessment scale, Apathy scale | Efficacy<br>Improvements favouring donepezil on the ADAS-cog were found at weeks 12 and 24 and at the end point (LOCF).<br>Improvements favouring donepezil on the MMSE were found at weeks 6, 12, and 24 and at the end point (LOCF).<br>Donepezil-treated patients showed significantly greater mean improvement compared with placebo-treated patients on the following CMBT subscales: facial recognition, first and last name total acquisition and name-face association delayed recall.<br>Safety<br>Donepezil was safe and well tolerated in this population; serious adverse events occurred in similar numbers of donepezil- and placebo-treated patients.<br>Authors' conclusion<br>These data suggest significant treatment benefits of donepezil in early-stage Alzheimer disease, supporting the initiation of therapy early in the disease course to improve daily cognitive functioning. |
| Tanaka | Observational | Japan | Mild to moderate AD | 70 | Donepezil 3 mg/day for first week then 5 mg/day | 12 weeks | NPI, MMSE | Caregivers were interviewed with the NPI for behavioural assessment and 4-point improvement at week 12 was accepted as a treatment response.<br>Twenty-one (30.0%) patients showed a behavioural response, while 42 (60.0%) showed no behavioural change and 7 (10.0%) worsened. |

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| | | | | | | | | Dysphoria, anxiety and apathy significantly improved after treatment among the responder group.<br>Statistical Parametric Mapping analysis of single photon emission computed tomography (SPECT) images at baseline showed that cerebral blood flow in the premotor and parietotemporal cortices was significantly higher in the responder group than in the worse group.<br>Authors' conclusion<br>The present study suggested usefulness of SPECT imaging in the prediction of behavioural response to donepezil among AD patients even with similar psychiatric symptoms and cognitive functions. |
| Tariot | Randomised, multicenter, parallel-group, double-blind, placebo-controlled | 27 nursing homes in the US | Probable or possible AD or AD with cerebro-vascular AD | 208 | Donepezil 5 mg/day for 28 days increasing to 10 mg/day | 24 weeks | NPI-NH, CDR-SB (nursing home version), MMSE, PSMS | Efficacy<br>Mean NPI-NH total scores improved relative to baseline for both groups, with no significant differences between the groups at any assessment. Mean change from baseline CDR-SB total score improved significantly with donepezil compared with placebo at Week 24 ($P$<.05). Differences in mean change from baseline on the MMSE favoured donepezil at Weeks 8, 16, and 20 ($P$<.05). No significant differences were observed between groups on the PSMS.<br>Safety<br>Overall rates of occurrence and severity of AEs were similar between the two groups (97% placebo, 96% donepezil). Gastrointestinal AEs occurred more frequently in donepezil-treated patients. In general, AEs were similar in older and younger donepezil-treated patients, with the majority of patients experiencing only AEs that were transient and mild or moderate in severity.<br>Authors' conclusion<br>Patients treated with donepezil maintained or improved in cognition and overall dementia |

| First Author[4] | Design | Centres, Countries | Population | N | Dose | Duration | Outcome measures | Results |
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| | | | | | | | | severity in contrast to placebo-treated patients who declined during the 6-month treatment period. The safety and tolerability profile was comparable with that reported in outpatient studies of donepezil. These findings also suggest that advanced age, comorbid illnesses, and high concomitant medication usage should not be barriers to donepezil treatment. Given the apparent improvement in behaviour in the placebo group, and the high use of concomitant medications in both groups, the impact of donepezil on behaviour in the nursing home setting is unresolved and merits further investigation. In summary, effects on cognition, overall dementia severity, and safety and tolerability findings are consistent with previous findings in outpatients and support the use of donepezil in patients with AD who reside in nursing homes. |
| Tinklenberg | Observational, open-label, donepezil compared to no treatment | Sites in California | Mild to moderate Ad | 306 | Dose determine by clinician as per normal practice | At least one year | MMSE | Patients treated with donepezil had a decline of 1.3 points on the MMSE compared to 3.3 points in patients not receiving treatment.<br>Authors' conclusion<br>A comparison of a randomised clinical trial of donepezil in AD and this observational data indicates that if appropriate methodological and statistical precautions are undertaken, then results from randomised clinical trials can be predictive with AD patients in clinical practice. This California study supports the modest effectiveness of donepezil in AD patients having clinical characteristics similar to those of the Nordic study. |

| First Author[4] | Design | Centres, Countries | Population | N | Dose | Duration | Outcome measures | Results |
|---|---|---|---|---|---|---|---|---|
| Wimo (subgroup analysis of Winblad 2001) | Double-blind, placebo-controlled trial | 28 sites in 5 North European countries | Mild to moderate AD | 286 | Donepezil 5 mg/day for 28 days increasing to 10 mg/day | 1 year | RUD question-naire (caregiver time) | This difference in caring time between the 2 groups, relative to baseline at Week 52, was 1.1 h (64.2 min) each day, and was significant ( $p$ = 0.03)<br>Authors' conclusion<br>Caregiver time devoted to helping an AD patient typically increases with the severity of the disease. By helping the patient maintain his/her ability to perform activities of daily living for longer, treatment with donepezil is not only beneficial to the patient, but also has positive time-burden implications for the caregiver. |
| Winblad 2001 | Multinational, randomised, double-blind, placebo-controlled, parallel-group study | 28 sites in 5 North European countries | Mild to moderate AD | 286 | Donepezil 5 mg/day for 28 days increasing to 10 mg/day | 52 weeks | Gottfries-Bråne-Steen, ADL, MMSE, PDS | Efficacy<br>The benefit of donepezil over placebo was demonstrated by the Gottfries-Bråne-Steen total score at weeks 24, 36, and 52 ($p$ <0.05) and at the study end point (week 52, LOCF; $p$ <0.054). Advantages of donepezil over placebo were also observed in cognition and activities of daily living (ADL) assessed by the Mini-Mental State Examination at weeks 24, 36, and 52, and the end point ($p$ <0.02) and by the PDS at week 52 and the end point ($p$<0.05).<br>Safety<br>Adverse events were recorded for 81.7% of donepezil- and 75.7% of placebo-treated patients, with 7% of donepezil- and 6.3% of placebo-treated patients discontinuing because of AE.<br>Authors' conclusion<br>As the first 1-year, multinational, double-blinded, placebo-controlled study of a cholinesterase inhibitor in AD, these data support donepezil as a well tolerated and effective long-term treatment for patients with AD, with benefits over placebo on global assessment, cognition, and ADL. |

| First Author[4] | Design | Centres, Countries | Population | N | Dose | Duration | Outcome measures | Results |
|---|---|---|---|---|---|---|---|---|
| Winblad 2006[16] (Winblad 2001 plus 2 year continuation phase) | Multicentre, 52-week, double-blind, placebo-controlled phase plus a 2-year, open-label continuation phase | 28 sites in 5 North European countries | Mild to moderate AD | 286 | Donepezil 5 mg/day for 28 days increasing to 10 mg/day | 3 years | Gottfries-Bråne-Steen, ADL, MMSE, Global deterioration Scale, NPI | Efficacy<br>There was a trend for patients receiving continuous therapy to have less global deterioration (Gottfries-Bråne-Steen scale) than those who had delayed treatment (p = 0.056). Small but statistically significant differences between the groups were observed for the secondary measures of cognitive function (Mini-Mental State Examination; p = 0.004) and cognitive and functional abilities (Global Deterioration Scale; p = 0.0231) in favour of continuous donepezil therapy.<br>Safety<br>Over 90% of the patients in both cohorts experienced one treatment-emergent adverse event; most were considered mild or moderate.<br>Authors' conclusion,<br>In conclusion, patients in whom the start of treatment is delayed may demonstrate slightly reduced benefits as compared with those seen in patients starting donepezil therapy early in the course of Alzheimer's disease. These data support the long-term efficacy and safety of donepezil. |

*ADAS-Cog = Alzheimer's Disease Assessment Scale – cognitive subscale; ADAS-J-cog = Japanese version of the ADAS-cog; AD = Alzheimer's Disease Functional Assessment and Change Scale; ADL = Activities of Daily Living; ADPS = Alzheimer's Disease with concomitant Parkinsonian Symptoms; AE = adverse event; BADLS = Bristol Activities of Daily Living Scale; CDR = Clinical Dementia Rating; CDR-SB = Clinical Dementia Rating – sum of boxes; CIBIC-plus = Clinician's Interview-Based Impression of Change with caregiver input; CMBT = Computerised Memory Battery Test; CMSC = Caregiver rated modified Crichton Scale; CSS = Caregiver Stress Scale; DAD = Disability Assessment for Dementia ; FRS = Functional Rating Scale; GAS = Goal Attainment Scaling: Gottfries-Bråne-Steen = a global assessment for rating dementia symptoms; IADL = Instrumental Activities of Daily Living Scale; IADL+ = modified Instrumental Activities of Daily Living Scale; J-CGIC = Japanese version of the Clinical Global Impression of Change; LOCF = last observation carried forward; LS = Least Squares; MENFIS = Mental Function Impairment Scale; MMSE = Mini-mental State Examination; NHP = Nursing Home Placement; NOSGER = Nurses Observation Scale for Geriatric Patients; NPI = Neuropsychiatric Inventory; NPI-NH = Neuropsychiatric Inventory – Nursing Home version; NR = not reported; PDS = Progressive Deterioration Scale; PMS = Post-Marketing Surveillance; PSMS = Physical Self-maintenance Scale; PSMS+ = modified Physical Self-maintenance Scale; RUD = Resource Utilisation in Dementia; SIB = Severe Impairment Battery; sMMSE = standardised Mini-mental State Examination; TOPS = Top Symptoms*

[16] This study assessed the effects of postponing donepezil treatment for 1 year by comparing patients treated continuously for 3 years with those who received placebo for 1 year followed by open-label donepezil for 2 years.

As can be seen from the studies included in **Table 4**, donepezil has been studied extensively since its PBS listing in 2001. The focus of the studies has been on the different domains, namely cognition, behaviour, function and global. Most studies found that donepezil provides a benefit on all of these domains. This reinforces the fact that the impact of acetylcholinesterase treatment should focus on effects in all of these domains and that only consideration of cognition is erroneous.

Studies were of a number of different designs and included randomised controlled studies, open-label extension studies and studies to consider the use of donepezil in routine clinical practice. These studies confirm the benefit of donepezil for AD patients.

A study published by Howard et al (2012) (DOMINO study), examined continued treatment with donepezil in patients with moderate or severe AD (MMSE 5-13), where the prescriber was considering a change in drug treatment (i.e. stopping donepezil or introducing memantine) on the basis of NICE guidelines. Continued treatment with donepezil was associated with cognitive benefits that exceeded the minimally clinically important difference (1.9 points higher on sMMSE) and with significant functional benefits vs patients discontinuing donepezil over the course of 12 months. The cognitive benefit associated with continued donepezil therapy was equivalent to 32% of the total deterioration (a decrease of 5.8 sMMSE points) over the course of 12 months. Similarly, continued therapy with donepezil showed functional benefits equivalent to 23% of the deterioration (an increase of 12.8% in BADLS points) seen over the course of 12 months in the group discontinuing donepezil.

The effectiveness of donepezil for behavioural symptoms is important due to the concerns with regard to the use of antipsychotics in an elderly AD population. A report for the Minister of State for Care Services in the UK by Professor Sube Banerjee, "The use of antipsychotic medication for people with dementia: Time for action" addressed the issue of antipsychotic use in dementia patients. The author stated that meta-analysed evidence from 15 randomised placebo-controlled trials of atypical antipsychotics provides robust evidence for an increased risk of cardiovascular adverse events (CVAEs), with a pooled relative risk of 2.57 (95% CI 1.41-4.66) and an absolute risk difference of +1.7% (95% CI +0.9% to +2.5%). NNH suggest that 58.8 people with dementia would need to be treated to result in one additional CVAE over the typical 6–12 week follow-up period. Professor Banerjee summarised the risks and benefits using NNT and NNH, the data suggest that treating 1,000 people with BPSD with an atypical antipsychotic drug for around 12 weeks would result in:

- an additional 91–200 patients with behaviour disturbance (or an additional 72 patients of 1,000 with psychosis) showing clinically significant improvement in these symptoms;
- an additional 10 deaths;
- an additional 18 CVAEs, around half of which may be severe;
- no additional falls or fractures; and
- an additional 58–94 patients with gait disturbance.

It is important to recognise that this balance of risks and benefits might alter markedly with longer periods of treatment. While it is unlikely that incremental treatment benefits would accrue over time, there is evidence, at least for mortality, that adverse events are likely to accumulate.

In 2011, the NPS issued a media release entitled: " Antipsychotic medicines and Dementia: a fine balancing act" due to concerns with regard to use in their use in this vulnerable population."

Holmes et al (2004) determined the efficacy of donepezil in the treatment of neuropsychiatric symptoms in patients with mild to moderate AD in a 24 week randomised withdrawal study. Patients were treated openly for 6 weeks with donepezil 5mg, followed by donepezil 10mg for a further 6 weeks. Patients were then randomised (60:40) to either placebo or 10mg donepezil daily. All patients were assessed at 6 weeks and 12 weeks post-randomisation. Following randomisation patients who continued on donepezil 10mg for 12 weeks had improvements in NPI compared with the placebo group (mean change -2.9 vs 3.3 points, p=0.02) and in NPI-Distress scores (median change -2.0 vs 1.0 points, p=0.01). The authors concluded that donepezil has significant efficacy in the treatment of neuropsychiatric symptoms in patients with mild to moderate AD.

These study results were also replicated in patients with mild to moderate AD in a naturalistic setting, in a study by Carrasco et al (2011). The primary outcome measure for this study was the incidence of adverse events. Secondary outcomes included the NPI, MMSE and caregiver burden measured by the Zarit scale. 529 patients were included of which 455 completed the study. NPI scores improved by 34.4% over the course of the 6 month study, with all items showing a statistically significant improvement in MMSE scores and Zarit caregiver burden scores also improved by 1.27 points and 5.9 points respectively.

The focus of some studies was on the impact of donepezil treatment on carers. Donepezil was shown to increase care-giver time and reduce caregiver distress. A study by Wimo et

al, 2004 assessed the impact of donepezil treatment compared with placebo on caregiver time spent assisting community-based patients with AD. This 1-year, randomised, prospective, double-blind, placebo-controlled trial used the Resource Utilisation in Dementia (RUD) questionnaire to record caregiver time at study baseline and at weeks 12, 24, 36 and 52. The active care-giver population was composed of 96 caregivers of donepezil-treated patients and 94 caregivers of patients receiving placebo. Caregiver time devoted to aiding patients with AD typically increases with increasing severity of the disease. By helping the patient maintain his/her ability to perform ADLs for longer, donepezil may be beneficial to both the patient and their caregiver. As expected, after 52 weeks, caregivers of placebo-treated patients were providing almost 2 hours each day (106.8 mins) more care than they had done at study baseline. Caregivers of donepezil-treated patients were also spending more time than they had done at study baseline but their time burden had only increased by 42.6 min more each day. This difference in caregiving time between the two groups relative to baseline was 1.1hr (64.2 mins) and was significant (p=0.03).

Another focus was on nursing home placement where donepezil was shown to increase time to nursing home placement. Geldmacher et al (2003) published a study assessing the relationship between donepezil treatment and time to nursing home placement (NHP) for patients with AD. Immediate precipitants of NHP include behavioural disturbances such as agitation, aggression, night-time wakefulness and depression. Caregiver burden has also been found to predict NHP. Patients from three previous randomised, double-blind, placebo-controlled clinical trials of donepezil and two subsequent open-label studies (total N= 1,115); 671 patients provided complete data for analysis. The authors found that use of donepezil 5mg/d or more was associated with significant delays in NHP. A cumulative dose-response relationship was observed between longer-term sustained donepezil use and delay of NHP. Treatment with donepezil for at least 9-12 months (at least 5mg/d) resulted in a time gained before NHP of 21.4 months for first dementia-related NHP and 17.5 months for permanent NHP.

Studies also show that early intervention is important, with benefits of donepezil when it is used early being superior to treatment at a later stage. A study by Winblad et al (2006) examined the effect of delaying treatment with donepezil by comparing those treated for three years with donepezil with those receiving placebo for the first year followed by open-label donepezil for 2 years. There was a trend for patients receiving continued therapy to have less global deterioration (Gottfires-Brane-Steen Scale) than those who had delayed treatment (p=0.056). Small but statistically significant differences between the groups were

observed on the MMSE scale for cognition and in functional abilities (Global Deterioration Scale; p=0.0231) in favour of continuous donepezil therapy.

Finally a study by Mohs et al (2001) demonstrated that AD patients treated with donepezil for 1 year had a 38% reduction in the risk of functional decline compared with placebo. These studies highlight the fact that donepezil may benefit AD patients and their carers not only by improvements in cognitive function but also through effects on other domains.

It is acknowledged that in most cases the effects were modest compared to placebo, however, for individual patients and carers these modest gains are clinically meaningful.

Additionally, the results highlight the fact that delay in deterioration is the most clinically appropriate outcome. This is supported by Johannsen (2006) as follows: "Initial decline or stabilisation does not necessarily indicate a lack of efficacy in Alzheimer's disease, and the decision to discontinue treatment should be based on an evaluation of all domains (cognition, behaviour and ADL) and performed at several timepoints."

Clinical studies which considered all the acetylcholinesterase inhibitors are included in **Table 5**. Additionally, extensive reviews and meta-analyses of donepezil (**Table 6**) and acetylcholinesterase inhibitors (**Table 7**) have been performed. This very large body of evidence confirms the benefits of both donepezil and the other acetylcholinesterase inhibitors for the treatment of AD patients. However as stated by Birks (2009) "debate on whether donepezil is effective continues despite the evidence of efficacy from the clinical studies because the treatment effects are small and are not always apparent in practice." Furthermore, Burns (2008) indicates: "the definition of treatment 'response' in a progressive neurodegenerative disease can encompass a variety of outcomes, including short-term improvement, longer-term stabilisation and a slowed decline in one or more clinically relevant symptoms or symptom domains."

Additionally reviews of the tolerability of donepezil and the other acetycholinesterase are included in **Table 8.**

Some of the reviews included in **Table 6** and **Table 7** also include a discussion on cost-effectiveness in addition to clinical effectiveness. They generally agree that these agents are cost-effective for the treatment of AD.

Formal cost-effectiveness analyses are included in **Table 9**.

## Table 5: Summary of clinical studies: acetylcholinesterase inhibitors

| First Author | Design | Centres, Countries | Population | N | Duration | Outcome measures | Results |
|---|---|---|---|---|---|---|---|
| Lopez | Cross-sectional and longitudinal | US | Probable AD | 135 matched pairs of patients | 1 year | MMSE,[17] BDRS, ADL extra-pyramidal signs, psychosis, major depression, and use of anti-depressants, anti-psychotics, and sedative/ hypnotics | Eighty-one (60%) of the patients on CEIs and 53 (39%) of the patients who never used CEIs were considered slow progressors (P=.001) at 1-year follow-up.<br>Slow progression was associated only with CEI use (relative risk (RR) = 2.45, 95% confidence interval (CI) = 1.45–4.16), and sedative/hypnotics use was associated with a MMSE change of 3 points or more (RR) = 0.35, 95% CI = 0.13–0.93). CEI use had a protective effect on nursing home admission (RR) = 0.095, 95% CI = 0.03–0.30), whereas higher scores on the BDRS for ADLs increased risk of admission at 24- and 36-month follow-up.<br>Authors' conclusion<br>CEI use had a clinically meaningful effect on the natural history of AD. Patients taking CEIs were 2.5 times more likely to progress slowly and had a lower risk of nursing home admission after 2 years, even after controlling for multiple factors that can alter the course of the disease and a slower rate of decline during the first year of follow-up. |
| López-Pousa | Open-label, prospective, observational with a retrospective control group | Spain | Mild and moderate AD | 147<br>Galan-tamine: 32,<br>Donepezil: 40,<br>Riva-stigmine: 30,<br>historical control group on no treatment: 45 | 6 months | MMSE | At 6 months, the difference in the MMSE score with respect to the untreated group was 1.6 points for donepezil (95% CI 0.79–2.37; p < 0.001), 0.99 points for galantamine (95% CI 0.14–1.85; p = 0.01) and 0.90 points for rivastigmine (95% CI 0.05–1.74; p = 0.03). No significant differences were observed in the efficacy among the groups treated with AChEIs (p >0.05).<br>Authors' conclusion<br>Treatment with AChEIs significantly delays the global cognitive impairment associated with AD for at least 6 months. Our study found no significant differences in efficacy between donepezil, galantamine and rivastigmine. Further studies in the context<br>of daily clinical practice will determine the clinical significance of the changes observed. An important variability of the |

[17] Slow progressors had a change of ≤2 on MMSE at 1 year of follow-up

| First Author | Design | Centres, Countries | Population | N | Duration | Outcome measures | Results |
|---|---|---|---|---|---|---|---|
| | | | | | | | response to the treatment was observed in treated patients. |
| Mossello | "Real world" study | Italy | Elderly patients with mild to moderate AD | 407 | | MMSE,[18] ADL, IADL | In 35 patients (8.6 %) treatment was withdrawn because of mostly gastrointestinal adverse events. Compared to the other drugs, donepezil was associated with a lower incidence of withdrawals due to adverse events.<br>Subjects who completed T3 follow-up (age 78 ± 6 years, MMSE scores 18.8 ± 3.9) showed an increase at T2 of 0.7 ± 2.7 (p = 0.001) and a decrease at T3 of -0.6 ± 3.4 (p = 0.008) in the MMSE scores, as compared to To. The ADL and IADL scores did not show significant changes at T2; however, both decreased significantly at T3. The patients R-at-T2 showed a better cognitive and functional outcome at T3 , compared to the nonresponders (NR-at-T2), displaying values of MMSE R-at-T2 0.4 ± 3.1 vs. NR-at-T2 -3.0 ± 2.5, p = 0.001, and ADL values of -0.3 ± 1.2 vs. -0.7 ± 1.3, p = 0.03, respectively. No significant difference was found in the changes of MMSE scores between donepezil and rivastigmine (galantamine was not included in the comparison due to the small number of treated subjects).<br>Authors' conclusion<br>In conclusion, in this sample of elderly subjects with mild to moderate AD, treated with ChEI, a small but significant decline in cognitive and functional status was observed after 9 months. Subjects who showed a good response to treatment after 3 months, had a better cognitive and functional outcome at 9 months. No significant difference in cognitive outcome was found between drugs, while donepezil was better tolerated. |
| Pakrasi | Retrospective study | UK | AD | 160 cons-ecutive patients on AChEIs | 4 years | CGI MMSE[19] | Results<br>A total of 62 (45%) patients achieved an MMSE response. A diagnosis of DLB and PDD was associated with a MMSE response, as were hallucinations, and lower MMSE scores at baseline. 125 (78%) patients achieved a CGI response for which there were no clinical predictors.<br>Authors' conclusion |

[18] Considers as responders if unchanged or improved
[19] Treatment response was defined in two ways: (a) clinical response was achieved when there was no deterioration or an improvement on CGI and (b) a MMSE response when there was an improvement of 2 or more points.

| First Author | Design | Centres, Countries | Population | N | Duration | Outcome measures | Results |
|---|---|---|---|---|---|---|---|
| | | | | | | | Severity of illness, a diagnosis of DLB and PDD, and presence of hallucinations at baseline were predictive of a MMSE response. Non-AD dementia and severe dementia responded equally well to AChEI treatment and results of further randomised, placebo-controlled studies are needed to clarify the role of AChEI in the treatment of these disorders. |
| Raschetti | Cohort study | Italy | Mild to moderate AD | 5,462 | 10.5 months | MMSE | Methods<br>From September 2000 to December 2001, a total of 5,462 patients diagnosed with mild to moderate Alzheimer's disease were enrolled at the time of their first prescription of the study drugs and followed up for an average of 10.5 months. Responders were defined as patients with a MMSE score improvement of 2 or more points from baseline after 9 months of therapy.<br>Results<br>At 9 months, 2,853 patients (52.2%) completed the study. The mean change from baseline in MMSE scores was an improvement of 0.5 points (±3.0). The proportion of responders to the therapy was 15.7% at 9 months. A greater probability of response at 9 months was observed among patients without concomitant diseases at baseline [odds ratio (OR)=2.1, 95% confidence interval (CI) 1.5–2.9] and among those with a response at 3 months (OR=20.6, 95% CI 17.2–24.6). During the study period, 285 patients (5.2%) discontinued the treatment because of an adverse drug reaction.<br>Conclusions:<br>Effectiveness of acetylcholinesterase inhibitors on cognitive symptoms of patients with mild to moderate Alzheimer's disease is modest. At 9 months, improvement was evident only in a subgroup of patients without concomitant diseases and who had demonstrated a response at 3 months. |

*AChEI = acetylcholinesterase inhibitor; ADL = Activities of Daily Living; BDRS = Blessed Dementia Rating Scale; CGI = Global Clinical Assessment; DLB = Dementia with Lewey Bodies; IADL = Instrumental Activities of Daily Living; MMSE = Mini-mental State Examination; NR = nonresponders; PD = Parkinson's Dementia; R = responders; T0 = time zero; T1 = after 1 month; T2 = after 3 months; T3 = after 9 months*

## Table 6: Summary of review and meta-analyses: donepezil

| First Author[20] | Included studies (by first author [year published] or study number) | Outcome measures/domains/ focus | Results |
|---|---|---|---|
| Birks 2009 | AD2000, Doody, Burns (1999)[21], Feldman (2000), Greenberg, Hegerl[22], Holmes, Homma 1998[23], Homma 2000, Johanssen (2004), Krishnan (2003)[24], Schindler (2004)[25], Seltzer (2004), Robert (1999), Robert (2000), Rogers (2000), Study 205[26], Study 306[27], Study 315[28], Tariot (2001), Tune (2003)[29], Winblad (2001), Winblad (2006) | ADAS-cog, SIB, MMSE | Efficacy<br>For cognition there is a statistically significant improvement for both 5 and 10 mg/day of donepezil at 24 weeks compared with placebo on the ADAS-Cog scale and for 10 mg/day donepezil compared with placebo at 24 weeks on the SIB and at 52 weeks on the MMSE (1.84 MMSE points, 95% CI, 0.53 to 3.15, P =0.006).<br>The results show some improvement in global clinical state (assessed by a clinician) in people treated with 5 and 10 mg/day of donepezil compared with placebo at 24 weeks for the number of patients showing improvement.<br>Benefits of treatment were also seen on measures of activities of daily living and behaviour, but not on the quality of life score.<br>Safety<br>Many adverse events were recorded, with more incidents of nausea, vomiting, diarrhoea, muscle cramps, dizziness, fatigue and anorexia (significant risk associated with treatment) in the 10 mg/day group, compared with placebo. There were more incidents of anorexia, diarrhoea, and muscle cramps in the 5 mg/day group compared with placebo, but not of dizziness, fatigue, nausea or vomiting. Very few patients left a trial as a direct result of the intervention.<br>Authors' conclusion<br>People with mild, moderate or severe dementia due to Alzheimer's disease treated for periods of 12, 24 or 52 weeks with donepezil experienced benefits in cognitive function, activities of daily living and behaviour. Study clinicians rated global clinical state more positively in treated patients, and measured less decline in measures of global disease severity. There is some evidence that use of donepezil is neither more nor less expensive compared with placebo when |

[20] Also included publication date if author had multiple publications
[21] Not presented in this submission as study was included in the Aricept PBAC submissions
[22] Not presented in this submission as used different outcome measure
[23] Not presented in this submission as study was included in the Aricept PBAC submission
[24] Not presented in this submission as study used different outcome measure
[25] Not presented in this submission as study employed a dose which is higher than recommended
[26] Not available for review
[27] Not available for review
[28] Not presented in this submission as study included AD patients for which donepezil is not PBS listed (severe AD)
[29] Not presented in this submission as study used different outcome measure

| First Author[20] | Included studies (by first author [year published] or study number) | Outcome measures/domains/ focus | Results |
|---|---|---|---|
| | | | assessing total health care resource costs. Benefits on the 10 mg/day dose were marginally larger than on the 5 mg/day dose. Taking into consideration the better tolerability of the 5 mg/day donepezil compared with the 10 mg/day dose, together with the lower cost, the lower dose may be the better option. The debate on whether donepezil is effective continues despite the evidence of efficacy from the clinical studies because the treatment effects are small and are not always apparent in practice. |
| Burns 2008 | Burns (1999), Gauthier (2002), Rogers (1998a), Seltzer (2004), Winblad (2001), | To explore the impact of employing different criteria to define a treatment 'responder' using analyses of patient-level data from randomised, placebo-controlled studies of donepezil in AD. | Methods:<br>Trials were included in the analysis if they met several criteria, including the following: randomised, placebo-controlled trial of donepezil 10 mg/day in mild-to-moderate AD; cognition measured by the ADAS-cog or MMSE; and a 24-week endpoint and outcomes that included global assessments.<br>Definitions of response were: improvements in cognition plus one other domain; improvement in cognition only; improvement or improvement/no change in global response; and improvement/stabilisation/less than expected decline by ≤2 or ≤4 or ≤6 points on the ADAS-cog.<br>Results<br>Five studies identified from the literature search met the specified criteria for inclusion. The response to donepezil measured by ADAS-cog varied from 26% to 63% and that of placebo from 14% to 47%, depending on the definition of improvement used. For definitions that included a less than expected decline on ADAS-cog, the more modest the effect defined, the less the drug versus placebo difference and the higher the percentage of patients meeting this definition.<br>Authors' conclusion<br>The definition of treatment 'response' in a progressive neurodegenerative disease can encompass a variety of outcomes, including short-term improvement, longer-term stabilisation and a slowed decline in one or more clinically relevant symptoms or symptom domains. The ability to identify groups of people who respond to donepezil underscores the clinical utility of the medication and may contribute to more focused assessments of the cost effectiveness of cholinesterase inhibitors. |
| Gauthier 2010 | Rogers (1996),[30] Burns (1999)[31], Feldman (2001), Mohs (2001), Tariot (2001), Winblad (2001) | ADL<br>Individual items | At Week 24, scores for the placebo group showed a numerically greater increase (worsening) compared with the donepezil group for 11 of the 12 standardised scale items. Statistically significant treatment differences were observed for five |

[30] Not presented in this submission as study was included in the PBAC submissions for Aricept
[31] Not presented in this submission as study was included in the PBAC submissions for Aricept

| First Author[20] | Included studies (by first author [year published] or study number) | Outcome measures/domains/ focus | Results |
|---|---|---|---|
| | | from nine ADL scales used in the trials were mapped to a stand-ardised functional scale comprising 12 domains (six basic, six instrum-ental); scores were transformed to a 0–100 scale. | items, all in favour of donepezil – two instrumental ADL items (meal preparation and leisure and housework) and three basic ADL items (hygiene, dressing and eating). Continence was the only item on which the donepezil group had a greater decline (<1 point).<br>Patients with moderate AD at baseline (MMSE 10–17) demonstrated the greatest treatment effect.<br>Authors' conclusion<br>A beneficial effect of donepezil treatment on function was demonstrated using this standardized functional scale. |
| Jelic | AD2000, Black (2007),[32] Burns (1999),[33] Feldman (2001), Homma (2000), Howard (2007),[34] Mohs (2001), Rogers (1996),[35] Rogers (1998a),[36] Rogers (1998b), [37]Selzer (2004), Tariot (2001), Winblad (2001), Winblad (2006) | Review of pharmacological characteristics and role in the management of AD | Abstract:<br>Donepezil is a potent, selective, noncompetitive, and rapidly reversible inhibitor of acetylcholinesterase (AChEI) licensed for the treatment of Alzheimer disease (AD); and is the first and only AChEI licensed for the treatment of severe AD.<br>Its efficacy as monotherapy, or in combination with the NMDA-agonist, memantine, has been documented in several randomised double-blind, placebo-controlled, short-term clinical trials, as well as long-term extension trials and observational studies.<br>Donepezil is a well tolerated drug that is generally safe as demonstrated even in patients with multiple co-morbidities receiving polypharmacy.<br>It has been shown that donepezil improves cognition and global function in patients with mild-to-moderate AD; and long-term efficacy is maintained for up to 50 weeks.<br>There is a dose-response relationship, with higher doses more likely to produce symptomatic benefit. Furthermore, donepezil-treated patients may improve cognitively and show global clinical improvement in all disease stages, including severe AD.<br>Less consistent results in all disease stages were obtained on measures of function and behaviour, and observations of mood. No effect on transition to AD |

[32] Not presented in this submission as it was in severe AD
[33] Not presented in this submission as it would have been in PBAC submissions for Aricept
[34] Not presented in this submission as study considered only one symptom
[35] Not presented in this submission as study was included in the PBAC submissions for Aricept
[36] Not presented in this submission as study was included in the PBAC submissions for Aricept
[37] Not presented in this submission as study was included in the PBAC submissions for Aricept

| First Author[20] | Included studies (by first author [year published] or study number) | Outcome measures/domains/ focus | Results |
|---|---|---|---|
| | | | has been found in long-term, randomised clinical trials in mild cognitive impairment (MCI).<br>Cost-effectiveness of the treatment has been questioned by one long-term open-label societal study of 2-years duration. This study reported modest improvement of cognition but no statistically significant benefits during donepezil treatment as compared to placebo, in terms of rates of institutionalisation and progression toward greater disability.<br>However, there is a need for further research on clinically meaningful outcomes and treatment benefits favoured by patients and caregivers, which are traditionally not defined as outcomes in clinical trials. Likewise, we need to know how to select responders, what is an optimal AChE inhibition particularly during the long-term treatment, in which patients the dosage should be increased for a sustained benefit, what is the optimal duration of treatment and when is meaningful to stop the treatment. After almost two decades of donepezil use in everyday clinical practice these issues are still unresolved. |
| Knowles | Clinical studies, meta-analyses and reviews: AD2000, Aguglia (2004)[38], Beusterien (2004),[39] Birks (2003), Clegg (2002), Fillit (2000), Froelich (2004), Frölich (2002), Gasper (2005), Geldmacher (2003), Hager (2003), Hashimoto (2005),[40] Holmes (2004), Kemp (2003),[41] Krishnan (2003),[42] Lopez (2005), Mossello (2004), NICE (2005),[43] Nobili (2002),[44] Petersen (2005),[45] Relkin (2003), Rockwood (2002)[46], Rodriguez (2002),[47] Saine (2002),[48] Santens (2003), Tanaka (2004), Warner (2004), Wolfson (2002)[49], Wimo (2003), | Clinical impact of donepezil from assessment of randomised controlled, open-label naturalistic and observational studies | <u>Evidence review</u><br>There is strong evidence that donepezil has efficacy against the three major domains of Alzheimer's disease symptoms, namely functional ability, behaviour, and cognition. The strongest evidence is for improvement or less deterioration in global outcomes and cognition in the short to medium term. There is limited evidence that improved global outcomes are maintained in the long term and clear evidence to support long-term maintenance of cognitive benefits. Also, donepezil appears to maintain function in the long term and there is some level 1 and 2 evidence of improved or limited deterioration in behaviour or mood in the short to medium term. Despite donepezil's effect on major symptoms of Alzheimer's disease, its impact on patient's quality of life has not been |

[38] Not presented in this submission as it compared donepezil, rivastigmine and galantamine
[39] Not presented in this submission as it was a rivastigmine study
[40] Not presented in this submission as outcome measure was hippocampal atrophy
[41] Not presented in this submission as the outcome measure was effect on muscarinic receptors
[42] Not presented in this submission as the outcome measures were neuronal markers and hippocampal volumes
[43] Not presented in this submission as it has been superseded by further NICE reviews
[44] Not presented in this submission as it considered rCBF in Alzheimer's disease patients treated with donepezil
[45] Not presented in this submission as study included patients with mild cognitive impairment
[46] Not presented in this submission as it did not study efficacy of donepezil
[47] Not presented in this submission as study considered EEG changes
[48] Not presented in this submission as study only considered 24 patients

| First Author[20] | Included studies (by first author [year published] or study number) | Outcome measures/domains/ focus | Results |
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| | | | consistently demonstrated, perhaps reflecting the difficulty of assessing this aspect in this patient population. Donepezil may also lessen caregiver burden. Donepezil has some effect on markers of brain function, but more data are needed to confirm a neuroprotective effect. There is limited and conflicting evidence that long-term donepezil treatment delays institutionalisation. There is some evidence that donepezil may be cost effective, especially when unpaid caregiver costs are considered. Donepezil is generally safe and well tolerated.<br>Clinical value<br>AChE inhibitors are the only agents recommended for the treatment of cognitive decline in patients with mild to moderate Alzheimer's disease. Donepezil is more effective than placebo and is well tolerated in improving the major symptoms of this disease. Improvements are usually modest, although stabilisation of cognitive and functional symptoms with donepezil can also be considered an important clinical outcome. Donepezil may lessen caregiver burden. Donepezil may also be cost effective, especially when unpaid caregiver costs are considered. More data are required for randomised controlled trials with long-term follow-up to confirm its cost effectiveness and impact on quality of life, disease progression, and time to institutionalisation. |
| Passmore | Whitehead meta-analysis (AD) and compared to Black (2003)[50] and Wilkinson (2003)[51] [VaD] | Cognition and Global Function | In both AD and VaD, donepezil provided significant benefits compared with placebo on measures of cognition and global function. Placebo-treated AD patients showed a decline in cognition and global function, whereas placebo-treated VaD patients remained stable, suggesting treatment effects of donepezil in VaD were driven by improvement rather than stabilisation or reduced decline. More VaD patients than AD patients received concomitant medications.<br>Cardiovascular adverse events were more common in VaD than AD patients but were not increased by donepezil.<br>Authors' conclusion<br>In conclusion, although there are differences between AD and VaD patients in comorbid conditions and concomitant medications, donepezil is effective and well tolerated in both types of dementia. |
| Waldemar (2001) | Did not consider specific studies, discussed all evidence identified through systematic review | Donepezil in the treatment of AD | Abstract<br>Donepezil is the most widely used acetylcholinesterase inhibitor licensed for symptomatic treatment of mild-to-moderate Alzheimer's disease. Clinical |

[49] Not presented in this submission as it compared donepezil to rivastigmine
[50] Not presented in this submission as patients had VaD
[51] Not presented in this submission as patients had VaD

| First Author[20] | Included studies (by first author [year published] or study number) | Outcome measures/domains/ focus | Results |
|---|---|---|---|
| | | | placebo-controlled trials and open-label extension studies have consistently shown that donepezil is well-tolerated and gives rise to statistically significant improvements in cognition, global function and activities of daily living for at least 12 months and to less deterioration of function possibly for more than 4 years. Furthermore, donepezil may reduce neuropsychiatric symptoms and caregiver burden. Health economic studies suggest that treatment with donepezil may reduce resource utilisation. Evidence-based international management guidelines recommend that treatment with a cholinesterase inhibitor should be considered in all patients with mild-to-moderate AD and based on a proper diagnostic evaluation. Treatment cannot replace continuous advice to patients and caregivers. |
| Waldemar (2011) | Feldman (2001), Winblad (2001) | NPI particularly apathy | Of all NPI items, apathy had the highest proportion of subjects scoring ≥3 at baseline. Donepezil was superior to placebo on both apathy milestone analyses (time-to-event log-rank test and shift table CMH test, p = 0.01). Aberrant motor behaviour demonstrated similar benefit.<br>Authors' conclusion<br>Donepezil treatment appears to have resulted in a significant reduction over 6 months of the emergence of apathy in patients with AD. |
| Whitehead | Individual patient data from: Burns (1999), Homma (2000), Italian Phase IIIb study (X-306), Japanese phase II study (J081-134), Krishnan (2003), Geldmacher (2000), Rogers (1996), Rogers (1998a), Rogers (1998b), Tune et al (2003)[52] | ADAS-cog CIBIC-plus | Efficacy<br>Cognitive performance was significantly better in patients receiving donepezil than in patients receiving placebo.<br>The odds ratios (OR) of improvement on the CIBIC-plus at 12 weeks were: 5 mg/day – placebo 1.8 (1.5 to 2.1; p<0.001), 10 mg/day–placebo 1.9 (1.5 to 2.4; p<0.001). The corresponding values at 24 weeks were 1.9 (1.5 to 2.4; p¼0.001) and 2.1 (1.6 to 2.8; p<0.001).<br>Safety<br>A total of 2376 patients with AD received at least one dose of study medication in the ten clinical trials that were included in the meta-analysis. Overall, 83.8%, 76.1% and 83.9% of patients treated with 5 or 10 mg/day donepezil or placebo, respectively, completed the trials. The most common reason for discontinuation was AEs. Discontinuations due to AEs were higher in the donepezil 10 mg/day group (13.9%) than in the donepezil 5 mg/day (6.3%) or placebo (5.8%) groups.<br>AEs occurred in 65% and 83% of patients treated with 5 or 10 mg/day donepezil, respectively, compared with 62% of placebo-treated patients. The majority of |

[52]These studies are not presented in this submission as they were either presented in the PBAC resubmissions for Aricept or the publications focused on different outcome measures

| First Author[20] | Included studies (by first author [year published] or study number) | Outcome measures/domains/ focus | Results |
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| | | | AEs that occurred with a significantly higher incidence in the donepezil-treated groups relative to placebo and considered possibly related to study drug were mainly cholinergic in nature. Indeed, of the AEs that occurred in ≥5% of patients, only diarrhoea, nausea, vomiting and dizziness were considered related to study medication in a majority of the patients in each treatment group.<br>Most AEs were mild, only occasionally moderate in intensity and generally transient in nature.<br>Authors' conclusion<br>Donepezil (5 and 10 mg/day) provides meaningful benefits in alleviating deficits in cognitive and clinician-rated global function in AD patients relative to placebo. Increased improvements in cognition were indicated for the higher dose. |
| Wilkinson | Feldman (2001), Rogers (1998)[53], Winblad (2001) | MMSE | Efficacy<br>At week 24, lower percentages of donepezil-treated patients than placebo patients met the criteria for clinical worsening. The odds of declining were significantly reduced for donepezil-treated versus placebo patients ($p < 0.0001$; all definitions). Among patients meeting criteria for clinical worsening, mean declines in MMSE scores were greater for placebo than donepezil-treated patients.<br>Author's conclusion<br>In this population, donepezil treatment was associated with reduced odds of clinical worsening of AD symptoms. Moreover, patients worsening on donepezil were likely to experience less cognitive decline than expected if left untreated. This suggests that AD patients showing clinical worsening on donepezil may still derive benefits compared with placebo/untreated patients. |

*ADAS-Cog = Alzheimer's Disease Assessment Scale – cognitive subscale; ADL = Activities of Daily Living; AE = adverse event; CIBIC-plus = Clinician's Interview-Based Impression of Change with caregiver input; MMSE = Mini-mental State Examination; NR = not reported; VaD = Vascular Dementia*

[53] Not presented in this submission as study was included in PBAC submissions for Aricept

## Table 7: Summary of reviews and meta-analyses of AD treatments: donepezil

| First Author[54] | Included studies (by first author [year published] or study number) | Outcome measures/domains/ focus | Results |
|---|---|---|---|
| Birks 2012 | Donepezil studies: DON-302 (Feldman, 2001), DON-304 (Burns, 1999), DON-311 (Tariot 2011), DON-402 (Seltzer, 2001), DON-Feldman (Feldman, 2003), DON-Nordic (Winblad, 2001), DON vs RIV | ADAS-cog | Efficacy<br>The results of 10 randomised, double-blind, placebo controlled trials demonstrate that treatment for 6 months, with donepezil, galantamine or rivastigmine at the recommended dose for people with mild, moderate or severe dementia due to Alzheimer's disease produced improvements in cognitive function, on average -2.7 points (95%CI -3.0 to -2.3, p<0.00001), in the midrange of the 70 point ADAS-Cog Scale.<br>Study clinicians rated global clinical state more positively in treated patients. Benefits of treatment were also seen on measures of activities of daily living and behaviour.<br>None of these treatment effects are large.<br>Safety<br>More patients leave ChEI treatment groups, 29%, on account of adverse events than leave the placebo groups (18%).<br>There is evidence of more adverse events in total in the patients treated with a ChEI than with placebo. Although many types of adverse event were reported, nausea, vomiting, diarrhoea, were significantly more frequent in the ChEI groups than in placebo.<br>Author's conclusion<br>The three cholinesterase inhibitors are efficacious for mild to moderate Alzheimer's disease. Despite the slight variations in the mode of action of the three cholinesterase inhibitors there is no evidence of any differences between them with respect to efficacy. The evidence from one large trial shows fewer adverse events associated with donepezil compared with rivastigmine. |
| Bullock | Donepezil studies: Mohs (2001), Winblad (2001), Doody (2001), Klatte (2003)[55], Rogers (2000) | Function | The data appear to suggest that patients, caregivers and physicians will still see some decline on ChE-Is after a period of stabilisation, but this may be slower and later than expected if the patients were left untreated. This applies across all domains of AD – not simply cognition – and function can be relatively preserved, even if cognitive scores are falling.<br>Authors' conclusion |

[54] Also included publication date if author had multiple publications
[55] Not presented in this submission as it is a retrospective review of 130 patients on donepezil and vitamin E

| First Author[54] | Included studies (by first author [year published] or study number) | Outcome measures/domains/ focus | Results |
|---|---|---|---|
| | | | Despite the limitations of current data, the information reviewed in this study may help practising doctors assess the long-term value of ChEIs in this consistently progressive disease. |
| Clegg | Systematic review and studies: Birks (2000), Burns (1999),[56] Greenberg (2000), Livingston (2000), Rogers (1996),[57] Rogers (1998a),[58] Rogers (1998b),[59] Wolfson (2000), | Clinical and cost-effectiveness of AChEIs for AD | Clinical effectiveness<br>Results of clinical reviews suggest that donepezil is beneficial when assessed using global and cognitive outcome measures.<br>Summary of benefits<br>It is difficult to quantify benefits from the results available in the literature. Statistically significant improvements in tests such as ADAS-cog may not be reflected in changes in daily life.<br>Costs/cost-effectiveness<br>The five studies of donepezil produced a variety of cost-effectiveness estimates. While the base case showed increased effectiveness and were cost saving in two studies, they were more costly in three. When sensitivity analyses are taken into consideration, estimates fluctuated more widely and there were, in some cases, conflicting results for sub-group analyses, thus casting doubt on the robustness of the estimates.<br>Authors' conclusion<br>On the basis of the current evidence, the implications of the use of donepezil, rivastigmine or galantamine to treat patients with Alzheimer's disease are unclear. The main issue is whether the modest benefits seen in the outcome measures used in the trials would translate into benefits significant to patients. |
| Campbell | Feldman (2001), Tariot (2001), Winblad (2001), Gauthier (2002), Nunez (2003), AD2000, Holmes (2004), Winblad (2006), Howard (2007)[60] | NPI | Among patients with mild to severe AD and in comparison to placebo, ChEIs as a class had beneficial effects on reducing BPSD with a standard mean difference (SMD) of −0.10 (95% confidence interval [CI]; −0.18, −0.01) and a weighted mean difference (WMD) of −1.38 neuropsychiatry inventory point (95% CI; −2.30, −0.46).<br>In studies with mild AD patients, the WMD was −1.92 (95% CI; −3.18, −0.66); and in studies with severe AD patients, the WMD was −0.06 (95% CI; −2.12, |

[56] Not presented in this submission as study was included in PBAC submissions for Aricept
[57] Not presented in this submission as study was included in PBAC submissions for Aricept
[58] Not presented in this submission as study was included in PBAC submissions for Aricept
[59] Not presented in this submission as study was included in PBAC submissions for Aricept
[60] Not presented in this submission as study only considers agitation

| First Author[54] | Included studies (by first author [year published] or study number) | Outcome measures/domains/ focus | Results |
|---|---|---|---|
| | | | +0.57).<br>Authors' conclusion<br>Cholinesterase inhibitors lead to a statistically significant reduction in BPSD among patients with AD, yet the clinical relevance of this effect remains unclear. |
| Grimmer | Donepezil studies: AD2000, Feldman (2001), Holmes (2004), Seltzer (2004), Tariot (2001), Winblad (2001), | NPI | Feldman and Holmes were the only donepezil studies that showed a statistically significant difference vs placebo.<br>Authors' conclusion<br>ChEIs have moderate effects when used as a blanket treatment for the cluster of behavioural disturbances in AD. |
| Hansen 2007 | Donepezil studies: AD2000, Burns (1999)[61], Feldman (2001), Homma (2000), Mohs (2001), Winblad (2001) | Functional outcomes | Efficacy<br>Overall, the standardised effect size for functional outcome measures was small ($d$ = 0.1–0.4) among included studies. However, effect sizes consistently favoured drug treatment over placebo. For all drugs, pooled standardised effect sizes were consistent in both short (<24 weeks; $d$ = 0.25; 95% CI 0.13, 0.37) and long trials (≥24 weeks; $d$ = 0.29; 95% CI 0.22, 0.36). The pooled effect size was not significantly affected by parameters such as disease severity, age, gender and drug dose.<br>Safety<br>Gastrointestinal-related adverse events such as nausea, vomiting and diarrhoea were most commonly reported in patients randomised to a cholinesterase inhibitor<br>Authors' conclusion<br>Standardised estimates of effect size across diverse functional outcome measures for drug treatment in patients with Alzheimer's disease were small and the data reflect only a modest trend favouring active treatment over placebo. However, given the current lack of other effective treatments for Alzheimer's disease, this trend supports the clinical benefits of these treatments with regard to this important health outcome. |
| Hansen 2008 | Donepezil studies: AD2000, Bullock (2005),[62] Burns (1999)[63], Feldman (2001), Homma (2000), | All domains | Meta-analyses of placebo-controlled data support the drugs modest overall benefits for stabilising or slowing decline in cognition, function, behaviour, |

[61]Not presented in this submission as this study was included in the Aricept PBAC submissions
[62] Not presented in this submission as study compares donepezil to rivastigmine
[63] Not presented in this submission as study was ncluded in the PBAC submissions for Aricept

| First Author[54] | Included studies (by first author [year published] or study number) | Outcome measures/domains/ focus | Results |
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| | Jones (2004)[64], Mohs (2001), Rogers (1996),[65] Rogers (1998a),[66] Rogers (1998b),[67] Tariot (2001), Wilcock (2003)[68], Wilkinson (2002)[69], Winblad (2001), Winblad (2006) | | and clinical global change.<br>Three open-label trials and one double-blind randomised trial directly compared donepezil with galantamine and rivastigmine. Results are conflicting; two studies suggest no differences in efficacy between compared drugs, while one study found donepezil to be more efficacious than galantamine, and one study found rivastigmine to be more efficacious than donepezil.<br>Adjusted indirect comparison of placebo-controlled data did not find statistically significant differences among drugs with regard to cognition, but found the relative risk of global response to be better with donepezil and rivastigmine compared with galantamine (relative risk = 1.63 and 1.42, respectively). Indirect comparisons also favoured donepezil over galantamine with regard to behaviour. Across trials, the incidence of adverse events was generally lowest for donepezil and highest for rivastigmine. |
| Kaduskiewicz | Donepezil studies: AD2000, Burns (1999),[70] Feldman (2001), Greenberg (2000), Holmes (2004), Homma (2000), Mohs (2001), Rogers (1996),[71] Rogers (1998a),[72] Rogers (1998b),[73] Tariot (2001), Winblad (2001) | Systematic review of randomised controlled trials | Results<br>22 trials met the inclusion criteria. Follow-up ranged from six weeks to three years. 12 of 14 studies measuring the cognitive outcome by means of the ADAS-cog showed differences ranging from 1.5 points to 3.9 points in favour of the respective cholinesterase inhibitors.<br>Benefits were also reported from all 12 trials that used the CIBIC-plus.<br>Methodological assessment of all studies found considerable flaws—for example, multiple testing without correction for multiplicity or exclusion of patients after randomisation.<br>Authors' conclusion<br>Because of flawed methods and small clinical benefits, the scientific basis for recommendations of cholinesterase inhibitors for the treatment of Alzheimer's |

[64] Not presented in this submission as study compared donepezil to galantamine
[65] Not presented in this submission as study was included in the PBAC submissions for Aricept
[66] Not presented in this submission as study was included in the PBAC submissions for Aricept
[67] Not presented in this submission as study was included in the PBAC submissions for Aricept
[68] Not presented in this submission as study compared donepezil to galantamine
[69] Not presented in this submission as study compared donepezil to rivastigmine
[70] Not presented in this submission as study was included in the PBAC submissions for Aricept
[71] Not presented in this submission as study was included in the PBAC submissions for Aricept
[72] Not presented in this submission as study was included in the PBAC submissions for Aricept
[73] Not presented in this submission as study was included in the PBAC submissions for Aricept

| First Author[54] | Included studies (by first author [year published] or study number) | Outcome measures/domains/ focus | Results |
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| | | | disease is questionable. |
| Lanctôt | Donepezil studies: Burns (1999),[74] Feldman (2001), Homma (2000), Mohs (2001), Rogers (1996),[75] Rogers (1998a),[76] Rogers (1998b),[77] Winblad (2001) | Meta-analysis of efficacy and safety of AChEIs. | Objective<br>To quantitatively summarise data on the efficacy and safety of ChEIs in Alzheimer's disease in a format useful to clinicians.<br>Methods:<br>Meta-analysis of randomised, double-blind, placebo-controlled, parallel-group trials of currently marketed ChEIs (donepezil, rivastigmine and galantamine), used in therapeutic doses for at least 12 weeks, from which a cognitive outcome was reported.<br>Results:<br>In the 16 identified trials that met the inclusion criteria, 5159 patients were treated with a ChEI and 2795 received a placebo. The pooled mean proportion of global responders to ChEI treatment in excess of that for placebo treatment was 9% (95% confidence interval [95% CI] 6%–12%). The rates of adverse events, dropout for any reason and dropout because of adverse events were also higher among the patients receiving ChEI treatment than among those receiving placebo, the excess proportions being 8% (95% CI 5%–11%), 8% (95% CI 5%–11%) and 7% (95% CI 3%–10%), respectively. The numbers needed to treat for 1 additional patient to benefit were 7 (95% CI 6–9) for stabilisation or better, 12 (95% CI 9–16) for minimal improvement or better and 42 (95% CI 26–114) for marked improvement; the number needed to treat for 1 additional patient to experience an adverse event was 12 (95% CI 10–18).<br>Interpretation:<br>Treatment with ChEIs results in a modest but significant therapeutic effect and modestly but significantly higher rates of adverse events and discontinuation of treatment. The numbers needed to treat to benefit 1 additional patient are small. |
| Lingler | Donepezil studies: AD2000, Feldman (2003), Jones (2004)[78], Kaufer (1998),[79] Matthews (2000), Robert (1999), Wilkinson (2002)[80], Wimo (2003) | Burden, time use, psychological wellbeing, healthcare | Seventeen studies involving 4,744 subjects were identified. Four trials (N =1,594) met criteria for inclusion in the burden analysis, and six trials (N =2,286) met criteria for inclusion in the time-use analysis. Donepezil was the |

[74] Not presented in this submission as study was included in the PBAC submissions for Aricept
[75] Not presented in this submission as study was included in the PBAC submissions for Aricept
[76] Not presented in this submission as study was included in the PBAC submissions for Aricept
[77] Not presented in this submission as study was included in the PBAC submissions for Aricept
[78] Not presented in this submission as study compared donepezil to galantamine

| First Author[54] | Included studies (by first author [year published] or study number) | Outcome measures/domains/ focus | Results |
|---|---|---|---|
| | | costs, and ease of use of or satisfaction with intervention | most frequently studied intervention in the set of studies.<br>Methodological quality varied across trials. The weighted average effect sizes were Cohen's *d* = 0.18 (95% confidence interval (CI) = 0.04–0.32) and *d* = 0.15 (95% CI =0.07–0.24) for the outcomes of caregiver burden and time use, respectively.<br>Authors' conclusion<br>Cholinesterase inhibitors have a small beneficial effect on burden and active time use among caregivers of persons with AD. |
| Livingston | Rogers 1998[81] | NNT based on ADAS-cog, CIBIC-plus, MMSE and PDS | Small numbers of patients (in most cases between 3 and 7) need to be treated with appropriate dosages of ChEIs to ameliorate the clinical symptoms, or postpone deterioration in one of them.<br>Authors' conclusion<br>These small NNTs suggest that, despite their expense, the cholinesterase inhibitors have a valuable place in the current clinical management of AD. |
| Miller | Donepezil studies: Cummings (2006), Feldman (2001), Holmes (2003), Tariot (2001), Winblad (2001) | Review of double-blind, placebo-controlled trials that examined the efficacy of cognitive enhancers in the psychopathology of Alzheimer's disease | Author's Conclusion<br>The majority of patients with Alzheimer's disease will experience behavioural disturbances during the course of their disease. Atypical antipsychotics are used routinely in these situations to treat the psychotic features and agitation. However, atypicals now carry a "black box" warning issued by the Food and Drug Administration on the basis of evidence that their use in geriatric patients with dementia-related psychosis may put patients at increased risk of mortality as a result of cardiovascular or infectious events. An alternative to the atypicals may be the acetylcholinesterase inhibitors and memantine, which have been shown to stabilse cognitive as well as behavioural issues in patients, utilising the "gold standard" for behaviour, the Neuropsychiatric Inventory. Efficacy varies among agents, with the greatest positive effects seen with donepezil, which also has the greatest number of studies. Drug benefits were harder to demonstrate for mild-to- moderate BPSD compared with moderate-to-severe symptoms. |
| Ritchie | Donepezil studies: Burns (1999),[82] Feldman (200), Homma (2000), Mohs (2001), Rogers (1996),[83] | Meta-analysis of efficacy and safety of | All three drugs showed beneficial effects on cognitive tests, as compared with placebo. For donepezil and rivastigmine, larger doses were associated |

[79] Not presented in this submission as it only considered 30 patients
[80] Not presented in this submission as study compared donepezil to rivastigmine
[81] Not presented in this submission as it would have been included in the PBAC submissions for donepezil
[82] Not presented in this submission as study was included in PBAC submissions for Aricept

| First Author[54] | Included studies (by first author [year published] or study number) | Outcome measures/domains/ focus | Results |
|---|---|---|---|
| | Rogers (1998a),[84] Rogers (1998b),[85] Tariot (2001), Winblad (2001 | AChEIs | with larger effect. This was not the case with galantamine. The odds of clinical global improvement demonstrated superiority over placebo for each drug, with no dose effects noted. Dropout rates were greater with galantamine and rivastigmine. There was little difference in dropout rate for each drug at each dose-level, except with high-dose donepezil. This was accounted for by the high dropout rate in two 52-week studies using larger doses.<br>Authors' conclusion<br>In summary, all three drugs had similar cognitive efficacy, with donepezil and rivastigmine showing a dose effect across the dosing levels studied. However, both galantamine and rivastigmine were associated with a greater risk of trial dropout than placebo, especially at higher dosing levels |
| Rodda | AD2000, Black (2007),[86] Feldman (2001), Holmes (2004), Howard (2007),[87] Seltzer (2004), Tariot (2001), Winblad (2001), Winblad (2006) | NPI, Behavioural and psychological symptoms | Authors' conclusion<br>The evidence base regarding the efficacy of cholinesterase inhibitors in BPSD is limited, in part due to methodological considerations. In the absence of alternative safe and effective management options, the use of cholinesterase inhibitors is an appropriate pharmacological strategy for the management of BPSD in Alzheimer's disease. |
| Seltzer (2007) | Did not consider specific studies, discussed all evidence identified through systematic review | Is long-term treatment of Alzheimer's disease with cholinesterase inhibitor therapy justified? | Abstract<br>The cholinesterase inhibitors (ChEIs) donepezil, rivastigmine and galantamine are the current mainstays in the drug treatment of Alzheimer's disease (AD). There is convincing evidence that these agents provide at least modest cognitive, behavioural and functional benefit for 6–12 months at all stages of the disease.<br>Longer term benefits cannot be directly examined by placebo-controlled trials. Nevertheless, the results of virtually all open-label extensions of the pivotal trials, studies of patients with AD at different levels of severity and clinical trials using other designs favour treatment over no treatment for periods of up to 5 years.<br>There are plausible biological reasons why ChEIs might be expected to work over a prolonged period of time although, to date, studies using various |

[83] Not presented in this submission as study was included in PBAC submissions for Aricept
[84] Not presented in this submission as study was included in PBAC submissions for Aricept
[85] Not presented in this submission as study was included in PBAC submissions for Aricept
[86] Not presented in this submission as study was in severe AD patients
[87] Not presented in this submission as study only considered agitation

| First Author[54] | Included studies (by first author [year published] or study number) | Outcome measures/domains/ focus | Results |
|---|---|---|---|
| | | | markers to chart the effects of medication on long-term disease progression have yielded mixed results.<br>The most contentious issue regarding long-term treatment is economic, but the majority of available economic analyses suggest net savings over the long term if patients with AD receive persistent treatment with ChEIs. |
| Standridge | Did not consider specific studies, discussed all evidence identified through systematic review | Pharmacotherapeutic approach to treatment of AD | Results<br>ChEI therapy was associated with quality-of-life improvements that included enhanced performance of activities of daily living, reduced behavioural disturbances, stabilised cognitive impairment, decreased caregiver stress, and delay in the first dementia-related nursing home placement.<br>In large clinical trials in moderate to severe AD (a stage that is associated with distress for patients and caregiver burden, and for which other treatments are not available), memantine showed an ability to delay cognitive and functional deterioration. The combination of memantine and ChEI therapy was significantly more efficacious than ChEI therapy alone ($P <$ 0.001) and was well tolerated.<br>Author's conclusion<br>The idea that AD is pharmacologically unresponsive appears to be changing. With the use of ChEI and NMDA-receptor antagonist therapy, the symptoms and outcomes of this devastating neurodegenerative disease can be improved and its course altered. |
| Takeda | Donepezil studies: Burns (1999),[88] Greenberg (2000, Homma (2000), Krishnan (2003), Rodgers (1996),[89] Rodgers (1998a),[90] Rodgers (1998b)[91] | Clinical effectiveness of AChEIs on cognition, quality of life and adverse events in Alzheimer's disease | Results<br>Twenty-six RCTs that compared any one of the cholinesterase inhibitors with either a control group or with another cholinesterase inhibitor were included. The quality of reporting and methodology was varied.<br>Treatment with donepezil, rivastigmine or galantamine resulted in significantly better cognitive performance using the ADAS-cog scale when compared with placebo. These findings were generally supported using the MMSE scale.<br>Results from head to head comparisons were limited by the low number of studies and the study quality; generally showing no robust support for any |

[88] Not presented in this submission as study was included in PBAC submissions for Aricept
[89] Not presented in this submission as study was included in PBAC submissions for Aricept
[90] Not presented in this submission as study was included in PBAC submissions for Aricept
[91] Not presented in this submission as study was included in PBAC submissions for Aricept

| First Author[54] | Included studies (by first author [year published] or study number) | Outcome measures/domains/ focus | Results |
|---|---|---|---|
| | | | one drug.<br>Few studies evaluated quality of life.<br>Adverse events were generally related to the gastrointestinal system, with a tendency for these to be more common in the treatment arms.<br>Authors' conclusion<br>The cholinesterase inhibitors donepezil, rivastigmine, and galantamine can delay cognitive impairment in patients with mild to moderately-severe AD for at least 6 months duration. |
| Wolfson (2000) | Donepezil studies: Burns (1999), Rogers (1996), Rogers (1998a), Rogers (1998b) | Comparative analysis of clinical trials of drug treatments for AD | From the Executive Summary<br>In this report we review those published clinical trials that we believe have the methodological integrity to provide the best evidence on the efficacy of donepezil, metrifonate, rivastigmine, selegiline, vitamin E, lecithin, linopirdine, propentofylline and gingko biloba for the treatment of Alzheimer's disease.<br>Twenty-seven randomized clinical trials were retrieved from the literature and found to meet appropriate methodological standards.<br>We conclude that for selegiline, vitamin E, lecithin, linopirdine, and propentofylline the published data do not provide support for efficacy.<br>Based on the evidence we reviewed, it is our conclusion that donepezil, metrifonate and rivastigmine, however, all provide statistically significant modest benefit on cognitive performance and global functioning to the elderly with probable AD who are eligible for inclusion in clinical trials. The magnitude of the effect is similar for all of the medications.<br>The results from the trials of gingko biloba are promising but the effects are smaller than those from the above mentioned therapies.<br>Although all of these medications appear to be well tolerated, in terms of the occurrence of adverse events, dropout rates are sometimes high and may have resulted in overestimation of apparent treatment effects.<br>It is important to note that this report is based on the results of published trials only and as a result may be subject to publication bias. In particular, if a bias exists such that trials showing no effect are less likely to be published then our findings may overestimate efficacy through the selective inclusion of positive trials. The exclusion of trials that were not published due to poor methodology, however, would not have resulted in a bias as it is unlikely that such trials would have met our standards of methodological rigour.<br>The ability to carry out a comparative analysis of therapies for AD depends not only on the comparability of design, duration, and outcome measures |

| First Author[54] | Included studies (by first author [year published] or study number) | Outcome measures/domains/ focus | Results |
|---|---|---|---|
| | | | used but also on the methods of reporting the results of the trials. There was no consistent method of reporting the results of the AD trials even when emanating from the same group of investigators. Although journals do have different guidelines for authors, we recommend that reports of clinical trials of therapies for AD follow a standardised format for presenting results, which would enhance the ability to compare results across studies. |
| Wolfson (2002) | Donepezil studies: Burns (1999),[92] Doody (2001), Feldman (2001), Greenberg (2000), Homma (2000), Matthews (2000), Mohs (2001), Rogers (1996),[93] Rogers (1998a),[94] Rogers (1998b),[95], Rogers (2000), Winblad (2001) | Efficacy and cost-effectiveness of donepezil and rivastigmine | In the RCTs of donepezil, the mean decrease in scores on the ADAS-cog was greater with active treatment than with placebo (lower scores indicate less cognitive deterioration).<br>Results of phase IV studies were consistent with RCTs.<br>Ten economic studies (7 donepezil, 3 rivastigmine) were identified and reviewed. In 4 of the donepezil studies and all 3 rivastigmine studies, use of the drug cost less than a no-drug strategy.<br>Authors' conclusion<br>The efficacy data indicate that both donepezil and rivastigmine can delay cognitive impairment and deterioration in global health for at least 6 months in patients with mild to moderate AD. Patients receiving active treatment will have more favourable ADAS-cog scores for at least 6 months, after which their scores will begin to converge with those of patients receiving placebo.<br>Differences in methodology, types of direct or indirect costs included, and sources of cost data made it difficult to compare and synthesise findings of the economic studies; therefore, the cost-effectiveness data are inconclusive. |

*AChEI = Acetylcholinesterase Inhibitor; ADAS-Cog = Alzheimer's Disease Assessment Scale – cognitive subscale; BPSD = behavioural and psychological symptoms of dementia; CIBIC-plus = Clinician's Interview-Based Impression of Change with caregiver input; ChEI = Cholinesterase inhibitor; MMSE = Mini-mental State Examination; NNT = Number Needed to Treat: PDS = Progressive Deterioration Scale*

[92] Not presented in this submission as study was included in PBAC submissions for Aricept
[93] Not presented in this submission as study was included in PBAC submissions for Aricept
[94] Not presented in this submission as study was included in PBAC submissions for Aricept
[95] Not presented in this submission as study was included in PBAC submissions for Aricept

## Table 8: Summary of safety and tolerability reviews of AChEIs or donepezil

| First Author | Included studies | Drug | Outcome measures | Results |
|---|---|---|---|---|
| Lockhart | Donepezil studies: Aguglia (2004),[96] De La Gastine (2007),[97] Fuschillo (2004), Huges (2004),[98] Lleshi (2004),[99] Lópes-Pouza(2005), Mossello (2004), Pakrasi (2003), Raschetti (2005), Shua-Haime (2004)[100], Sobow (2006)[101], Turon Estrade (2003)[102] | AChEIs | Considers "real world" evidence of safety and tolerability of AChEIs | Background/Aims<br>The purpose of this systematic review was to compare the safety and tolerability of the cholinesterase inhibitors (ChEIs) donepezil, rivastigmine and galantamine for treating mild to moderate Alzheimer's disease (AD) patients in routine clinical practice.<br>Results<br>Twelve head-to-head studies comparing ChEIs met the pre-specified inclusion criteria; 6 retrospective analyses and 6 prospective cohort studies. Donepezil was the most widely studied treatment and galantamine the least widely prescribed therapy.<br>Fewer donepezil-treated subjects withdrew due to adverse events (AEs) compared with rivastigmine and galantamine-treated subjects. The incidence of gastrointestinal (GI) AEs was lower following treatment with donepezil compared with rivastigmine and galantamine. Non-GI (CNS and cardiovascular) AEs occurred at a low frequency, and had a similar incidence in subjects treated with the different ChEIs.<br>Authors' conclusion:<br>Subjects with mild to moderate AD treated in routine clinical practice with donepezil were more adherent to pharmacotherapy, and had a lower risk of GI AEs compared with rivastigmine or galantamine. Thisfinding accords with results reported in the randomised clinical trial literature. |
| Pratt | Burns (1999)[103], Rogers (1996),[104] Rogers (1998a)[105], Phase III US study[106] | Donepezil | Tolerability and safety review of double-blind placebo-controlled studies | A high completion rate (79%) was achieved in these trials. Of the 1291 patients receiving donepezil, only 142 (11%) withdrew because of an adverse event compared with 43 of the 629 (7%) placebo patients. The most common adverse events included nausea, diarrhoea, headache, insomnia, dizziness, rhinitis, vomiting, asthenia/fatigue and anorexia. Donepezil had no |

[96] Not presented in this submission as the study compared donepezil, rivastigmine and galantamine
[97] Not presented in this submission as it only considered adverse events
[98] Not presented in this submission as it only considered gastrointestinal adverse events
[99] Not presented in this submission as it is in a foreign language
[100] Not presented in this submission as study compared donepezil and rivastigmine
[101] Not presented in this submission as study compared donepezil to rivastigmine
[102] Not presented in this submission as it only considered tolerance and adverse events
[103] Not presented in this submission as it would have been included in PBAC submissions for Aricept
[104] Not presented in this submission as it would have been included in PBAC submissions for Aricept
[105] Not presented in this submission as it would have been included in PBAC submissions for Aricept
[106] Unable to identify this study

| First Author | Included studies | Drug | Outcome measures | Results |
|---|---|---|---|---|
| | | | | clinically significant effect on any laboratory evaluations and was not associated with hepatotoxicity.<br>Authors' conclusion<br>These results demonstrate that donepezil is well tolerated and has a favourable safety profile at clinically effective once-daily doses of 5 mg and 10 mg. |

## Table 9: Summary of international cost-effectiveness analyses: donepezil and AChEIs

| First Author | Abstract |
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| Bond | **Background:**<br>Alzheimer's disease (AD) is the most commonly occurring form of dementia. It is predominantly a disease of later life, affecting 5% of those over 65 in the UK.<br>**Objectives:**<br>Review and update guidance to the NHS in England and Wales on the clinical effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine [acetylcholinesterase inhibitors (AChEIs)] and memantine within their licensed indications for the treatment of AD, which was issued in November 2006 (amended September 2007 and August 2009).<br>**Data sources:**<br>Electronic databases were searched for systematic reviews and/or meta analyses, randomised controlled trials (RCTs) and ongoing research in November 2009 and updated in March 2010; this updated search revealed no new includable studies. The databases searched included The Cochrane Library (2009 Issue 4, Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials), MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, PsycINFO, EconLit, ISI Web of Science Databases--Science Citation Index, Conference Proceedings Citation Index, and BIOSIS; the Centre for Reviews and Dissemination (CRD) databases--NHS Economic Evaluation Database, Health Technology Assessment, and Database of Abstracts of Reviews of Effects.<br>**Review methods:**<br>The clinical effectiveness systematic review was undertaken following the principles published by the NHS CRD. We included RCTs whose population was people with AD. The intervention and comparators depended on disease severity, measured by the Mini Mental State Examination (MMSE). Interventions: mild AD (MMSE 21-26) -- donepezil, galantamine and rivastigmine; moderate AD (MMSE 10-20) – donepezil, galantamine, rivastigmine and memantine; severe AD (MMSE < 10) -- memantine. Comparators: mild AD (MMSE 21-26) -- placebo or best supportive care (BSC); moderate AD (MMSE 10-20) -- donepezil, galantamine, rivastigmine, memantine, placebo or BSC; severe AD (MMSE < 10) -- placebo or BSC. The outcomes were clinical, global, functional, behavioural, quality of life, adverse events, costs and cost-effectiveness. Where appropriate, data were pooled using pair-wise meta-analysis, multiple outcome measures, meta-regression and mixed treatment comparisons. The decision model was based broadly on the structure of the three-state Markov model described in the previous technology assessment report, based upon time to institutionalisation, parameterised with updated estimates of effectiveness, costs and utilities.<br>**Results:**<br>Notwithstanding the uncertainty of our results, we found in the base case that the AChEIs are probably cost saving at a willingness-to-pay (WTP) of £'30,000 per quality adjusted life-year (QALY) for people with mild-to-moderate AD. For this class of drugs, there is a > 99% probability that the AchEIs are more cost-effective than BSC. These analyses assume that the AChEIs have no effect on survival. For the AchEIs, in people with mild to moderate AD, the probabilistic sensitivity analyses suggested that donepezil is the most cost-effective, with a 28% probability of being the most cost-effective option at a WTP of £'30,000 per QALY (27% at a WTP of £'20,000 per QALY). In the deterministic results, donepezil dominates the other drugs and BSC, which, along with rivastigmine patches, are associated with greater costs and fewer QALYs. Thus, although galantamine has a slightly cheaper total cost than donepezil (£'69,592 vs £'69,624), the slightly greater QALY gains from donepezil (1.616 vs 1.617) are enough for donepezil to dominate galantamine. The probability that memantine is cost-effective in a moderate to severe cohort compared with BSC at a WTP of £'30,000 per QALY is 38% (and 28% at a WTP of £'20,000 per QALY). The deterministic ICER for memantine is £'32,100 per/QALY and the probabilistic ICER is £'36,700 per/QALY.<br>**Limitations:**<br>Trials were of 6 months maximum follow-up, lacked reporting of key outcomes, provided no subgroup analyses and used insensitive measures. Searches were limited to English language, The model does not include behavioural symptoms and there is uncertainty about the model structure and parameters.<br>**Conclusions:** |

| First Author | Abstract |
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| | The additional clinical effectiveness evidence identified continues to suggest clinical benefit from the AChEIs in alleviating AD symptoms, although there is debate about the magnitude of the effect. Although there is also new evidence on the effectiveness of memantine, it remains less supportive of this drug's use than the evidence for AChEIs. The conclusions concerning cost-effectiveness are quite different from the previous assessment. This is because both the changes in effectiveness and costs between drug use and non-drug use underlying the ICERs are very small. This leads to highly uncertain results, which are very sensitive to change. RESEARCH PRIORITIES: RCTs to include mortality, time to institutionalisation and quality of life, powered for subgroup analysis. |
| Colin | **Objective:** To estimate the cost effectiveness (from the UK NHS and personal social services perspective) of the cholinesterase inhibitors donepezil, rivastigmine and galantamine compared with usual care in the treatment of mild to moderately severe Alzheimer's disease. Patients had a mean age of 74 years, a mean disease duration of 1 year and a mean Alzheimer's disease assessment scale-cognitive subscale score of 24.<br>**Methods:** A pharmacoeconomic model was used to predict long-term outcomes over a 5-year time horizon and to estimate the cost effectiveness of cholinesterase inhibitors for the management of Alzheimer's disease. The model structure is informed by a systematic review of the literature on the clinical and cost effectiveness of cholinesterase inhibitors and a review of the literature on the costs and outcomes associated with treatment for Alzheimer's disease. The main outcome measure used was the cost per quality-adjusted life-year (QALY) gained. All healthcare costs (excluding cholinesterase inhibitor costs) were indexed to £ (2003 values). Drug costs are 2005 values. Multivariate probabilistic sensitivity analysis and scenario analysis were undertaken to assess uncertainty in the results.<br>**Results:** The clinical benefits on cognition from treatment with cholinesterase inhibitors resulted in an incremental cost per QALY gained ranging from £53 780 to £74 735, over 5 years (vs usual care). Uncertainty analysis suggests that the probability of any of these treatments having an incremental cost per QALY of <£30 000 is <21%. The key determinants of cost effectiveness were the effectiveness of treatment, the mean treatment cost and the cost savings associated with an expected delay in disease progression.<br>**Conclusions:** Results presented in this paper suggest that the use of cholinesterase inhibitors may not be a cost-effective use of NHS resources. Guidance from the National Institute for Health and Clinical Effectiveness (NICE) in the UK on their judgements surrounding the acceptability of technologies as an effective use of resources, indicates there would need to be special reasons for accepting cholinesterase inhibitors as a cost-effective use of NHS resources. |
| Fagnani | In the present study, the socioeconomic impact of the use of the acetylcholinesterase inhibitor donepezil in patients with mild to moderate Alzheimer's disease (AD) living in France was examined. A model was created to extrapolate over a 3-year period the results from placebo-controlled trials together with epidemiological and prevalence data. Costs considered in the model were net societal costs associated with paid and unpaid assistance, general medical consumption and institutional care. The model suggested that delays in cognitive decline and functional dependence due to treatment reduced the time spent in institutional care and the burden on caregivers. Over a 3-year period, total net costs of caring for untreated patients with an initial Mini-MentalState Examination score ranging from 10 to 26 were €53,206 compared with € 42,720 for a patient treated with donepezil – an annual cost saving of approximately € 3,500 per patient. Cost savings were mainly due to savings in unpaid caregiver time, which, apart from patient institutionalisation, represented the most costly component of total care in this study but had no direct budgetary impact. Overall, these data suggest that donepezil is a cost-effective treatment for mild to moderately impaired AD patients living in France. |
| Feldman 2004 | **Objective:** To investigate the costs to society of Alzheimer disease (AD) care in a multinational, randomized, placebo-controlled trial of donepezil in patients with moderate to severe AD.<br>**Methods:** A total of 290 patients with AD (screening standardized Mini-Mental State Examination score 5 to17) were randomized to receive either donepezil (n =144; 5 mg/day for 28 days, followed by 10 mg/day as per clinician's judgment) or placebo (n = 146) for 24 weeks. The authors collected data on patient and caregiver health resource utilization prospectively using the Canadian Utilization of Services Tracking questionnaire. Costs were calculated for patients and caregivers in each group based on resource utilization multiplied by the unit prices for each resource. A cost (the average Ontario minimum |

| First Author | Abstract |
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| | wage for 1998 [Can $6.85 per hour]) was assigned to unpaid time that caregivers spent assisting the patient with activities of daily living (ADL).<br>**Results:** Patient and caregiver demographics at baseline were similar across the two groups. After adjusting for baseline total cost per patient, the mean total societal cost per patient for the 24-week period was donepezil, Can $9,904 (US $6,686) and placebo, Can $10,236 (US $6,910). This net cost saving of Can $332 (US $224) included the average 24-week cost of donepezil treatment. Most of the cost-saving with donepezil treatment was due to less use of residential care by patients, and caregivers spending less time assisting patients with ADL.<br>**Conclusion:** This cost-consequence analysis reveals economic benefits of treatment of moderate to severe AD with donepezil. |
| Fuh | **Background**: Donepezil is a drug used for treatment in patients with Alzheimer's disease (AD). Information regarding the cost-effectiveness of this medication was previously rare in Asia. We used techniques of decision analysis and economic evaluation in conjunction with available local epidemiological and clinical data on costs of mild to moderate AD to assess the cost-effectiveness of donepezil in Taiwan.<br>**Methods**: A four-state Markov model was built to simulate the disease progression of AD patients. Local transition probabilities and costs of different stages were from the studies published earlier.<br>**Results:** Over a 5-year span, donepezil treatment for mild or moderate AD patients is predicted to result in the gain of 0.505 QALYs when comparing to usual care, while at the same time reducing the cost by US$7,691. The incremental cost was US$3,647 from the payer perspective; thus, the incremental cost-effectiveness ratio was estimated to be US$7,226 when considering only the medical expenditures.<br>**Conclusions:** Under some assumptions, donepezil treatment might be a cost saving strategy for mild to moderate AD patients in Taiwan from a societal perspective. It is inconclusive from the payer's part since we still lack a consensus for judging the cost-effectiveness of a new health care technology. |
| Getsios | **Background**: Recommendations in the UK suggest restricting treatment of Alzheimer's disease with cholinesterase inhibitors, on cost-effectiveness grounds, to patients with moderate cognitive decline. As the economic analyses that informed these recommendations have been the subject of debate, we sought to address the potential limitations of existing models and produce estimates of donepezil treatment cost effectiveness in the UK using the most recent available data and simulation techniques.<br>**Methods**: A discrete-event simulation was developed that predicts progression of Alzheimer's disease through correlated changes in cognition, behavioural disturbance and function. Patient-level data from seven randomised, placebo-controlled donepezil trials and a 7-year follow-up registry provided the basis for modelling longitudinal outcomes. Individuals in the simulation were assigned unique demographic and clinical characteristics and then followed for 10 years, with severity of disease tracked on continuous scales. Patient mix and costs were developed from UK-specific literature. Analyses were run for severity subgroups to evaluate outcomes for sub-populations with disease of mild versus moderate severity from both a healthcare payer and societal perspective. All costs are reported in £ year 2007 values, and all outcomes are discounted at 3.5% per annum.<br>**Results**: Over 10 years, treatment of all patients with mild to moderate disease reduces overall direct medical costs by an average of over £2300 per patient. When unpaid caregiver time is also taken into consideration, savings increase to over £4700 per patient.<br>Compared with untreated patients, patients receiving donepezil experience a discounted gain in QALYs averaging 0.11, with their caregivers gaining, on average, 0.01 QALYs. For the subset of patients starting treatment with more severe disease, savings are more modest, averaging about £1600 and £3750 from healthcare and societal perspectives, respectively.<br>In probabilistic sensitivity analyses, donepezil dominated no treatment between 57% and 62% of replications when only medical costs were considered, and between 74% and 79% of replications when indirect costs were included, with results more favourable for treatment initiation in the mild versus moderate severity stages of the disease.<br>**Conclusions**: Although the simulation results are not definitive, they suggest that donepezil leads to health benefits and cost savings when used to treat mild to moderately severe Alzheimer's disease in the UK. They also indicate that both benefits and savings may be greatest when treatment is started while patients are still in the mild stages of Alzheimer's disease. |

| First Author | Abstract |
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| Lopez-Bastida | Available treatments for Alzheimer's disease (AD) need to be evaluated in order to determine whether the clinical benefits justify their additional costs. This study evaluated the cost-effectiveness of donepezil treatment compared with no-drug treatment of mild and moderate AD from the perspective of society and the health care system in Spain. A Markov model was designed to simulate the natural history of a cohort of patients with mild and moderate AD. Monthly transition probabilities were estimated from the international literature and donepezil clinical trials. Direct medical and non-medical costs and utilities were derived from Spanish studies. Local data on tolerance and medication withdrawal rates were incorporated into the model. Incremental cost-effectiveness ratios for a range of realistic treatment options were calculated. A probabilistic sensitivity analysis was carried out using a Monte Carlo approach with 10,000 iterations. In the baseline scenario (24 months, patients initially with mild AD) incremental cost-effectiveness for direct medical costs was 20,353€/QALY. When all costs were taken into account, donepezil treatment was the dominant strategy. Incremental cost-effectiveness ratios vary according to the selected perspective. For the baseline scenario, donepezil treatment is cost-effective with a probability of 95% for a threshold efficiency of 25,000€/QALY. |
| Pouryamout | **Introduction**: Alzheimer's disease (AD) is common among the elderly; it is responsible for 60–80% of all dementia cases. AD is characterized by cognitive decline, behavioural and psychological symptoms, and reductions in functioning and independence. Because of its progressive neurodegenerative nature and unknown aetiology, the burden of AD becomes increasingly significant in an aging population. Estimates indicate that 35.6million people worldwide suffered from AD in 2010. By 2030 and 2050, this figure is predicted to increase to 65.7 million and 115.4million, respectively. Costs will also rise along with the increase in the number of people diagnosed with AD. In 2010, the worldwide costs associated with dementia were estimated to be $US604 billion.<br>**Objective**: The objective of this study was to conduct a systematic review of current publications dealing with the pharmacoeconomic factors associated with AD medications and to describe the decision-analytic models used to evaluate long-term outcomes.<br>**Methods**: A systematic literature search was performed to identify articles published between 1 January 2007 and 15 July 2010. The search was also based on a previous systematic review, which included literature up to 2007. Articles were included if they were complete and original economic evaluationsof AD and if they were comparative in nature. A quality assessment of the included publications was conducted and relevant information was extracted into tables.<br>**Results**: Seven out of 2067 identified articles were included in this systematic review. Four articles evaluated treatment with donepezil,[107] one with galantamine and two with memantine. The studies were conducted in America, Europe and Asia. Five different groups of medications were compared. The incremental cost-effectiveness ratios (ICERs) for the group of patients treated with donepezil versus no drug treatment ranged from a dominant value to EUR 281 416.13 per quality-adjusted life-year (QALY). Patients treated with donepezil versus placebo showed ICERs with a range from a dominant value(not specified) up to EURO 20 866.77 per QALY. Treatment with memantine in addition to donepezil versus treatment with donepezil alone showed an ICER range from a dominant value to EUR 6818.33 per QALY. In comparison with the memantine treatment as an add-on therapy, the ICER of memantine monotherapy versus standard care (without cholinesterase inhibitors [CEIs]) ranged from a dominant value to EUR 63 087.20 per QALY. Finally, the economic evaluation of galantamine in comparison with usual care without any AD drugs showed ICERs ranging from EUR 1894.70 to EUR 6953 per QALY.<br>**Conclusion**: The seven identified publications included in this review indicate that treatment with CEIs or memantine seems to be reasonable in terms of clinical effects and costs for patients with AD. Depending on different hypotheses, assumptions and variables (e.g. time horizon, discount rates, initial number of patients in different states, etc.) in the sensitivity analyses, treatment with these drugs seems to be primarily a cost-effective strategy or even a cost-saving strategy. Nevertheless, the results generally are associated with a degree of uncertainty. The comparability of the results from the different economic evaluations is limited because of the different assumptions made. |

[107] Fuh (2008), Getsios (2010), Lopez-Bastida (2009), Teipel (2007)

| First Author | Abstract |
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| Tipel | **Background**: (Acetyl-)cholinesterase (ChE) inhibitors have been approved for the treatment of mild to moderate Alzheimer's disease (AD). However, use of ChE inhibitors is limited by budget constraints and disincentives on the side of health insurances and nursing care insurances.<br>**Objective**: To analyse under what conditions the application of the acetylcholinesterase inhibitor donepezil is favourable for the treatment of patients with AD from the perspective of health insurance and nursing care insurance companies in Germany, taking into account factors such as start and duration of treatment, duration of follow-up, drug costs, internalization of opportunity costs and varying mortality and efficacy rates.<br>**Methods:** Transition probabilities from a Swedish study and German cost data for donepezil were merged in a Markov model to follow a cohort of patients over a period of 5–10 years. We defined a base case with 1 year treatment and follow-up over 5 years and varied treatment length, follow-up interval and cost factors in sensitivity analyses. Results In the base case, the ChE inhibitor donepezil did not lead to cost savings but to a cost-effective outcome on side of health insurances and nursing care insurances. Early treatment of AD and internalization of opportunity costs (caring time devoted to patients) led to less costs per quality adjusted life years gained. However, results are very sensitive with respect to varying mortality and efficacy rates.<br>**Conclusion**: The application of donepezil may be cost-effective, but considerable uncertainties remain. Moreover, the way the reimbursement system in Germany is presently arranged does not support the application of ChE inhibitors. |
| Wimo 2003 | The costs and consequences of donepezil versus placebo treatment in patients with mild to moderate Alzheimer's disease (AD) were evaluated as part of a 1-year prospective, double-blind, randomised, multinational clinical trial. Patients received either donepezil (n = 142; 5 mg/day for 28 days followed by 10 mg/day according to the clinician's judgement) or placebo (n = 144). Unit costs were assessed in 1999 Swedish kronas (SEK) and converted to US dollars (USD). Donepezil-treated patients gained functional benefits relative to placebo on the Progressive Deterioration Scale (p = 0.042) and Instrumental Activities of Daily Living scale (p = 0.025) at week 52. Caregivers of donepezil-treated patients spent an average of 400 h less annually providing care than caregivers of placebo-treated patients. Mean annual healthcare costs were SEK 137,752 (USD 16,438) per patient for the donepezil group and SEK 135,314 (USD 16,147) in the placebo group. With the average annual cost of donepezil at SEK 10,723 (USD 1,280) per patient, the SEK 2,438 (USD 291) cost difference represented a 77% cost offset. When caregiver time and healthcare costs were included, mean annual costs were SEK 209,244 (USD 24,969) per patient in the donepezil group and SEK 218,434 (USD 26,066) in the placebo group, a total saving associated with donepezil treatment of SEK 9,190 (USD 1,097) per patient [95% CI of SEK –43,959 (USD –5,246), SEK 25,581 (USD 3,053); p = 0.6]. The positive effects on the efficacy outcome measures combined with no additional costs from a societal perspective indicate that donepezil is a cost-effective treatment, representing an improved strategy for the management of patients with AD. |

## Term of reference d. Review the current PBS restriction continuation rule and the likely effect it has on cost-effective utilisation of donepezil

Due to the short time provided for response to the terms of reference, it was not possible to conduct a formal cost-effectiveness analysis. However, it is important to note the extracts of the minutes of the December PBAC meeting included in **Figure 6**.

**Figure 6: Extracts of minutes from the December 2000 PBAC meeting**

*Economic evaluation:*
7.7.7. The submission did not present an economic evaluation as advised by the PBAC at the September meeting.

**Recommendations and Reasons:**
7.7.11 The PBAC recommended listing on the basis of acceptable cost-effectiveness in this patient group.

Therefore the PBAC recommended listing on the basis of acceptable cost-effectiveness in this patient group although cost-effectiveness had not been demonstrated.

In April 2013, donepezil will lose exclusivity. As a consequence, the molecule will be subject to a 16% price reduction followed by price disclosure reductions beginning 18 months thereafter. As shown under Term of Reference a, the Commonwealth Payment in 2011 was lower than would have been forecasted from the estimates provided to the PBAC in December 2000. As the price of donepezil decreases, these payments will decrease, and it is highly likely that a cost-effectiveness analysis performed using the current persistence data and reduced prices will show it to be cost-effective.

Additionally, as shown in the large number of clinical- and cost-effectiveness reviews and analyses, in most cases it is agreed that acetylcholinesterase inhibitors are cost-effective interventions for AD particularly when the impact on care-givers and nursing home placement is considered.

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# Appendix 1: Pfizer response to House of Representatives Standing Committee Enquiry

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2 May 2012

**John Latham**
Chairman and Managing Director

Committee Secretary
House of Representatives Standing Committee on Health & Ageing
PO Box 6100
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CANBERRA ACT 2600

Dear Committee Secretary

**Inquiry into Dementia: Early diagnosis and Intervention**

Thank you for providing Pfizer Australia with the opportunity to contribute to the House of Representatives Standing Committee on Health and Ageing inquiry into *Dementia: Early diagnosis and Intervention*.

Pfizer Australia[1] is the nation's leading pharmaceutical company, employing approximately 1,600 colleagues. Since 1849, Pfizer has been dedicated to discovering and developing new, and better, ways to prevent and treat disease and improve the health and quality of life for people around the world. Pfizer manufactures innovative and generic medicines in Australia and overseas. Pfizer Australia is the sponsor of the anti-dementia medicine[2] donepezil (Aricept®), which has been listed on the Pharmaceutical Benefits Schedule for the treatment of mild to moderately severe Alzheimer's disease since 2002.[3] Pfizer remains committed to the development of novel and innovative medicines and vaccines for Alzheimer's disease.[4]

The government has recently released their comprehensive report, *Living Longer. Living Better.*, which recognises one of the challenges facing the aged care system and the ageing population, is the complex management arrangements for dementia and the increasing prevalence of the disease. A number of key initiatives to improve the lives not only of those individuals with dementia, but also their carers, are included in the report. We commend the Government for their report and the recognition that dementia should be considered as a National Health Priority[5].

Dementia is a progressive condition with multiple causes, for which there is presently no cure. Alzheimer's disease and other causes of dementia result in impaired memory, thinking and behaviour. Alzheimer's disease accounts for the majority of dementia cases, approximately 70%. Dementia, and therefore Alzheimer's disease, is recognised as a national epidemic[6].

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[1] This submission has been prepared by Pfizer Australia – a wholly owned subsidiary of Pfizer Inc., based in New York. Pfizer Australia is a member of Medicines Australia – the peak industry body for the innovative medicines industry in Australia.
[2] Defined by WHO Body System Classification, NO6D www.pbs.gov.au
[3] Other medicines PBS listed for the treatment of mild to moderately severe Alzheimer's disease are galantamine and rivastigmine.
[4] Pfizer's pipeline includes several molecules in Phase 1, a vaccine in Phase 2 and a beta amyloid inhibitor in Phase 3 testing, representing the range of research into a complex and complicated disease area. For more information see www.pfizer.com /research/product_pipeline/product_pipeline.jsp
[5] Standing Council on Health. (2012). *Communique 27th April 2012*. Retrieved from http://www.health.gov.au/internet/main/publishing.nsf/Content/26D7A8371CE29ED4CA2579ED002047B9/$File/120427.pdf
[6] Commonwealth of Australia. (2012). *Living Longer. Living Better*. Retrieved from http://www.health.gov.au/internet/publications/publishing.nsf/Content/CA2578620005D57ACA2579E2007B9DFC/$File/D0769-Living-Longer-Living-Better-200412.pdf

In 2011 it was estimated that 266,574 Australians had dementia, with this figure expected to double by 2030 (553,285), increasing to 942,624 affected individuals by 2050[7]. This is consistent with international estimates, with dementia recognised as a global public health challenge as populations' age[8].

Dementia is often overwhelming not just for individuals but for their families and caregivers; it is estimated that while there are 260,000 Australians with dementia there are over 1.2 million caregivers. This represents not only a significant health and medical challenge but also an increasing social and economic challenge for communities and governments. The current cost of dementia care in Australia is $6 billion per annum and as more people develop dementia, the cost to Australia is estimated to grow to $83 billion by the 2060s[9].

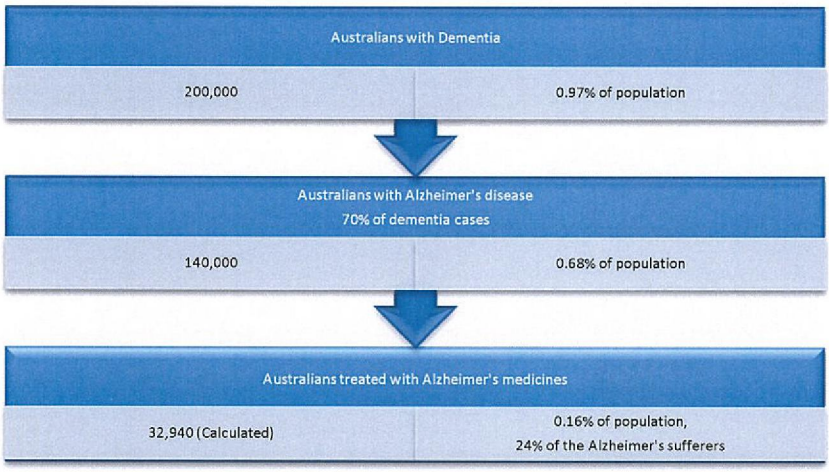
Our submission focuses on the issue of *support for more timely diagnosis,* with the flow-on benefits to sufferers and their families and carers.

***There is a need for greater community awareness***

Dementia has been incorrectly regarded as a natural part of ageing. The level of understanding and awareness of the disease amongst the general community is very low. The *Dementia is Everybody's Business"* Health Report[10], published in 2011, highlighted the need for more awareness about the impact of dementia in the community. While most Australians associate dementia with memory loss, they are still unclear about how common dementia is or what other symptoms are associated with dementia. While dementia is the third leading cause of death in Australia, only 1 in 5 Australians is aware that dementia is a progressive illness and sufferers experience a reduced life expectancy. Approximately 63% of Australians fear getting Alzheimer's disease or another form of dementia, this is second only to the fear of having cancer (reported by 66% of respondents)[11].

A study[12] of the utilisation of medicines to treat Alzheimer's disease in Australia highlighted the low diagnosis rates, as illustrated by Figure 1 below.

*Figure 1 Estimated number of Australians receiving pharmacotherapy for Alzheimer's*




[7] Deloitte Access Economics. (2011). *Dementia Across Australia 2011-2050*. Retrieved from http://www.fightdementia.org.au/common/files/NAT/20111014_Nat_Access_DemAcrossAust.pdf

[8] World Health Organisation and Alzheimer's Disease International. (2012). *Dementia: A Public Health Priority*. Retrieved from www.whqlibdoc.who.int/publications/2012/9789241564458_eng.pdf

[9] Fight Alzheimer's Save Australia. (2012). *Media Release: Australia dementia research is falling behind, 4 April 2012*. Retrieved from www.fightdementia.org.au/common/files/NAT/20120403_Nat_MR_DemResearchFallingBehind.pdf

[10] The Pfizer Health Report "Dementia is everybody's business", was developed by Alzheimer's Australia and supported by Pfizer Australia to highlight the need for more awareness about the impact of dementia in the community.

[11] Pfizer Health Report. (2011). *Issue 45: Dementia is Everybody's Business*. Retrieved from http://www.fightdementia.org.au/common/files/NAT/20110314_Nat_report_Pfizer-Health-Report-2011.pdf

[12] Hollingworth S, Byrne G. (2011). *Prescribing trends in cognition enhancing drugs in Australia*. International Psychogeriatric, 23:2, 238-45.

The rate of treatment for Alzheimer's is probably lower than 24%, reported in Figure 1, with some estimates indicating the rate of treatment could be as low as 16.5%. The hypothesis behind the low treatment rate is that insufficient access to diagnostic and treatment services, complex prescribing rules for anti-dementia medications and negative perceptions about the efficacy of these medicines contribute to a low treatment rate in this population[13].

Greater access to information and a better understanding of dementia should increase help-seeking and help-giving and promote awareness of the lifestyle changes that may reduce the risk of dementia. This would encourage diagnosis and intervention as early as possible for individuals who are suspected to be suffering from dementia. It is essential in any health related condition that a diagnosis is followed by the appropriate support for the individual and their family/carer not only from healthcare professionals but also any social, housing and medico-legal issues which may arise. It is important to ensure that awareness-raising and support is not limited to the pre-diagnosis and diagnosis stage.

The Alzheimer's Society UK ran a successful *Worried about your memory?* awareness campaign spanning public, GP clinics and pharmacy environments in 2008 which increased patient referral to GPs.[14] The Department of Health in the United Kingdom supported the campaign as part of their commitment to a National Dementia Strategy, where raising public awareness and increasing rates of diagnosis were big recommendations. In relation to the committee's terms of reference on raising community awareness of dementia and dementia-related services, we would like to draw the Committee's attention to the 2012 WHO and ADI *Dementia: A Public Health Priority* report which provides case studies of awareness campaigns across the world including Japan, UK and Brazil.[15] The WHO review identified these key tenets for dementia awareness-raising campaigns:

- raising public awareness and understanding of dementia;
- reducing the stigma of dementia and challenging discriminatory behaviour;
- recognising the early signs of dementia to aid early diagnosis;
- living well with dementia;
- the importance of a healthy lifestyle and reducing risk.

In Australia Pfizer has supported the dementia awareness activities of Alzheimer's Australia over the last 12 years. These activities have generated significant information sharing and awareness-raising across a broad cross-section of the population. We believe there needs to be a national communication strategy in Australia which addresses the objectives put forward above, and involves a broad range of stakeholders including Alzheimer's Australia.

Raising community awareness will open avenues for disease support and management for patients and break down the stigma sometimes associated with the disease. It will provide caregivers and families helpful information and opportunities to seek assistance.

***Access to early diagnosis, intervention and treatment***

There is presently no cure for dementia, however early diagnosis and intervention have the capacity to provide benefits for patients, carers and the community.

An early diagnosis of dementia gives the individual and their family time to adjust to the diagnosis and start making legal and financial decisions while the individual with dementia can still have an active role in decision making. An early diagnosis can also help in providing much needed access to services and medicines to help maintain function and quality of life in some people. When dementia services are accessed early, they can potentially avoid "emergency" admissions to nursing homes by providing caregivers with the necessary information and support to facilitate care in the community.

In 2004 the Australian Institute of Health and Welfare reported that in nursing homes almost 96% of residents requiring the two highest levels of care were those individuals with probable or possible dementia.

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[13] Hollingworth SA, Byrne GJ. (2011). *Prescribing trends in cognition enhancing drugs in Australia*. International Psychogeriatric, 23:2, 238-245.

[14] Alzheimer's Society Memory campaign boosts dementia diagnosis, April 2009. www.alzheimers.org.uk/site/scripts/news_article.php?newsID=446

[15] World Health Organisation and Alzheimer's Disease International. (2012). *Dementia: A Public Health Priority*. Retrieved from www.whqlibdoc.who.int/publications/2012/9789241564458_eng.pdf

Of all the residents in nursing home care approximately 80% were classified as having dementia.[16] If the average onset of Alzheimer's disease could be delayed by even 5 months, starting

In response to a review by the Productivity Commission review in 2005 it was reported that if the average onset of Alzheimer's disease could be delayed by even 5 months, starting, in 2005, then by 2020 $1.3 billion dollars would be saved.[17] Clearly, reducing the prevalence or delaying the onset of Alzheimer's disease would be very important in reducing the impact of the disease, both financially and on individuals.

Since the introduction of the first cholinesterase inhibitor in 1997, most clinicians and probably most patients would consider the cholinergic drugs, donepezil, galantamine and rivastigmine, to be the first line pharmacotherapy for mild to moderate Alzheimer's disease.[18] This supports the recommendations by the Pharmaceutical Benefits Advisory Committee to list donepezil, galantamine and rivastigmine on the PBS for the treatment of Alzheimer's disease diagnosed as mild to moderately severe.

To quantify the benefits to individuals and their caregivers a 2004 study[19] demonstrated that those individuals receiving no active treatment required almost 2 hours more care per day after one year of follow-up, whereas those individuals receiving donepezil required almost 45 minutes of extra care per day. This highlights not only the benefits to the sufferer of active treatment but also the benefits to caregiver. Although the patients receiving treatment did not show an improvement in care required, there is clearly a case for a delay or slowing in the inevitable burden of disease with a progressive illness such as dementia and more specifically Alzheimer's disease.

An Australian study[20] has shown the persistence and adherence to the anti-Alzheimer's medicines are reasonable (57.3% and 79.4%) once treatment was established; prompting the authors to conclude there was an unexpectedly high continuation rate beyond the initial six months of treatment.

The physical and emotional demands of caring for someone with dementia can be high. As the disease progresses, and the patient remains in the community, an increasing amount of time is spent by the caregiver[21], often at the expense of their own health[22], well-being and finances[23]. A general study in 1999[24] concluded that elderly caregivers who reported strain in caring for their disabled partner experienced a significantly higher risk of mortality than elderly participants whose spouses where not disabled, effectively *caregivers who report strain associated with caregiving are more likely to die than noncaregiving controls.*

A timely diagnosis helps facilitate access for caregivers to different types of support programs, respite care and access to financial support. It is essential to ensure there is reasonable and equitable access to diagnostic services, the best treatment management options, the appropriate healthcare professionals, respite care, home assistance and nursing homes, for example. The ability to provide an early diagnosis and appropriate disease management is clearly changing with the advances in care, the recognition of the value of a multi-disciplinary team approach and this will need to be balanced in view of the increasing prevalence of dementia in Australia. Any roadmap for the management of aged care and more specifically dementia must include recognition of the need for the appropriate infrastructure to support delivery of existing and innovative management options.

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[16] Australian Institute of Health and Welfare 2004. The impact of dementia on the health and aged care systems. AIHW Cat. No. AGE 37. Canberra: AIHW. http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=6442454088

[17] *Delaying the Onset of Alzheimer's Disease: Projections and Issues,* Access Economics, August 2004.

[18] Birks J. (2006). *Cholinesterase inhibitors for Alzheimer's disease*. Cochrane Database of Systematic Reviews 2006, 1: CD005593. Retrieved from: http://summaries.cochrane.org/CD005593/cholinesterase-inhibitors-cheis-donepezil-galantamine-and-rivastigmine-are-efficacious-for-mild-to-moderate-alzheimers-disease

[19] Wimo A, Winblad B, Shah SN, Chin W, et al. (2004). *Impact of donepezil treatment for Alzheimer's disease on caregiver time.* Current Medical Research and Opinions, 20, 8:1221-1225.

[20] Le Couteur DG, Robinson M, Leverton A, et al. (2011). *Adherence, persistence and continuation with cholinesterase inhibitors in Alzheimer's disease*. Australasian Journal of Ageing, published online 4 Sep 2011.

[21] Wimo A, von Strauss E, Nordberg G, et al. (1994). *Time spent on informal and formal caregiving for persons with dementia.* Gerontologist, 34:199-205.

[22] Schulz R, O'Brien AT, Boolwala J, et al. (1995). *Psychiatric and physical morbidity effect of dementia on caregiving: prevalence, correlates, and causes.* Gerontologist, 35:771-91.

[23] Stommel M, Collins CE, Given BA. (1994). *The costs of family contributions to the care of persons with dementia*. Gerontologist, 34:199-205.

[24] Schulz RS, Beach SR. (1999). *Caregiving as a Risk Factor for Mortality: The Caregiver Health Effect Study*. Journal American Medical Association, 282:2215-2219.

However access to a diagnosis isn't always easy. Often this is the first step in a potentially long and complicated journey for individuals to access post-diagnosis services, services which ensure the benefits of early diagnosis are realised. In Australia, symptoms of dementia were noticed by families on average of 1.9 years prior to the first health professional consultation and there was an average of 3.1 years before a firm diagnosis was made.[25]

The 2011 *Dementia is Everybody's Business* Health Report reported that 16% of Australians know someone who might have dementia who has not sought diagnosis or treatment.[26] Amongst carers this figure rises to 41%. There is a stigma and fear associated with dementia, leading to an aversion by some in the community to actively seek a diagnosis.[27]

Further, in the absence of a treatment that can reverse the underlying pathological process some doctors remain reluctant to offer a diagnosis to patients.[28] This further limits access to services and medication that can be used to help treat the symptoms and make a difference to the lives of people with dementia and their families.

Access to early diagnosis and treatment is crucial to helping patients maintain their ability to perform activities of daily living for longer. This also has very important implications for families who devote time and resources to caring for a loved one.

The community, through its governments and health systems, should work to reduce barriers to diagnosis and treatment.

***Treatment advances are needed***

Currently around 260,000 Australians are estimated to have dementia and unless an effective prevention or cure is discovered, that number will grow to almost one million by 2050[29]. Current medicines treat symptoms rather than the disease. More needs to be done.

Pfizer continues to invest in the research and development necessary to advance the treatment and/or prevention of Alzheimer's disease and neurological and neurodegenerative disorders.

Discovery, innovation and the development of medicines is high risk and resource intensive with thousands of promising compounds investigated to bring only one or two innovative treatments to patients who need them. It routinely requires a decade to get a new medicine to patients.

The Government has committed to the significant investments in the health and aged care sector in response to the growing prevalence of dementia within the setting of an ageing population. As part of this system reform we urge government to be mindful of medical advances and the role they play in the public health, social and fiscal challenges that dementia presents. Ensuring access to treatment is timely and equitable is compassionate, efficient and effective. Early diagnosis and intervention as central tenets to ensuring long-term quality of life of dementia sufferers, their families and carers and to the broader community is clear from the terms of reference the committee is considering.

Pfizer Australia thanks the Committee for the opportunity to contribute to this inquiry. Pfizer is available at any time to provide further information if it would assist the Committee.

Yours faithfully

**John Latham**

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[25] Timely Diagnosis of Dementia: Can we do better? A report for Alzheimer's Australia, Paper 24, Philipps J, Pond D, Goode S, 2011
[26] Pfizer Health Report. (2011). *Issue 45: Dementia is Everybody's Business.*
[27] Pfizer Health Report 2011 found that 44% of people interviewed believe people with Alzheimer's disease or other forms of dementia are discriminated against or unfairly treated, whereas 56% of carers believe there is discrimination.
[28] Hansen EC, Hughes C, Routley G, Robinson AL. (2008). *General practitioners' experiences and understandings of diagnosing dementia: factors impacting on early diagnosis.* Social Science and Medicine, 67:11, 1776-1783.
[29] Deloitte Access Economics. (2011). *Dementia Across Australia 2011-2050.*
www.fightdementia.org.au/common/files/NAT/20111014_Nat_Access_DemAcrossAust.pdf