ODPRN ONTARIO DRUG POLICY RESEARCH NETWORK

FINAL REPORT

Cognitive Enhancers for the Treatment of Alzheimer's disease

Pharmacoeconomics Unit

Doug Coyle, Karen M. Lee, Mirhad Lončar, Kylie Tingley, Kathryn Coyle, Lanre Medu, Tara Gomes

August 5th, 2015

Executive Briefing

- This report assesses the current evidence for cost-effectiveness of pharmacotherapies for the treatment of Alzheimer's disease (AD) and analyzes the economic impact of alternative changes to the funding status of AD treatments.

- Previously published studies, including six Canadian economic evaluations, were generally supportive of the cost-effectiveness of these drugs. Results, however, should be interpreted with caution due to receipt of industry funding or industry affiliation, a limited range of active treatment comparisons, as well as the age of the evidence base.

- Based on the results of a de novo economic model, donepezil was the most cost-effective monotherapy across all patient subgroups. Memantine monotherapy and rivastigmine-patch were not cost-effective. Combination therapy involving memantine and an AChEI (specifically donepezil) may be cost-effective although there is a great degree of uncertainty around this finding.

- Listing donepezil as general benefit (with a generic price that is 18% of the brand price) and enforcing generic substitution for donepezil would result in reduced expenditure for AChEIs in the treatment of AD. However, strategies increasing access to patients with severe AD or allowing access to the rivastigmine-patch would result in increased expenditure for AChEIs.

- Based on further results of the de novo modelling, a strategy of listing of donepezil as general benefit can be considered cost-effective. Strategies relating to the reimbursement of rivastigmine-patch were not cost-effective. Analysis did not consider reimbursement strategies relating to the coverage of memantine.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADL	activities of daily living
BSC	best supportive care
CAD	Canadian dollars
CEA	cost-effectiveness analysis
CMA	cost-minimization analysis
CUA	cost-utility analysis
DON	donepezil
EQ-5D	European Quality of Life-5 Dimensions
FTC	full time care
GBP	British Pound
GAL	galantamine
HTA	Health Technology Assessment
HUI	Health Utilities Index
ICER	incremental cost-effectiveness ratio
ICUR	incremental cost-utility ratio
KT	Kylie Tingley
ML	Mirhad Lončar
MMSE	Mini Mental State Examination
MOHLTC	Ministry of Health and Long-Term Care (Ontario)
N/A	not applicable
NHSEED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
ODPRN	Ontario Drug Research Policy Network
OWSA	one-way sensitivity analysis
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life year
RCT	randomized controlled trial
RVS	rivastigmine

Acknowledgments

This review was funded by grants from the Ontario Ministry of Health and Long-Term Care (MOHLTC) Health System Research Fund and Drug Innovation Fund. The work was supported by the Institute for Clinical Evaluative Sciences (ICES), a non-profit research institute sponsored by the Ontario MOHLTC, and by the Canadian Institute for Health Information (CIHI). The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources. No endorsement by ICES, CIHI, or the Ontario MOHLTC is intended or should be inferred.

Executive Summary

Research Questions

RQ1. What is the current evidence for the cost-effectiveness of cognitive enhancers, as compared with placebo, other cognitive enhancers, or best supportive care, for the treatment of Alzheimer's disease (AD)?

RQ2. Based on a de novo economic model, what is the cost-effectiveness of cognitive enhancers versus other cognitive enhancers, other therapies or best supportive care for the treatment of AD?

RQ3. What is the budget impact of alternative policies for reimbursing cognitive enhancers versus placebo, other cognitive enhancers, or best supportive care for the treatment of AD?

RQ4. Based on a de novo economic model, what is the cost-effectiveness of alternative policies for reimbursing cognitive enhancers versus for the treatment of AD?

Systematic Review of Published Economic Evaluations

In brief, this review highlights the current published evidence for the comparative cost-effectiveness of pharmacologic treatments for the management of Alzheimer's disease (AD). Given that there were two recently well conducted reviews of economic evaluations related to the use of cognitive enhancers in the treatment of AD, this review assessed the cost-effectiveness evidence since 2010, when the last search was completed by the previous review authors. All economic evaluations selected for inclusion in this updated review either received financial support from a pharmaceutical manufacturer or had some affiliation with industry, and study findings consistently favoured the sponsor's product. The dearth of well-conducted independent analyses relevant to the current decision-making context precluded any inferences regarding the cost-effectiveness of drug therapies for AD treatment in Canada.

The two previous reviews of published economic evidence relating to acetylcholinesterase inhibitor (AChEI) drugs and memantine for treating AD were conducted by the NHS HTA programme and served as the basis for evaluating the cost-effectiveness evidence prior to this update. The first review was published in 2006 and identified a total of 26 studies, most of which comprised European country-specific analyses with a substantial proportion of industry-funded research. An update of this review was then published in 2012 which identified 17 additional studies; many of these studies were also conducted within European settings and were largely funded by drug manufacturers. Overall, studies varied in their modeling approaches as well as the effectiveness data used to model disease progression; there was also variability among the chosen perspectives, although a greater portion of studies adopted a societal perspective. Findings from both reviews were generally supportive of the cost-effectiveness of AChEI drugs and memantine, with some evidence suggesting that treatment may only be cost-effective within certain patient subgroups. However, the large number of country-specific analyses and dominance of industry-funded research limits the applicability of these economic evaluations.

Since 2010, eleven additional published economic evaluations have been identified; of these, 10 were conducted across a range of European settings and there was one Canadian economic analysis. The published evidence comprised nine cost-utility analyses (six Markov models, two DES models, and one MMSE-ADL model), one cost-effectiveness/cost-minimization study (DES model), and one cost-comparison analysis based on trial data. None of these evaluations were free from industry sponsorship

or affiliation, and direct comparisons between active treatments were limited with only two studies comparing two monotherapies and three studies comparing combination therapy to monotherapy. In addition, study findings consistently supported the sponsor's product. As a result, the generalizability of the results of these studies to the current decision-making context was deemed to be poor as they failed to adequately address the research question of interest in this review.

When focusing on Canadian studies specifically, which are likely to be more closely aligned with the current decision-making context and specific research questions, there were a total of six economic evaluations which examined the cost-effectiveness of AChEI medications and memantine in AD patients; yet, five of these studies were published more than 8 to 15 years ago and their findings may not accurately reflect current clinical evidence or cost data. These evaluations were also limited by their narrow research questions and receipt of industry funding or industry affiliation. Only one Canadian study was conducted after 2010 (since the last NHS HTA update). This study examined the cost-utility of memantine+AChEI combination therapy compared with AChEI treatment alone from both the health care payer and societal perspective. The authors found that the concomitant use of memantine and an AChEI was dominant over AChEI monotherapy from both examined perspectives, even when sensitivity analyses adjusted for the clinical characteristics of patients of the observational study upon which analysis was based. Factors limiting the applicability of this study for the specific research question in this review include a lack of transparency in the economic model and clarity surrounding the modeled patient population, not accounting for the effects of treatment waning, as well as the adoption of a seemingly narrow research question and reliance on a single observational study to provide estimates of disease progression. In addition, assumptions regarding the impact of treatment on delay to institutionalization remain unsupported by clinical data. This study is also susceptible to bias due to industry sponsorship and the age of the study may not represent current cost data or clinical practice.

Given the shortcomings within the published literature, limiting the applicability and generalizability of existing cost-effectiveness evidence, a de-novo economic model which incorporates more recent evidence from the Canadian context is required to assess the comparative cost-effectiveness of these pharmacological treatments.

For a detailed report of the review of economic literature relative to this drug class, please refer to Appendix A - A Systematic Review of Economic Evidence.

De novo Economic Evaluation

The objectives of the de novo economic evaluation were to assess the cost-effectiveness of various treatment options for AD compared to each other or no pharmacologic treatment. Options included an AChEI (donepezil, galantamine, or rivastigmine (oral or patch)) alone, memantine alone, or the concomitant use of memantine with an AChEI drug. The patient groups that were considered included mild, moderate, and severe AD patients in the community or in institutional care.

Costs and quality-adjusted life years (QALYs) of AChEI monotherapy or memantine monotherapy and the concomitant use of AChEI with memantine compared with no treatment among elderly patients with AD were assessed using a Markov model. These estimates were then used to estimate the relative cost-effectiveness of alternative reimbursement strategies for the coverage of different pharmacotherapies. Within the Markov model, disease progression was modeled using hybrid states comprising single mini-mental state examination (MMSE) scores and location of care (institution/nursing home or community/home care). Transition probabilities, costs and utility values were informed by the

literature. Detailed deterministic and probabilistic sensitivity analyses were conducted.

In patients with moderate AD in the community, no pharmacologic treatment is the least costly treatment option though it is less effective than all other treatment options except for combination therapy with rivastigmine and memantine. Donepezil in combination with memantine was the most effective strategy and donepezil was the most effective of the monotherapies. At a willingness to pay of less than $12,000 per QALY, no pharmacologic treatment is optimal. If a payer's willingness to pay per QALY is between $12,000 and $29,000, a strategy of initiating donepezil monotherapy is optimal. At a willingness to pay value greater than $29,000 per QALY, a strategy of initiating combination therapy with donepezil and memantine is optimal. The probabilistic sensitivity analysis highlighted the great degree of uncertainty concerning the underlying results, particularly with respect to the effectiveness and cost-effectiveness of combination therapies. Results were similar across the other five patient subgroups.

In conclusion, donepezil was the most cost-effective monotherapy across all patient subgroups. Memantine monotherapy and rivastigmine-patch were not cost-effective. Combination therapy involving memantine and a cognitive enhancer (specifically donepezil) may be cost-effective although there is a great degree of uncertainty around this specific finding.

Budget Impact Analysis

Expenditure for AChEIs used to treat AD has increased from $14 million in 2000 to almost $120 million in 2010. Recently, there has been a reduction in the expenditure for AChEIs to $49 million in 2014 with the introduction of generic products. In 2014, donepezil had the largest market share at 85%, while galantamine had 12% and RVS had 3%.

Without any changes to current reimbursement for AChEIs, expenditure is expected to be $45.4 million in 2017. Listing generic donepezil as general benefit would result in a 12% reduction in expenditure for AChEIs by 2017, assuming between 1% and 10% of users will switch to donepezil.

All other alternative reimbursement strategies would result in an increased expenditure for AChEIs by 2017.

Refer to Appendix C-Budget Impact Analysis for a detailed report of the reimbursement based economic assessment.

Reimbursement Based Economic Evaluation

Based on the de novo economic model developed as above, the cost-effectiveness of alternative policies for reimbursing cognitive enhancers for the treatment of AD were assessed.

Analysis considered five reimbursement strategies:

1. No change to current limited use (LU) listing for AChEIs (status quo).
2. LU listing for AChEIs for mild and moderate AD and exceptional access program (EAP) criteria for rivastigmine-patch.
3. LU listing for AChEIs for patients with mild, moderate, and severe AD.
4. Strategy 2 + 3: LU listing for AChEIs for mild, moderate, and severe AD patients, and EAP criteria for the rivastigmine-patch.
5. General benefit (GB) listing for donepezil and LU listing for oral galantamine and rivastigmine (oral).

Strategy 4 will lead to the greatest QALY gain over Strategy 1 and with the highest costs. The incremental cost per QALY gained for Strategy 5 over Strategy 1 is $12,572. The incremental cost per QALY gained for Strategy 4 over Strategy 5 is $208,528.

Based on the results, Strategy 5 (the listing of donepezil as general benefit, LU for galantamine and rivastigmine) can be considered cost-effective. Strategies relating to the reimbursement of rivastigmine-patch were not cost-effective.

Analysis did not consider the cost-effectiveness of reimbursement strategies with respect to memantine.

Appendices

Appendix A - A Systematic Review of Economic Evidence

Research Question

What is the current evidence for the cost-effectiveness of cognitive enhancers, as compared with placebo, other cognitive enhancers, or best supportive care, for the treatment of Alzheimer's disease (AD)?

Review of Published Literature

Search Strategy and Search Findings

Search Strategy

Two health technology assessments (HTAs) exploring the clinical and cost-effectiveness of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease (AD) were conducted by the National Health Service Technology Assessment programme (NHS HTA) in the UK; one was published in 2006 and an update in 2012.[1] Given that both of these HTAs contained a systematic review of the cost-effectiveness literature relating to pharmacotherapies of direct relevance to the current review, they were used as the basis for assessing health economic evidence identified in the literature prior to February 2010, when the last search was completed by the authors.

A further search of the medical literature was conducted in Ovid MEDLINE (indexed, in-process and other non-indexed citations) and EMBASE Classic & EMBASE from 2010 to present (2015 February 10) in order to capture all relevant literature since the last search was completed by NICE. Key words relating to pharmacologic treatments for AD approved for use in Canada (donepezil, galantamine, rivastigmine, and memantine) were coupled with a standardized search strategy for identifying economic analyses adopted by the National Health Service Economic Evaluation Database (NHS EED). The complete search strategy can be found in Appendix A1: Search Strategy.
Additional citations were retrieved for screening from the Tufts CEA Registry and NHS EED databases. Grey literature was identified through the Canadian Agency for Drugs and Technologies in Health (CADTH) and the National Institute for Health and Care Excellence websites. Finally, reference lists of retrieved studies were hand searched for additional relevant articles.

Search Findings

A total of 579 citations relating to cost-effectiveness of treatments for AD since January 2010 were identified from the initial searches, 544 of which were found through database searching. No additional records were identified from grey literature sources. Following the removal of duplicate records, 496 unique citations were retrieved for screening.

Two reviewers (ML and KT) independently assessed the titles and abstracts of studies identified by the search strategy in order to identify potential articles for critical appraisal. Namely, of the 496 unique records screened, 36 citations were selected for full-text review. A total of 460 records were therefore excluded in the first phase of screening, and an additional 25 records were excluded following assessment of full-text articles. Any disagreements during this two-stage screening process were

resolved through consensus. Figure 1 in Appendix A2 presents the search results, including reasons for exclusion of full-text publications.

Among the 36 references that were retrieved for full-text review, a total of 11 unique studies addressed the objective of the review and were selected for inclusion. No additional potentially relevant studies were identified from hand-searching citations of included papers or manufacturer submissions. A list of excluded studies along with reasons for exclusion is presented in Table 1 of Appendix A3.

Included Studies

A comprehensive list of included studies post 2010 can be found in Table 2 of Appendix A4.

Prior Reviews Conducted by NHS HTA programme (UK)

Review by NHS HTA in 2006

Loveman et al.[2] conducted a systematic review of published economic evaluations focusing on AChEI medications and memantine for the management of AD and identified a total of 26 studies, two of which were available only as abstracts. Approximately 65% of the selected review studies were conducted within European settings (UK, Sweden, Finland, Norway, Spain, The Netherlands, Poland, and France), with seven economic evaluations from the UK alone; the remainder comprised four studies from the US, four Canadian studies, and one Japanese study. Most studies were labelled as CEAs, but also included three CUAs, four CUA/CEA studies, one CMA, one CCA, and one economic evaluation alongside a clinical trial. There was considerable variation in the way studies measured efficacy, with some analyses quantifying efficacy in terms of QALYs gained, while others reported either a delay in disease progression or a reduced time in need of full-time care. Among the selected analyses, 13 adopted a societal perspective, eight were conducted from a health care payer perspective, and two studies presented findings from both the societal and health care payer perspective, while three others did not clearly identify a perspective. Furthermore, over half of the included studies received sponsorship from the pharmaceutical industry and an additional five reported industry affiliation, while seven studies did not disclose any funding support.

The review authors summarized these studies and presented findings separately for each drug: donepezil (11 studies), rivastigmine (5 studies), galantamine (5 studies), and memantine (5 studies). Collectively, however, base-case results for AD treatment with acetylcholinesterase inhibitors suggested that relative to no treatment, AChEI monotherapy was cost saving or cost neutral in 21 of the studies, cost incurring in four studies (donepezil only), and unclear in one donepezil study published only in abstract form. In the economic evaluation studies for memantine, base-case findings across studies revealed that treatment with memantine was consistently cost-saving over time, with increased time spent in an independent state. In general, cost savings occurred in studies adopting a societal perspective, and many of the cost calculations excluded the cost of the drug. Moreover, some studies found active treatments to be only cost-effective for certain patient subgroups. For instance, one study of donepezil and three galantamine studies found these AChEIs to be more cost-effective in moderate AD patients than in mild AD patients, while most subgroup analyses in rivastigmine studies found active treatment to be more cost-effective in mild AD patients as compared with moderate AD patients. In considering the body of cost-effectiveness literature, the authors acknowledge that the transferability of included studies is limited owing to the country-specific analyses and associated differences in methodological approaches, the adopted perspective and effectiveness data used to model disease

progression, as well as the dominance of industry-funded analyses.

Review by NHS HTA in 2012

More recently in 2010 (published in 2012), Bond et al.[1] provided an update of the review of cost-effectiveness literature which identified 17 additional economic analyses regarding the same AD treatments. There were nine economic evaluations published in full, with the rest only available as abstracts. Analogous to the 2006 review, most of the included studies in this updated appraisal were conducted within Europe (UK, Spain, Sweden, Germany, and Norway); additionally, there were two Canadian studies, two Korean studies, and one study each from China, Thailand, and the United States. About half of the included studies were CUAs, and the rest comprised four CEAs – two economic evaluations alongside an RCT and two studies did not state or were unclear in their modeling approach. A societal perspective was adopted in nine economic analyses, as compared with four studies which reported findings solely from the perspective of the health care payer, and another three which adopted both the societal and health care payer perspective; one study did not state the perspective of the analysis. Much like the previous review, most studies were not free from industry funding or affiliation. There were only three independent analyses, and three other studies did not report any funding sources.

Bond et al. summarized these studies and again presented drug-specific results for donepezil (7 studies), rivastigmine (2 studies), galantamine (2 studies), and memantine (6 studies). As a group, base-case results for treatment with AChEI drugs demonstrated that, in comparison with no treatment, AChEI monotherapy was either cost saving or highly cost-effective in 11 studies; however, one independent analysis found donepezil to be cost-effective only for mild AD patients and not cost-effective for those with moderate disease from the perspective of the healthcare payer, and another independent study suggested that donepezil may be a cost-effective treatment, but that considerable uncertainty surrounds the study findings. Unlike many of the included studies which compared active treatment against placebo, there was one abstract-only study which compared the cost-effectiveness of donepezil with high and low dose rivastigmine and no drug treatment. Results of this study found high dose rivastigmine to be more cost-effective than donepezil (10 mg), which in turn was found to be more cost-effective than low dose rivastigmine; however, the authors warn that the lack of detail surrounding this study may not reflect reliable findings. In studies examining the cost-effectiveness of memantine, base-case results found treatment with memantine to be cost-saving or cost-neutral when compared with standard care; conversely, when the concomitant use of memantine and donepezil was compared with donepezil alone, findings suggested that combination therapy lead to higher benefits with reduced healthcare costs.

Although the review team was able to identify additional studies which addressed the cost-effectiveness of AChEIs and memantine in the management of AD at all stages of disease, and while these studies were generally supportive of the cost-effectiveness of these pharmacologic treatments, the review authors pointed out that most studies reapplied modeling approaches considered as part of the previous cost-effectiveness review and were therefore felt to add little to this update. A number of limitations were also presented, including poor transferability of studies as a result of jurisdiction-specific analyses and the fact that many studies were supported by the drug manufacturers.

Review and Critical Appraisal of Included Studies Post 2010

Included Studies

Among the 11 economic evaluations selected for inclusion, 10 were conducted in European countries (France, Germany, Netherlands, Norway, Sweden, Switzerland, UK),[3-12] and there was one Canadian study.[13] Half of the economic analyses conducted in Europe came from the UK and Germany.[3-5,7,10] Furthermore, 82% of included studies received direct sponsorship from the pharmaceutical industry,[3-5,7,9-13] with Lundbeck as the most common sponsor,[9-11,13] while the remaining two studies were non-funded but reported affiliation to industry.[6,8] A brief overview of the study characteristics of these 11 economic analyses is presented in Table 3 of Appendix A5.

Six of the included studies were cost-utility analyses which applied a Markov state transition model for estimating costs and outcomes,[6,8-11,13] and two additional cost-utility analyses used a discrete event simulation model to compare the cost-effectiveness of different pharmacotherapies.[3,5]. There was one additional cost-utility analysis, but the authors did not report the type of model used in the study; rather, there was only mention of a comparison of two distinct models, one based on MMSE data alone, and a revised model also incorporating ADL data (MMSE-ADL model).[7] Moreover, one study was a cost-effectiveness/cost-minimization analysis conducted using a discrete simulation model,[4] and the remaining analysis was a cost-consequence analysis based on a 6-month RCT which included 80 patients.[12] The time horizon considered in these studies spanned the period form 6 months[12] to 10 years,[4,5] with the majority of analyses adopting either a 5- or 7-year timeframe. Moreover, 82% of included studies were conducted from both the health care payer and societal perspectives.[3-9,11,13] The CCA by Wimo et al. (2012) exclusively adopted a societal perspective,[12] while indirect costs to patients and their families were excluded from the CUA by Rive et al (2010).[10]

Comparators were most frequently considered as active treatment options versus no treatment or placebo.[3,6,7,9,10,12] Analyses considered to a much lesser extent the direct comparison of active treatments against each other, or compared to combination therapy. In these cases, comparison consisted primarily of combination therapy versus a monotherapy option,[8,11,13] or two active treatments compared to no treatment.[4,5]

The target populations across studies varied mostly by level of disease severity, as measured by the MMSE. Namely, five studies modeled patients with mild to moderate AD exclusively (i.e. MMSE ≥ 10),[3-5,7,12] while three evaluations modeled moderate to severe AD patients[6,9,10]. Another three studies did not specify the level of disease progression in the modeled patient population;[8,11,13] in two of these cases, patients were only described as those who had not been previously institutionalized.[11,13]

Most studies expressed their outcomes in terms of quality-adjusted life years (QALYs) gained;[3,5-13] however, one analysis assessed cost-effectiveness via clinical outcomes such as time not spent in severe state of disease, time in institutional care, and caregiver time,[4] and another trial-based analysis measured costs of ADL lost.[12] Utility estimates for modeled patient groups were largely derived from previously published literature reporting on the EQ-5D instrument, and literature reporting on the SF-36 tool was used to derive utilities for caregivers.

Collectively, findings reported in the selected review articles were quite variable. However, when comparing studies which evaluated the cost-effectiveness of an active treatment against no treatment

or placebo, results of these studies were consistently positive toward the use of the active treatment as the most cost-effective option. Conversely, studies which examined a combination therapy in comparison to a single active treatment, the use of dual therapy always dominated the monotherapy option. A detailed synthesis of the interventions and results of the included economic evaluations is presented in Table 4 of Appendix A5.

Concerns and Considerations Relating to the Literature

Canadian Content

There are six published economic evaluations which examined the comparative cost-effectiveness of pharmacotherapies for AD from a Canadian perspective. Unfortunately, five of these studies were published more than 8 to 15 years ago and therefore might not reflect the current clinical evidence base or cost data. In addition, none of these studies are free from industry funding or affiliation.

Sponsorship and Industry Affiliated Studies

In the previous reviews conducted by the UK NHS HTA programme, the majority of studies were sponsored by manufacturers or had ties with industry. There were only three independent analyses within the updated 2012 review, and a total of 10 studies from both publications that did not report any funding sources.

Among the 11 additional studies selected for inclusion in this post-2010 update, none were independent of industry funding or affiliation. Nine studies received direct financial support from pharmaceutical manufacturers and two other studies had some link to industry. These studies may be susceptible to biases and limitations that have been found in manufacturer-sponsored evaluations.[14]

Canadian Studies

There were six published economic evaluations which examined the comparative cost-effectiveness of pharmacologic treatments for AD from a Canadian perspective; however, most of the studies are quite dated, and only one was conducted after January 2010. A summary of these studies with an assessment of their limitations is provided below, from most to least recent publication date.

Lachaine et al. (2011)

In 2011, Lachaine et al. conducted a cost-utility analysis, sponsored by Lundbeck, comparing the concomitant use of memantine and an AChEI with the use of AChEI monotherapy in AD patients who had not previously been institutionalized. The severity of disease in the modeled patient group was not specified, but the characteristics of patients were adopted from an observational study by Lopez et al. (2009). The evaluation was conducted using a three-state Markov model run over a 7-year time horizon with annual cycles. The perspectives adopted in the analysis were that of the Canadian health care payer as well as a societal perspective, with costs presented in 2010 Canadian dollars.

Treatment effectiveness data were derived from a single observational study and evaluated in terms of the impact on time to nursing home admission (institutionalization). In addition, the probability of dying was estimated from Canadian survival tables; however, it was assumed that treatment had no effect on survival. The final outcome of the analysis was expressed in terms of quality-adjusted life-years (QALYs)

gained, and utility values associated with institutionalization and non-institutionalization were taken from the Canadian AHEAD (Assessment of health economics in Alzheimer's disease) model by Getsios et al. (2001). The robustness of the results was evaluated by virtue of both deterministic and probabilistic sensitivity analyses.

Base case results demonstrated that combination therapy with memantine and an AChEI was a dominant strategy over the use of AChEI alone from both a health care payer and societal perspective. Complementary analyses adjusting for age and sex of patients in the Lopez et al. study (2009) were also conducted and demonstrated that the concomitant use of memantine with an AChEI remained both less costly and more effective than AChEI monotherapy. Results of the sensitivity analyses confirmed robustness of the base-case results. In particular, AChEI+memantine was dominant in 100% and in 99.8% of MCS iterations from the health care payer and societal perspectives, respectively.

Overall, this study appeared well-designed and adopted a Canadian perspective. However, certain factors may limit the applicability and generalizability of the results. Namely, there is a lack of transparency within the model, and it is unclear whether the patient population reflects individuals with a specific disease severity. There is further ambiguity surrounding the AChEI comparator since it remains unclear whether this is meant to represent donepezil, rivastigmine, and galantamine separately or consider them collectively as a drug class. Given that the clinical parameters used in the model are entirely based on findings from a single observational study, any limitations of this study would influence the generalizability of the results. In addition, improvements in cognitive functioning with treatment, as measured by the MMSE metric, were associated with delayed institutionalization; yet, this relationship has not been directly demonstrated in clinical trials. Moreover, treatment waning was not accounted for in the modeling, further limiting the results. Finally, this study is not free from industry sponsorship, and the age of the study may not be reflective of the current clinical evidence base and cost data.

Gagnon et al. (2007)

Gagnon et al. examined the cost-effectiveness of memantine in comparison with standard care (without AChEI treatment) in moderate-to-severe AD patients. A Markov-based model with health states based on dependence in ADL and severity of disease (as measured by MMSE) was run over a 2-year time horizon with 6-month cycles. Progression of disease with memantine was modeled based on data obtained from a 26-week RCT, and costs were derived from Canadian sources including the Canadian Study of Health and Aging (CSHA). The analysis adopted a societal perspective incorporating costs of unpaid care, with all costs presented in 2005 Canadian dollars.

Results of the base-case analysis suggested that memantine monotherapy was dominant over standard care as it was both more effective and less costly. Namely, treatment with memantine was estimated to produce an additional 1.1 months free of complete dependence, 0.031 additional QALYs, and cost savings of $1276 over the 2-year time period, as compared with standard care alone. When subjected to probabilistic sensitivity analyses, findings revealed that there was a 83.3% probability that memantine would be cost-neutral, and that the probability of being cost-effective increased to 89.5% and 96.2% for WTP thresholds of $20,000/QALY gained and $100,000/QALY gained, respectively. While the authors concluded that treatment with memantine leads to health benefits with no additional costs as compared with standard care, some factors may limit the use of this study in aiding decision-making. Namely, there was a lack of transparency in the economic model, a disregard for other AChEI therapy

options, and the effects of treatment waning were overlooked. In addition, this study is not free from industry sponsorship, and the age of the study may not reflect current clinical and cost data.

Feldman et al. (2004)

Feldman et al. conducted a cost-comparison analysis comparing the use of donepezil (5-10 mg) with placebo in moderate to severe AD patients. The analysis was conducted alongside an RCT (MSAD study, n=290) which spanned three countries (Canada, Australia, and France) over a 24-week time frame, with 65% of recruited patients receiving care in Canada. Costs were derived from Canadian sources using the Canadian Utilization of Services Tracking (CAUST) questionnaire, which assesses dementia-specific resource use. The analysis was conducted from a societal perspective, with costs presented in 1998 Canadian dollars.

Findings revealed that the societal cost per patient was $9904 in the donepezil group and $10,236 in the placebo group, representing cost savings of $332 per patient. Costs were reduced to $4355 and $4321 in the donepezil and placebo groups, respectively, when caregiver costs were excluded from the analysis. Although the authors concluded that donepezil was cost saving, the applicability of this study is limited due mainly to factors related to the trial-based nature of this analysis. These include the reliance on data from a single study for quantifying effectiveness, restricted choice of relevant comparators, a truncated time horizon, and difficulty in generalizing results to all AD patients in the current decision context. This study was also funded by the pharmaceutical industry, and the age of the study may not reflect the current clinical evidence base or cost data.

Getsios et al. (2001)

Getsios et al. compared the cost-effectiveness of galantamine (24 mg) with non-pharmacological treatment in patients with mild to moderate AD from a Canadian health care payer perspective. The evaluation was conducted using the three-state AHEAD model (pre-full time care (pre-FTC), FTC and death) which mainly uses US data to populate the model, and run over a 10-year time horizon. Efficacy data was derived from two 6-month placebo controlled trials, and costs included within the model were limited to costs of with formal care, such as the costs associated with physician visits, emergency room visits, hospitalizations and medications, and the costs of institutionalization and paid home help. Resource use for the initial six month period of the model was derived from the clinical trials; for the long-term modeling portion, the Canadian Study of Health and Aging was used. Costs were derived from Quebec healthcare system resources and all costs were presented in 1999 Canadian dollars.

Base-case results demonstrated that galantamine was associated with a 5.3% increase in time spent in the pre-FTC state and a decrease of 9.9% in time spent in FTC in patients with mild to moderate disease. Conversely, for patients with moderate disease, time in pre-FTC care increased 10.1% and time in FTC decreased 11.2%. Furthermore, results showed that per-patient costs were $788 lower in the galantamine treatment group as compared with the no treatment group when considering all patients and $3718 lower when considering only moderate AD patients. While findings of this analysis are robust to changes in modeling assumptions, results should be interpreted with cautions as certain factors may limit the utility of this study in aiding decision-making. One limitation is the age of the study, given that it was completed over 14 years ago. Moreover, there is a lack of consideration for other pharmacologic treatments, and waning of benefits was only explored in a sensitivity analysis. In addition, the inclusion of paid home care is a cost that is generally not borne by the Canadian health care system, and

assumptions regarding a correlation between slowed decline in cognitive function and both a delay in need for FTC and reduced duration of FTC were not measured within the clinical trials. Finally, although the study did not cite any financial support, the authors of this study are employees of a consulting firm which completed two previous analyses that received pharmaceutical industry sponsorship.

Hauber et al. (2000)

Hauber et al. conducted a cost-consequence analysis to estimate the potential per-patient cost savings associated with a delay in transition to more severe stages of AD in patients receiving rivastigmine (1-4 mg/day or 6-12 mg/day), as compared with no treatment. Deterioration in disease was modeled over a 2 year time horizon in three patients subgroups (mild, mild-to-moderate, and moderate AD) using a parametric hazard model of disease progression based on MMSE scores from two rivastigmine clinical trials. The analysis was conducted from a societal perspective which incorporated costs of nursing home care, use of medications, caregivers' use of community support services, and unpaid caregiver time; all costs are presented in 1997 Canadian dollars.

Results of the base-case analysis indicated that treatment with rivastigmine is expected to delay the transition of mild AD patients to a more severe disease stage by 188 days, mild to moderate AD patients by 106 days, and moderate AD patients by 44 days. These delays were associated with cost savings of $6.44 per patient per day for mild AD patients and $4.93 per patient per day for all patients combined. Medication costs are excluded from these estimates given that rivastigmine was not marketed at the time of the study. Factors which may limit the utility of this study in facilitating decision-making include the narrow research question, the lack of inclusion of the price of rivastigmine, and the very short time horizon. In addition, this study received industry sponsorship and it is quite dated given that it was completed almost 15 years ago.

O'Brien et al. (1999)

In 1999, O'Brien et al. conducted a cost-effectiveness analysis comparing donepezil (5 mg) versus no treatment in patients with mild to moderate AD. A decision tree with a Markov process was used to model the progression of disease and to estimate the costs and benefit of treatment over a 5-year time horizon with 6-month cycles. Efficacy was measured as the increased number of years per patient in a non-severe disease state (MMSE≥10), and costs were derived from Canadian sources including the Canadian Study of Health and Aging. The modeled patient cohort adopted the clinical characteristics of patients in a donepezil RCT, which were weighted by the population in an Alberta-based AD clinic. The analysis was conducted from the perspective of the health care payer, as well as the societal perspective, which accounted for the value of unpaid caregiver time. All costs are presented in 1997 Canadian dollars.

Base-case results revealed that treatment with donepezil is associated with societal costs of $80,305, as compared with $81,187 for no pharmacological treatment, representing a cost saving of $882 per patient over the over the five year time period, while the expected years per patient in a non-severe disease state with donepezil treatment are 2.41 in comparison to 2.21 with no treatment, giving an incremental benefit of 0.2 years or approximately 2.4 months in non-severe AD states. Donepezil treatment was therefore dominant over no treatment as it was both less costly and more effective. Factors which may limit the utility of this study in aiding decision-making include the narrow research question including the restricted choice of comparators, receipt of industry funding, and the age of the

study given that it was completed over 15 years ago.

Non-Canadian Studies

Independent studies

Two independent economic analyses were conducted by the NHS HTA programme as part of the aforementioned HTA reports published in 2006 and 2012. Study findings are summarized below.

NHS HTA Economic Analyses (2006, 2012)

As part of the 2006 NHS HTA report, the Southampton Health Technology Assessment Centre (SHTAC) group conducted a cost-utility analysis to compare the cost-effectiveness of donepezil, rivastigmine, and galantamine with standard care in mild to moderately severe AD patients. A three-state Markov-based model (pre-full time care (FTC), FTC, and death) was used to simulate disease progression over a course of 5 years from the perspective of the UK healthcare system. Data on natural history of disease came from a UK-based patient cohort, and efficacy data was sourced from the clinical systematic review which assessed the effect of treatment on cognitive function. Utility values were assigned to each of the model's health states based on mapping cognitive function to utility values found in the literature, and costs associated with pre-FTC, FTC in the community, and FTC in an institution were obtained from published UK sources.

Results of the base-case analysis showed that in comparison with standard care, galantamine was associated with the greatest increase in QALYs of 0.039, followed by gains of 0.037 and 0.036 QALYs for rivastigmine and donepezil, respectively. The highest per-patient incremental cost over 5 years was attributed to donepezil with a value of £2895 (1.00 GBP = 1.91 CAD), as compared with standard care; conversely, galantamine was associated with an incremental cost of £2647 per patient, and rivastigmine with £2121. Therefore, the resulting ICERs for AChEIs in comparison with no pharmacologic treatment ranged from £57,000 to £80,000 per QALY gained. Base-case results were sensitive to changes in assumptions within the DSA, and estimated ICERs consistently failed to drop below the generally accepted WTP threshold of £30,000/QALY gained in all scenario analyses. It was further estimated by virtue of a PSA that there was a less than 10% probability that the treatments were cost-effective at a WTP threshold of £30,000/QALY gained. Based on the cost-effectiveness evidence, the authors concluded that funding of pharmacologic treatments for AD should be restricted to patients with moderate AD given that estimates of cost-effectiveness exceeded the commonly accepted WTP threshold when considering all patient subgroups. A number of concerns were raised with respect to the modeling exercise within this analysis; these criticisms were subsequently addressed in the economic analysis published in 2012.

Within the more recent 2012 NHS HTA, a new cost-utility model was developed by the Peninsula Technology Assessment Group (PenTAG) to re-examine the cost-effectiveness of each of the AChEI drugs in comparison with standard care, incorporating changes that would address the limitations of the original analysis. The updated Markov model included three health states: pre-institutionalization, institutionalization, and an absorbing death state. Unlike the previous SHTAC model, deterioration in disease was modeled over a 20-year time horizon, and both treatment costs and utilities were accumulated from the moment of treatment onset. Moreover, time to institutionalization and to death

was estimated by way of a retrospective cohort analysis of UK patients diagnosed with AD or vascular dementia, and the proportions of patients who were institutionalized at different levels of cognitive functioning (as measured by MMSE) was derived from the UK literature. Delay in time to institutionalization as a result of treatment was predicted by both MMSE and ADL scores. Efficacy data were derived from 6-month clinical trials and benefits were assumed to decline after this period at a rate parallel to those not receiving treatment. Finally, utility values found in the literature were mapped onto MMSE scores, and a UK-based study was used to inform the model's cost parameters.

Base-case findings revealed that all treatments produced greater QALYs than standard care: donepezil was associated with the most QALYs gained (1.619), followed by galantamine (1.617) and by rivastigmine capsules and patches (1.613 and 1.616, respectively). Costs of treatment associated with each AChEI were lower than the costs of standard care (standard care: £70,212; rivastigmine capsule: £69,678; donepezil £69,624; rivastigmine patch: £69,598; galantamine: £69,592). Treatment with galantamine was dominant over standard care and rivastigmine, and donepezil treatment generated an ICER of £17,900/QALY gained as compared with galantamine. PSA results did not identify any one treatment as having a significantly greater probability of being cost-effective than another. While considerable uncertainty remained within the estimates of cost-effectiveness, the authors concluded that assuming AChEIs have no effect on survival, there drugs may be cost-effective at a WTP threshold of £30,000/QALY in the treatment of mild to moderate AD.

Industry-sponsored and industry-affiliated studies

There were 10 non-Canadian studies published after 2010 which received financial support from the pharmaceutical industry or whose authors disclosed industry affiliation. Eight of these were cost-utility analyses[3,5-11], one was a cost-effectiveness/cost-minimization analysis[4], and another was a cost-consequence analysis[12]. Markovian health state transition modeling underpinned one half of these evaluations,[6,8-11] while three studies developed a discrete event simulation model for estimating costs and outcomes,[3-5] one study adopted a trial-based analysis,[12] and another study did not report the type of model used.[7] Furthermore, time horizons variably spanned the period from 6 months[15] to 10 years,[4,5] with 40% of analyses adopting a 5-year time frame.[6,7,9,10] Eighty percent of the industry-sponsored or industry-affiliated studies were conducted from both the health care payer and societal perspectives;[3-9,11] conversely, Wimo et al. (2012) and Rive et al. (2010) only considered the societal perspective and that of the health care payer, respectively.[10,12]

In the three studies sponsored by Lundbeck,[9-11] results were positive and favourable toward memantine or the concomitant use of memantine and an AChEI. Similarly, results of two non-funded studies whose authors reported previous affiliation with Lundbeck suggested that memantine or memantine+AChEI combination therapy were less costly and more effective than competing alternatives or standard care.[6,8] Moreover, treatment strategies involving galantamine resulted in greater reductions in time spent in institutionalized care, time spent in a severe disease state, and in caregiver time, or showed no significant difference in cost between patients receiving placebo (cost-neutral), as evidence by two studies sponsored by Janssen-Cilag and Janssen Pharmaceutica, respectively.[4,12] In the two studies which received sponsorship from pharmaceutical company Eisai,[3,4] results consistently demonstrated dominance of donepezil over memantine or no treatment. Finally, the CUA sponsored by Novartis revealed the most cost-effective treatment strategy to be rivastigmine patch, as compared with rivastigmine capsule or best supportive care.[7] On the whole, the manufacturer's product appears to be favoured in most cases. This finding is not surprising given that skew in industry-funded

pharmacoeconomic studies is well documented.[14]

Overall Conclusions

In brief, the majority of studies identified in this updated review (post-2010) are of limited applicability to the current Canadian setting. All of the included studies were either industry-sponsored or linked to industry. Only one Canadian study was published after 2010, and this study was sponsored by Lundbeck. Previous reviews by the NHS HTA programme identified a total of five Canadian economic analyses; however, all studies are fairly outdated and none were independently conducted.

Cost-effectiveness evidence suggests that well-designed independent analyses from the Canadian perspective are lacking; as a result, de novo modeling is required to address this evidence gap.

Appendix A1: Search Strategy

The following is the search strategy used in Ovid interfaces MEDLINE and EMBASE.

Embase Classic+Embase 1947 to 2015 February 10, **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)** 1946 to Present (2015 February 10)

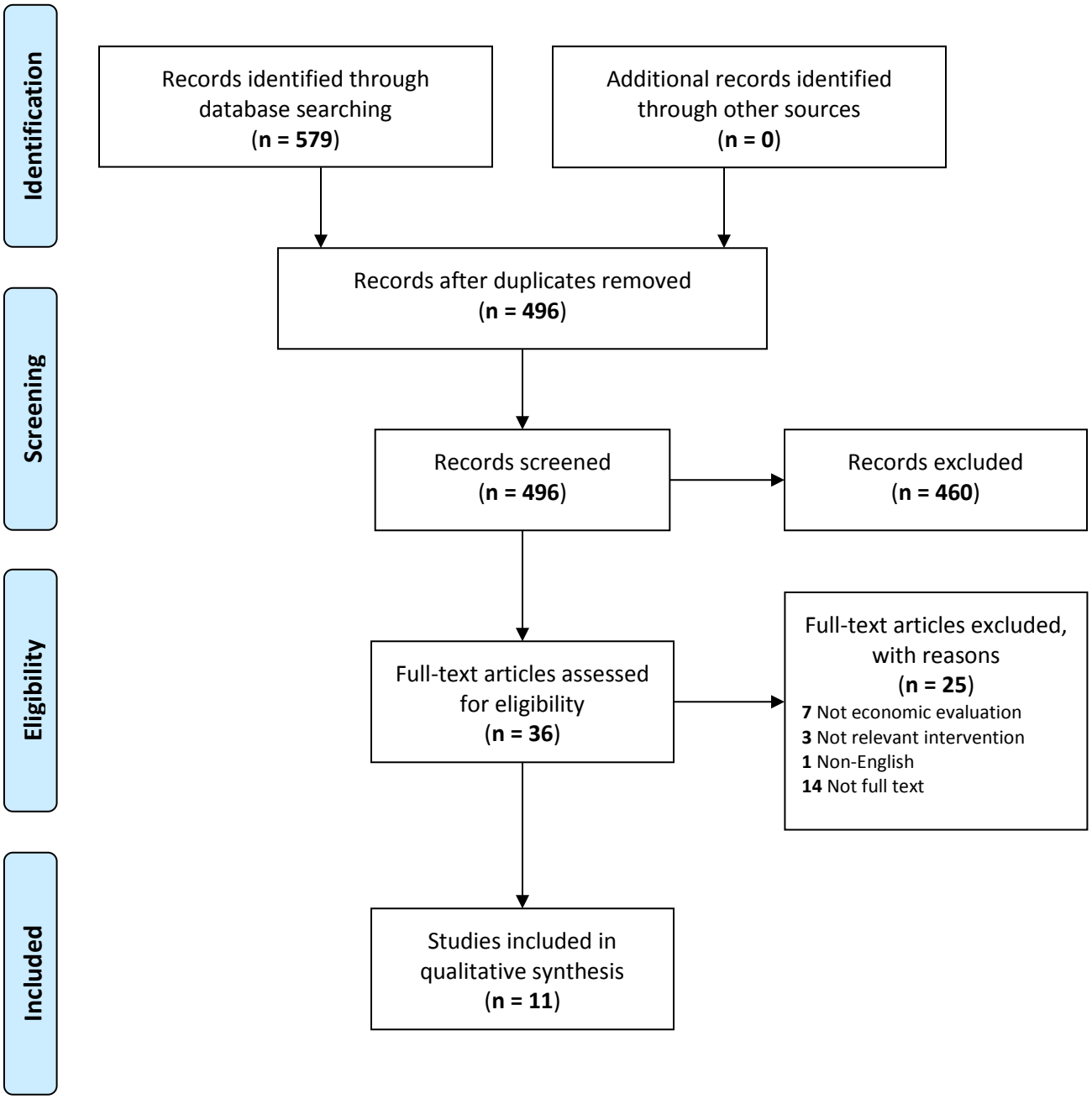
1. alzheimer$.mp.
2. Alzheimer Disease/
3. 1 or 2
4. abixa.tw.
5. aricept.tw.
6. (acetylcholinesterase adj inhibitor$).mp.
7. axura.tw.
8. akatinol.tw.
9. (anticholinesterase? or anti-cholinesterase?).tw.
10. cognitive adjenhanc$.mp.
11. (cholinesterase adj inhibitor$).mp.
12. ChEI.tw.
13. donepezil.mp.
14. ebixa.tw.
15. eranz.tw.
16. exelon.tw.
17. galant?amin$.tw.
18. lycoremine.tw.
19. memantin$.tw.
20. memox.tw.
21. namenda.tw.
22. nimvastid.tw.
23. nivalin$.tw.
24. "N-Methyl-D-aspartic acid receptor antagonist$".tw.
25. prometax.tw.
26. razadyne.tw.
27. reminyl.tw.
28. rivastigmine.mp.
29. exp Cholinesterase Inhibitors/
30. Galantamine/
31. Memantine/
32. Galantamin.rn.
33. Memantine.rn.
34. Donepezil.rn.
35. Donepezil Hydrochloride.rn.
36. Rivastigmine.rn.
37. or/4-36
38. 3 and 37
39. Economics/

40. exp "Costs and Cost Analysis"/
41. "Value of Life"/
42. exp Economics, Hospital/
43. Economics, Medical/
44. Economics, Nursing/
45. Economics, Pharmaceutical/
46. or/39-45
47. (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
48. (expenditure$ not energy).ti,ab.
49. (value adj1 money).ti,ab.
50. budget$.ti,ab.
51. or/47-50
52. 46 or 51
53. 38 and 52
54. alzheimer$.mp.
55. Alzheimer disease/
56. 54 or 55
57. abixa.tw.
58. aricept.tw.
59. acetylcholinesteraseadj inhibitor$.tw.
60. axura.tw.
61. akatinol.tw.
62. (anticholinesterase? or anti-cholinesterase?).tw.
63. cognitive adjenhanc$.mp.
64. (cholinesterase adj inhibitor$).mp.
65. ChEI.tw.
66. donepezil.mp.
67. ebixa.tw.
68. eranz.tw.
69. exelon.tw.
70. galant?amin$.tw.
71. lycoremine.tw.
72. memantin$.tw.
73. memox.tw.
74. namenda.tw.
75. nimvastid.tw.
76. nivalin$.tw.
77. "N-Methyl-D-aspartic acid receptor antagonist$".tw.
78. prometax.tw.
79. razadyne.tw.
80. reminyl.tw.
81. rivastigmine.mp.
82. exp cholinesterase inhibitor/
83. donepezil/ or donepezil plus memantine/
84. galantamine/

85. memantine/
86. rivastigmine/
87. 357-70-0.rn.
88. 19982-08-2.rn.
89. 120011-70-3.rn.
90. 120014-06-4.rn.
91. rivastigmine.rn.
92. or/57-91
93. 56 and 92
94. health economics/
95. exp economic evaluation/
96. exp "health care cost"/
97. exp pharmacoeconomics/
98. or/94-97
99. (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
100. (expenditure$ not energy).ti,ab.
101. (value adj2 money).ti,ab.
102. budget$.ti,ab.
103. or/99-102
104. 98 or 103
105. 93 and 104
106. 53 or 105
107. remove duplicates from 106
108. limit 107 yr="2010-current"

Appendix A2: Results of Search

Figure 1. Flow diagram of the selection process for potentially relevant studies.



Appendix A3: List of Excluded Studies

Table 1. List of excluded studies and reasons for exclusion.

Study Reference	Reason for exclusion
Menchola M, Weiss BD. Addressing Alzheimer's: A pragmatic approach. Journal of Family Practice. 2015;64(1):10-8.	Not economic evaluation
Guo S, Getsios D, Revankar N, Xu P, Thompson G, Bobula J, et al. Evaluating Disease-Modifying Agents: A Simulation Framework for Alzheimer's Disease. PharmacoEconomics. 2014;32(11):1129-39.	Not relevant intervention
Bae J. Economic evaluation of alzheimer [abstract]. Value in Health Conference: ISPOR 17th Annual European Congress Amsterdam Netherlands. 2014;17(7):A769.	Not full text
Thibault CSL, Stillman IO, Chen S, Getsios D, Proskorovsky I, Hernandez L, et al. Cost-effectiveness of memantine extended release for treatment of moderate-to-severe Alzheimer's disease in the united states [abstract]. Alzheimer's and Dementia Conference: Alzheimer's Association International Conference 2014 Copenhagen Denmark. 2014;10:596-7.	Not full text
Benkovic V, Mimica N, Stevanovic R. Pharmacoeconomic modelling of alzheimer's disease-assessment of memantine in treating moderate to severe alzheimer patients [abstract]. Acta Clinica Croatica, Supplement Conference: 51st International Neuropsychiatric Pula Congress, INPC 2011 Pula Croatia. 2011;50:104.	Not full text
Chen TS, Lang HC. Cost-effectiveness analysis of donepezil and rivastigmine for mild to moderate alzheimer's disease in taiwan [abstract]. Value in Health Conference: ISPOR 18th Annual International Meeting New Orleans, LA United States. 2013;16(3):A104.	Not full text
Skoldunger A, Johnell K, Winblad B, Wimo A. Mortality and treatment costs have a great impact on the cost-effectiveness of disease modifying treatment in Alzheimer's disease - a simulation study. Current Alzheimer Research. 2013;10(2):207-16.	Not relevant intervention
Knapp M. Future of dementia care: An economic perspective. Neurodegenerative Disease Management. 2013;3(1):23-6.	Not economic evaluation
Skoldunger A, Johnell K, Winblad B, Wimo A. Assumptions of mortality have a great impact on the cost-effectiveness of disease- modifying drugs in AD [abstract]. Journal of Nutrition, Health and Aging Conference: 5th Conference Clinical Trials on Alzheimer's Disease Monte Carlo Monaco. 2012;16(9):796.	Not full text
Hyde C, Peters J, Bond M, Rogers G, Hoyle M, Anderson R, et al. Evolution of the evidence on the effectiveness and cost-effectiveness of acetylcholinesterase inhibitors and memantine for Alzheimer's disease: Systematic review and economic model. Age and Ageing. 2013;42(1):14-20.	Not economic evaluation
Lachaine J, Beauchemin C, Legault M, Le LA. Economic evaluation of the impact of memantine on time to nursing home admission in the treatment of Alzheimer's disease [abstract]. Value in Health Conference: 15th Annual International Meeting of the International Society for Pharmacoeconomics and Outcomes Research, ISPOR 2010 Atlanta, GA United States. 2010;13(3):A140.	Not full text
Permsuwan U, Niwatananun W, Pimkrai A. Cost-utility analysis of donepezil for the treatment of alzheimer's disease in Thailand [abstract]. Value in Health Conference: ISPOR 5th Asia-Pacific Conference Taipei Taiwan (Republic of China). 2012;15(7):A648.	Not full text

Study Reference	Reason for exclusion
Pfeil A, Szucs T. Economic evaluation of the combination therapy of a cholinesterase inhibitor and memantine in Alzheimer's dementia in Switzerland [abstract]. Alzheimer's and Dementia Conference: Alzheimer's Association International Conference 2012 Vancouver, BC Canada. 2012;8(4 Suppl 1):387.	Not full text
Stefanacci RG. The costs of Alzheimer's disease and the value of effective therapies. The American journal of managed care. 2011;17()(pp S356-362), 2011. Date of Publication: Nov 2011.):S356-S362.	Not economic evaluation
Cognitive enhancers provide some benefits in patients with moderate to severe Alzheimer's disease. Drugs and Therapy Perspectives. 2011;27(4):9-12.	Not economic evaluation
Sandner F. Treatment with memantine according to current guidelines: Effectiveness and cost-saving in Alzheimer's dementia. Journal fur Pharmakologie und Therapie. 2011;20(1):18-20.	Non-English
Knoth R, Bentley T, Richardson S, Ramos H. Cost-effectiveness of donepezil 23 MG in the treatment of moderate to severe Alzheimer's disease from a us payor perspective [abstract]. Alzheimer's and Dementia Conference: Alzheimer's Association International Conference, AAIC 11 Paris France. 2011;7(4 Suppl 1):S797.	Not full text
McKeage K. Spotlight on memantine in moderate to severe alzheimers disease. Drugs and Aging. 2010;27(2):177-9.	Not economic evaluation
Kasuya M, Meguro K. Health economic effect of donepezil treatment for CDR 0.5 converters to Alzheimer's disease as shown by the Markov model. Archives of Gerontology and Geriatrics. 2010;50(3):295-9.	Not relevant intervention
Gavrilova S, Kalyn Y, Gerasimov N, Gantman M. Pharmacoeconomic aspects of dementia therapy [abstract]. European Psychiatry Conference: 18th European Congress of Psychiatry Munich Germany. 2010;25.	Not full text
Rive B, Grishchenko M, Guilhaume C, Katona C, Lamure M, Livingston G, et al. Cost-effectiveness of memantine in the treatment of moderate and severe alzheimer's disease patients with agitation, aggression and psychosis-The UK example [abstract]. Value in Health Conference: ISPOR 13th Annual European Congress Prague Czech Republic. 2010;3(7):A452.	Not full text
Touchon J, Lachaine J, Beauchemin C, Crochard A, Rive B, Bineau S. Memantine delays the admission of alzheimer's disease patients to nursing home: Cost-effectiveness analysis in France [abstract]. Value in Health Conference: ISPOR 13th Annual European Congress Prague Czech Republic. 2010;13(7):A390-A391.	Not full text
Guo S, Hernandez L, Wasiak R, Gaudig M. Modeling the clinical and economic implications of galantamine in the treatment of mild to moderate alzheimer's disease in Germany [abstract]. Value in Health Conference: ISPOR 13th Annual European Congress Prague Czech Republic. 2010;13(7):A390.	Not full text
Turongkaravee S. Cost-utility analysis of cholinesterase inhibitors in the treatment of mild to moderate Alzheimer's disease [abstract]. Value in Health Conference: ISPOR 4th Asia-Pacific Conference Phuket Thailand. 2010;13(7):A502.	Not full text
Oremus M, Tarride JE. Modeling cost-effectiveness of pharmaceuticals in Alzheimer's disease. Expert rev. 2012 Jun;pharmacoecon. outcomes res.. 12(3):275-7.	Not economic evaluation
Menchola M, Weiss BD. Addressing Alzheimer's: A pragmatic approach. Journal of Family Practice. 2015;64(1):10-8.	Not economic evaluation

Appendix A4: List of Included Studies

Table 2. List of included studies within the review.

Ref. #	Study Reference
8	Pfeil AM, Kressig RW, Szucs TD. Alzheimer's dementia: budget impact and cost-utility analysis of a combination treatment of a cholinesterase inhibitor and memantine in Switzerland. Swiss medical weekly. 2012;142()(pp w13676), 2012. Date of Publication: 2012.):w13676.
12	Wimo A, Gaudig M, Schauble B, Jedenius E. The economic impact of galantamine vs placebo: An analysis based on functional capacity in a Swedish cohort study. Journal of Medical Economics. 2012;15(4):786-91.
9	Rive B, Aarsland D, Grishchenko M, Cochran J, Lamure M, Toumi M. Cost-effectiveness of memantine in moderate and severe Alzheimer's disease in Norway. International Journal of Geriatric Psychiatry. 2012;27(6):573-82.
5	Hartz S, Getsios D, Tao S, Blume S, Maclaine G. Evaluating the cost effectiveness of donepezil in the treatment of Alzheimer's disease in Germany using discrete event simulation. BMC neurology. 2012;12.
13	Lachaine J, Beauchemin C, Legault M, Bineau S. Economic evaluation of the impact of memantine on time to nursing home admission in the treatment of Alzheimer disease. Canadian Journal of Psychiatry. 2011;56(10):596-604.
6	Hoogveldt B, Rive B, Severens J, Maman K, Guilhaume C. Cost-effectiveness analysis of memantine for moderate-to-severe Alzheimer's disease in The Netherlands. Neuropsychiatric Disease and Treatment. 2011;7(1):313-7.
7	Nagy B, Brennan A, Brandtmuller A, Thomas SK, Sullivan SD, Akehurst R. Assessing the cost-effectiveness of the rivastigmine transdermal patch for Alzheimer's disease in the UK using MMSE- and ADL-based models. International Journal of Geriatric Psychiatry. 2011;26(5):483-94.
10	Rive B, Grishchenko M, Guilhaumegoulant C, Katona C, Livingston G, Lamure M, et al. Cost effectiveness of memantine in Alzheimer's disease in the UK. Journal of Medical Economics. 2010;13(2):371-80.
4	Guo S, Hernandez L, Wasiak R, Gaudig M. Modelling the clinical and economic implications of galantamine in the treatment of mild-to-moderate Alzheimer's disease in Germany. Journal of Medical Economics. 2010;13(4):641-54.
3	Getsios D, Blume S, Ishak KJ, Maclaine GDH. Cost effectiveness of donepezil in the treatment of mild to moderate Alzheimer's disease: A UK evaluation using discrete-event simulation. PharmacoEconomics. 2010;28(5):411-27.
11	Touchon J, Lachaine J, Beauchemin C, Granghaud A, Rive B, Bineau S. The impact of memantine in combination with acetylcholinesterase inhibitors on admission of patients with Alzheimer's disease to nursing homes: cost-effectiveness analysis in France. Eur J Health Econ. 2014 Nov;15(8):791-800. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4201748

Appendix A5: Characteristics of Reviewed Studies

Table 3. Brief overview of all included studies.

First author, Year	Country	Sponsorship	Study type	Model type	Time horizon	Included interventions
Getsios, 2010	UK	Eisai	CUA	DES	7 years	Donepezil, no treatment
Guo, 2010	Germany	Janssen-Cilag	CEA/CMA	DES	10 years	Galantamine, ginko biloba, no treatment
Hartz, 2012	Germany	Eisai	CUA	DES	10 years	Donepezil, memantine, no treatment
Hoogveldt, 2011	Netherlands	Non-funded; pharma affiliation	CUA	Markov	5 years	Memantine, standard care (no treatment)
Lachaine, 2011	Canada	Lundbeck	CUA	Markov	7 years	Memantine+AChEI, AChEI monotherapy
Nagy, 2011	UK	Novartis	CUA	NR	5 years	Rivastigmine patch, rivastigmine capsule, BSC
Pfeil, 2012	Switzerland	Non-funded; pharma affiliation	CUA	Markov	7 years	AChEI, AChEI+memantine
Rive, 2010	UK	Lundbeck	CUA	Markov	5 years	Memantine, standard care (no treatment or background AChEI)
Rive, 2012	Norway	Lundbeck	CUA	Markov	5 years	Memantine, standard care (no treatment or background AChEI)
Touchon, 2014	France	Lundbeck	CUA	Markov	7 years	Memantine+AChEI, AChEI monotherapy
Wimo, 2012	Sweden	Janssen Pharmaceutica	CCA	TBA	6 months	Galantamine, placebo

Note: CEA=cost-effectiveness analysis; CMA=cost-minimization analysis; CUA=cost-utility analysis; CCA=cost-comparison analysis; DES=discrete event simulation; NR=not reported; TBA=trial-based analysis

Table 4. Detailed overview of all included studies.

First Author, Year	Getsios, 2010	Guo, 2010	Hartz, 2012
Sponsorship	Eisai	Janssen-Cilag	Eisai
Country	UK	Germany	Germany
Perspective	Health care payer & societal	Health care payer & societal	Health care payer & societal
Study type	CUA	CEA/CMA	CUA
Comparators	Donepezil (10mg) No treatment	Galantamine Ginkgo biloba No treatment	Donepezil (10mg) Memantine (20mg) No treatment
Target population	Mild to moderate AD patients analyzed in three subgroups: (1) Modified MMSE scores ≥ 10 and ≤ 26 (2) Treatment onset at MMSE ≥ 20 and ≤ 26 (3) Treatment onset at MMSE ≥ 10 and <20	Patients with mild to moderate AD	Mild to moderately severe AD patients analyzed in two subgroups: (1) Mild to moderate AD patients (26 ≥ MMSE ≥ 10) (2) Patients with moderate AD (MMSE (10-19))
Time horizon	7 years	10 years	10 years
Type of model	DES	DES	DES
Results	MMSE score ≥ 10 and ≤ 26: *HCP perspective:* Donepezil dominant *Societal perspective:* Donepezil dominant MMSE score ≥ 20 and ≤ 26: *HCP perspective:* Donepezil dominant *Societal perspective:* Donepezil dominant MMSE score ≥ 10 and <20: *HCP perspective:* Donepezil dominant *Societal perspective:* Donepezil dominant	Galantamine resulted in greater reductions in time spent in institutional care (by about 2.4 months over 10-year time horizon), time spent in a severe state and in caregiver time relative to the other two treatment options. Galantamine was also associated with lower costs versus placebo (net savings of €3978) and versus gingko biloba (net saving of €3972).	Patients with MMSE ≥ 10 and ≤ 26 (mild to moderate AD) : *HCP perspective:* Donepezil dominant *Societal perspective:* Donepezil dominant Patients with MMSE ≥ 10 and < 20 (moderate AD): *HCP perspective:* Donepezil dominant *Societal perspective:* Donepezil dominant

First Author, Year	Hoogveldt, 2011	Lachaine, 2011	Nagy, 2011
Sponsorship	Non-funded; pharma affiliation	Lundbeck	Novartis
Country	Netherlands	Canada	UK
Perspective	Health care payer & societal	Health care payer & societal	Health care payer & societal
Study type	CUA	CUA	CUA
Comparators	Memantine Standard care (no treatment)	Memantine+AChEI AChEI monotherapy	Rivastigmine patch (9.5mg/24hr) Rivastigmine capsule (12mg/day) BSC (placebo)
Target population	Moderate to severe AD patients	AD patients with no previous institutionalization; severity of disease unspecified.	Mild to moderate AD patients
Time horizon	5 years	7 years	5 years
Type of model	Markov	Markov	NR
Results	Memantine was the dominant strategy (1.265 QALYs, €110,097), being more effective and less costly than standard care (1.207 QALYs, €113,927). Compared to standard care, memantine monotherapy produced an additional 0.149 years of independence, 0.091 years in the moderate disease state, and 0.058 additional QALYs.	Base case analysis: *Health care system perspective* ChEI+memantine dominant over ChEI monotherapy Base case analysis: *Societal perspective* ChEI+memantine dominant over ChEI monotherapy Complementary analysis*: *Health care system perspective* ChEI+memantine dominant over ChEI monotherapy Complementary analysis: *Societal perspective* ChEI+memantine dominant over ChEI monotherapy *Complementary analysis is adjusted for age and sex based on Lopez et al. (2009) study	Rivastigmine patch vs. BSC: *MMSE model:* £10,579/QALY *MMSE-ADL model:* £9114/QALY Rivastigmine capsules vs. BSC: *MMSE model:* £15,154/QALY *MMSE-ADL model:* £13,758/QALY Rivastigmine patch vs. capsules: *MMSE model*: Patch dominates *MMSE-ADL model:* Patch dominates

First Author, Year	Pfeil, 2012	Rive, 2010	Rive, 2012
Sponsorship	Non-funded; pharma affiliation	Lundbeck	Lundbeck
Country	Switzerland	UK	Norway
Perspective	Health care payer & societal	Health care payer	Health care payer & societal
Study type	CUA	CUA	CUA
Comparators	AChEI monotherapy AChEI+memantine	Memantine Standard care (no treatment or background AChEI treatment)	Memantine Standard care (no treatment or background AChEI treatment)
Target population	AD patients (details unspecified)	Moderate to severe AD patients	Moderate to severe AD patients
Time horizon	7 years	5 years	5 years
Type of model	Markov	Markov	Markov
Results	*Healthcare system perspective:* AChEI+memantine dominated AChEI monotherapy *Societal perspective:* AChEI+memantine dominated AChEI monotherapy	Memantine (1.533 QALYs, £93,076 [€112,082]) dominated standard care (1.502 QALYs, £94,787 [€114,143]). Treatment with memantine prolonged time to FTC on average by 6 weeks per patient compared to standard care over the 5-year evaluation period.	MEM (1.24 QALYs, €168,291 [1,352,282 NOK]) dominated standard of care (1.21 QALYs, €172,030 [1,382,323 NOK]).

First Author, Year	Touchon, 2014	Wimo, 2012
Sponsorship	Lundbeck	Janssen Pharmaceutica
Country	France	Sweden
Perspective	Health care payer & societal	Societal
Study type	CUA	CCA
Comparators	AChEI+memantine AChEI monotherapy	Galantamine Placebo
Target population	AD patients who had not previously been admitted to a nursing home; severity of disease unspecified.	Mild to moderate AD patients
Time horizon	7 years	6 months
Type of model	Markov	Trial-based analysis
Results	*Healthcare system perspective:* AChEI+memantine dominant *Societal perspective:* AChEI+memantine dominant	No significant difference in costs between patients receiving galantamine compared to placebo, regardless of living arrangement; therefore, galantamine is cost-neutral.

Appendix B – De novo Economic Evaluation

Research Question

RQ2: Based on a de novo economic model, what is the cost-effectiveness of cognitive enhancers versus other cognitive enhancers, other therapies or best supportive care for the treatment of AD?

Study Objectives

Based on the research question, the objectives of the study were to address the following specific question:

- What is the cost-effectiveness of various treatment options for AD compared to each other or no pharmacologic treatment? Options included either an AChEI (donepezil, galantamine, or rivastigmine (oral or patch)) or memantine, or the concomitant use of memantine with an AChEI drug.

Economic Evaluation

Model Structure

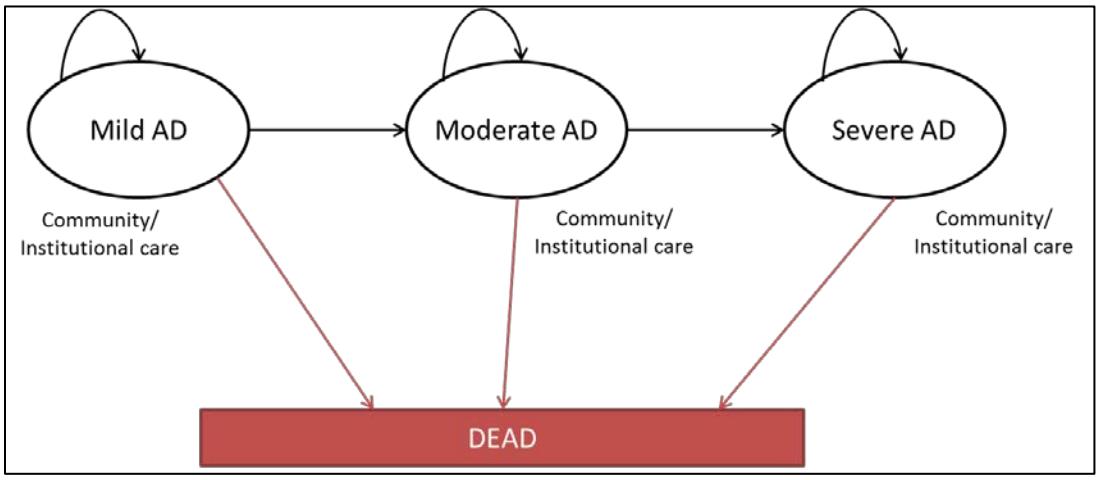
Costs and quality-adjusted life years (QALYs) of AChEI monotherapy or memantine monotherapy and the concomitant use of AChEI with memantine compared with no treatment among elderly (aged over 65 years) patients with AD were assessed using a Markov model. These estimates were then used to estimate the relative cost-effectiveness of alternative reimbursement strategies for the coverage of different pharmacotherapies.

Disease progression was modeled using hybrid states comprising single mini-mental state examination (MMSE) scores and location of care (institution/nursing home or community/home care) in addition to death, an absorbing state. Parameters within the model were either MMSE score-specific or were specific to categories of MMSE: mild (MMSE score >21); moderate disease (MMSE score 11–20); and severe (MMSE score <11).[16] Figure 2 presents a simplified schematic of the Markov model used in this study.

A time horizon of 10 years was chosen based on the natural history of the disease which ranges from 1 to 10 years from diagnosis until death.[17] The choice of a 10 year time horizon is aligned with other models, such as Nagy et al. (2011) who estimate at least 8.6 years for patients to deteriorate from an MMSE of 26 to six.[18] Because of the rapid progression from one MMSE level to another in later stages of the condition, a cycle length of one-month was selected; although, the initial cycle relating to the impact of treatment was assessed at six months.

During each cycle, patients can be in a health state, defined by any combination of AD severity and location of care, and may progress to the next level of AD severity. Given the progressive nature of AD, transitions are unidirectional from mild to moderate to severe disease, and from community care to institutional care.

Figure 2. Simplified Schematic of Markov model.



Note: Progression was modelled over individual MMSE scores, not the categories of severity.

Data Inputs

Progression of Disease

The progress of disease from diagnosis to death is reported to range from 1-10 years. This has been validated in an untreated cohort of 719 AD patients who were followed over a period of seven years.[19] This pattern of progression was found to be predicted by the model equation shown below.

Equation 1: Time to 1-point MMSE decline (years) = $(0.00334*MMSE^2)-(0.073*MMSE) + 0.6013$

Transition probabilities relating to the need for hospitalization within different diseases states were obtained from an analysis of data from the National Alzheimer Coordinating Center.[20] Sensitivity analysis was based on earlier data from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD).[21]

Utilities

The literature was reviewed for the utility values associated with MMSE scores. Analysis adopted values from Brazier et al whereby utility values were estimated as a function of MMSE score.[22] Sensitivity analysis adopted utility values which varied by category of MMSE and location of care. (Table 8)

Resource Use and Costs

The costs associated with the management of AD include medication costs, cost due to provision of care in the community and the costs associated with institutional care varied by disease severity which dictates the level of care required. All costs were inflated to 2015 dollars using the Bank of Canada Inflation calculator.[23] We excluded from our model costs of health professionals such as the physician or geriatrician, given that we do not expect that this will vary by drug therapy as there is no assumed impact on life expectancy or differences in administration.

Costs of medication

Costs of medications are based on the most commonly prescribed dose for each product within the Ontario Public Drug Programs (OPDP). The costs for these medications are derived from the Ontario drug formulary with 8% added for pharmacy mark-up and four dispensing fees of $8.83.

Cost of institutionalization

Institutionalization is considered placement in long term care (LTC) facilities and not retirement homes or assisted living facilities. LTC facilities offer a higher degree of personal care, provide help with activities of daily living, and provide access to 24-hour nursing care or supervision in a secure setting. Depending on the severity of AD, there is a commensurate increase in the care needs in the LTC facility. These figures were obtained from the guideline document prepared by the Health System Performance Research Network.[24]

The formula used to calculate the annual cost of institutionalization is as shown below.

Equation 1: Case cost = {(NPC * CMI) + PSS + RF + OA} * 365 days
where NPC = Nursing and Personal Care;
CMI = Case Mix Index;
PSS = Program and Support Services;
RF = Raw Food; and
OA = Other Accommodation

Using the guidance from the Health System Performance Research Network and the work of Nagy et al., Complex Continuing Care RUG-III groups and Case Mix Index values with IB2, IB1 and IA1 interpreted as severe, moderate and mild AD, respectively were used.

Cost of community care

These are obtained from the work of Hux et al. (1998) and inflated to present day value using the Bank of Canada inflation calculator.[23,25]

Treatment Effectiveness

Data with respect to the effectiveness of treatments were obtained from the concurrent network meta-analysis which provided estimate of the impact of treatment on absolute changes in MMSE scores (Table 10).

Cost Effectiveness

Costs and effects over a course of 10 years, as measured by quality-adjusted life years gained associated with various AD treatment strategies were estimated via the model in comparison with no pharmacologic treatment.

Primary analysis was conducted for patients with moderate AD treated initially in the community. Analysis was repeated for five additional patient profiles specific to patients with mild, moderate, and severe progression of disease (as measured by MMSE), and either institutionalized or living in the community. Costs and QALYs were discounted at a standard rate of 5% per annum. The cost-

effectiveness of each of the treatments was assessed through a sequential analysis based on incremental cost per quality-adjusted life year gained.

Treatment Comparators

Treatment strategies included the use of either AChEI or memantine monotherapy, or the use of an AChEI drug in combination with memantine. AChEI medications comprised oral formulations of donepezil, galantamine, and rivastigmine, as well as the rivastigmine patch.

The base case sought to compare the following treatment strategies.

1. No treatment
2. Donepezil
3. Galantamine
4. Rivastigmine (oral)
5. Rivastigmine (patch)
6. Memantine
7. Donepezil+Memantine
8. Galantamine+Memantine
9. Rivastigmine(patch)+Memantine

Deterministic Sensitivity Analyses

One-way sensitivity analyses were conducted to evaluate the sensitivity of the base case results to changes in assumptions. The following were tested within these sensitivity analyses:

- Assuming a time horizon of 3 years and 5 years.
- Assuming a discount rate of 0% and 3% per annum.
- Incorporation of alternative utility values by class and institutionalization.
- Incorporation of alternative transition probabilities (based on CERAD transitions)

In addition threshold analysis was conducted to assess the necessary price reduction for the rivastigmine patch for it to be considered cost effective based on a threshold of $50,000 for the incremental cost per QALY gained.

Probabilistic Sensitivity Analyses

A probabilistic sensitivity analysis (PSA) was conducted in order to estimate the impact of parameter uncertainty on the cost-effectiveness. The PSA involved a Monte Carlo simulation with 5000 estimates of outcomes obtained by sampling from the probability distributions for each parameter. The parameters included within the PSA and their corresponding distributions are as follows: a gamma distribution was used for costs, beta distributions for probabilities, normal distribution for change in MMSE score and coefficients for utility regression.

The results of the PSA are presented by cost effectiveness acceptability curves depicting the probability, that each comparator is the most cost effective given different threshold values for a QALY.

Findings

Base Case

In patients with moderate AD who are living in the community, no pharmacologic treatment is the least costly treatment option though it is less effective than all other treatment options except for combination therapy with rivastigmine and memantine. Donepezil in combination with memantine was the most effective strategy and donepezil was the most effective of the monotherapies.

At a willingness to pay of less than $12,000 per QALY, no pharmacologic treatment is optimal (Table 5). If a payer's willingness to pay per QALY is between $12,000 and $29,000, a strategy of initiating donepezil monotherapy is optimal. Lastly, at a willingness to pay value greater than $29,000 per QALY, a strategy of initiating combination therapy with donepezil and memantine is optimal. All other treatment strategies are either dominated or subject to extended dominance.

Table 5. Cost-effectiveness of Treatment Strategies in Moderate AD in the community

	QALYs	Costs	Incremental cost per QALY gained vs. no treatment	Sequential incremental cost per QALY gained
Non-dominated treatment options				
No treatment	0.692	$10,612.05		
Donepezil	0.784	$11,721.41	$12,122.02	$12,122.02
Donepezil+Memantine	0.818	$12,693.03	$16,627.00	$28,882.50
Dominated treatment options				
Memantine	0.721	$11,522.62	$31,642.64	Subject to extended dominance
Galantamine	0.769	$11,677.82	$13,947.63	Subject to extended dominance
Galantamine+Memantine	0.796	$12,618.61	$19,445.76	Subject to extended dominance
Rivastigmine - Oral	0.777	$11,741.00	$13,336.52	Dominated
Rivastigmine - Patch	0.796	$14,002.03	$32,635.57	Dominated
Rivastigmine+Memantine	0.656	$14,167.20	Dominated	Dominated

Subgroup analysis

Results were similar across all subgroups although the incremental cost per QALY gained estimates varied a little by disease severity and location of care (full results are detailed in Appendix B2: Results of Subgroup Analysis).

Deterministic Sensitivity Analysis

Detailed tables for the results of the deterministic sensitivity analyses can be found within Appendix B3: Results of Deterministic Sensitivity Analysis.

For each of the six patient profiles, the results of the cost-effectiveness analysis were robust to changes in all parameters. The one notable difference was the use of older transition probabilities from CERAD,

where donepezil monotherapy was dominant over no pharmacologic treatment.

Across the six patient profiles, the rivastigmine patch was not cost effective. For it to be cost effective, the necessary price reduction ranged from 45% for mild patients within the community to 68% for moderate patients living in institutionalized care.

Probabilistic Sensitivity Analysis

The results of the probabilistic sensitivity analysis are similar to the base case analysis. The incremental cost per QALY gained for donepezil versus no treatment was $11,954 and the incremental cost per QALY gained for donepezil in combination with memantine versus donepezil alone was $16,427. The analysis however demonstrates the uncertainty around the incremental effects of therapies especially the combination therapies where the credible intervals around the estimates of incremental QALYs were large (Table 6).

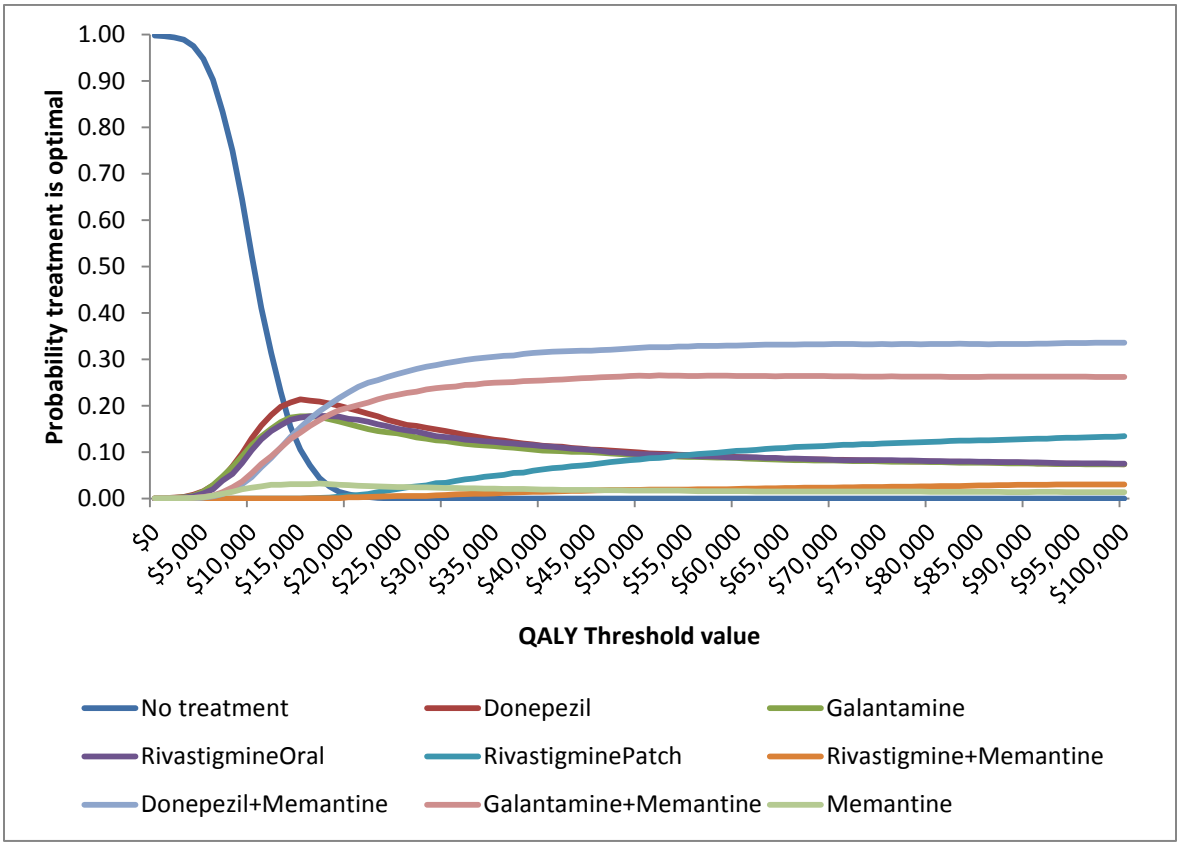
Table 6. Incremental costs and QALYs associated with treatment versus no treatment based on the probabilistic sensitivity analysis

	Incremental Costs versus no Treatment	Incremental QALYs versus no Treatment
Donepezil	$1104 (537-1880)	0.09 (0.04-0.14)
Galantamine	$1069 (581-1940)	0.08 (-0.01-0.17)
RivastigmineOral	$1125 (604-1956)	0.08 (0.02-0.16)
RivastigminePatch	$3386 (2680-4588)	0.11 (-0.01-0.22)
Memantine	$911 (488-1531)	0.03 (-0.07-0.13)
RivastigminePatch + Memantine	$3570 (1913-5023)	-0.03 (-0.24-0.20)
Donepezil + Memantine	$2065 (1295-3288)	0.13 (0.01-0.25)
Galantamine + Memantine	$2001 (1241-3379)	0.11 (-0.06-0.29)
Donepezil	$1104 (537-1880)	0.09 (0.04-0.14)

Note: Figures in parenthesis are 95% credible intervals.

The cost-effectiveness acceptability curve further highlighted the great degree of uncertainty concerning the underlying results. At a threshold of $50,000 per QALY, the combination of donepezil and memantine was cost effective in 32.5% of simulations. This was followed by galantamine and memantine at 26.5%, donepezil monotherapy at 10%, rivastigmine oral monotherapy at 9.6%, galantamine monotherapy at 8.9%, rivastigmine patch monotherapy at 8.8%, rivastigmine and memantine at 1.9%, memantine monotherapy at 1.8% and no treatment at 0%.

Figure 3. Cost Effectiveness Acceptability Curve for Moderate AD in the Community



Overall Summary

Across most subgroups donepezil in combination with memantine was the most cost-effective strategy based on a threshold of $50,000 per QALY, the exception were institutionalized patients living with moderate disease, where donepezil monotherapy is the most cost-effective therapy.

Donepezil was the most cost-effective monotherapy. Neither memantine monotherapy nor rivastigmine in patch format were cost-effective compared to other monotherapies.

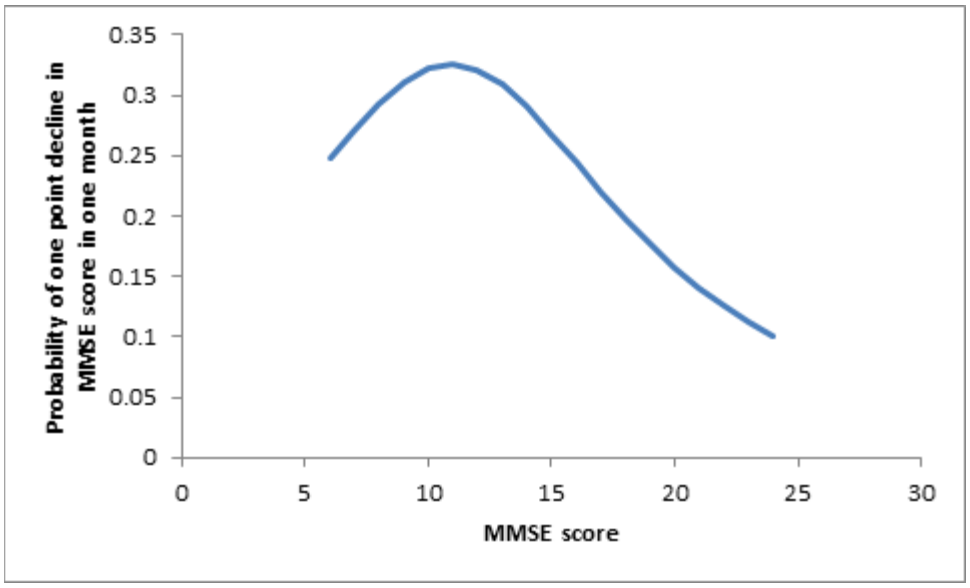
Results were robust to the assumptions within the sensitivity analysis although probabilistic sensitivity analysis found a high degree of uncertainty around the incremental effects of combination therapy.

Conclusions

Donepezil was the most cost-effective monotherapy across all patient subgroups. Memantine monotherapy and rivastigmine in patch format were not cost-effective. Combination therapy involving memantine and an AChEI (specifically donepezil) may be cost-effective although there is great degree of uncertainty around this specific finding.

Appendix B1: Data Estimates

Figure 4. Transition probabilities with respect to disease progression



Source: Mendiondo et al. (2000).[19]

Table 7. Annual probability of death or transition to nursing home by disease severity

TRANSITION	ANNUAL PROBABILITY	DISTRIBUTION	SOURCE
Progression to Nursing Home			
Mild to NH	0.012	Beta (2.3, 186.3)	20
Moderate to NH	0.034	Beta (3.6, 101.4)	20
Severe to NH	0.066	Beta (4.1, 57.5)	20
Mortality			
Mild to Dead	0.055	Beta (135.5, 2328.5)	20
Moderate to Dead	0.215	Beta (165.5, 604.4)	20
Severe to Dead	0.48	Beta (226.8, 245.7)	20

Table 8. Utility estimates based on regression of individuals' MMSE scores versus utility

VARIABLE	Coefficient	DISTRIBUTION	SOURCE
Constant	0.0982	Normal (0.0982, 0.0126)	22
MMSE score	0.0298	Normal (0.0298, 0.0006)	22

Table 9. Cost estimates

INPUT	DATA	VALUE	DISTRIBUTION	SOURCE
Drug costs	Donepezil	$450.41	Fixed	[26]
	Galantamine	$454.97		
	Rivastigmine - Oral	$475.52		
	Rivastigmine - Patch	$1,749.57		
	Memantine	$460.52		
	Rivastigmine - Patch +Memantine	$2,210.09		
	Donepezil+Memantine	$910.93		
	Galantamine+Memantine	$915.49		
Annual institutionalization costs	Mild dementia	$48,420.90	Gamma^	[23,24]
	Moderate dementia	$55,891.78	Gamma^	
	Severe dementia	$56,739.26	Gamma^	
Annual community costs	Mild dementia	$2,798.04	Beta and Gamma*	[23,25]
	Moderate dementia	$3,613.81	Beta and Gamma*	
	Severe dementia	$5,539.07	Beta and Gamma*	

^ Derived from Gamma distributions relating to specific resource items within overall institutionalization costs per day (Nursing and personal care $86.05, Program services $8.35, Raw food $7.33 and Other accommodation $50.39) assuming a 25% standard error of the mean, severity specific case mix indices and inflated to 2015.
* Derived from Gamma distributions for annualized costs for relating to specific resource items (Day care $7,800, Respite care $2,380, homemaking $1,887.60, meal delivery $1,019.20, in home nursing $2,412.86, health professional visits $2,433.60, caregiver counselling $462 and caregiver support $178.90) assuming a 25% standard error of the mean, different severity specific uptakes (modelled based on beta distributions) and inflated to 2015.

Table 10. Change in MMSE score by treatment from NMA.

INPUT	DATA	VALUE	DISTRIBUTION
Change versus no therapy	Donepezil	1.38	Normal (1.38, 0.37)
	Galantamine	1.16	Normal (1.16, 0.63)
	Rivastigmine - Oral	1.28	Normal (1.28, 0.52)
	Rivastigmine - Patch	1.56	Normal (1.56, 0.85)
	Memantine	0.44	Normal (0.44, 0.72)
	Rivastigmine - Patch +Memantine	-0.58	Normal (-0.58, 1.77)
	Donepezil+Memantine	1.87	Normal (1.87, 0.91)
	Galantamine+Memantine	1.55	Normal (1.55, 1.28)

Appendix B2: Results of Subgroup Analysis

Table 11. Cost-effectiveness of Treatment Strategies in Mild AD in the community

	QALYs	Costs	Incremental cost per QALY gained vs. no treatment	Sequential incremental cost per QALY gained
Non-dominated treatment options				
No treatment	1.644	$11,462.51		
Donepezil	1.861	$12,837.21	$6,332.97	$6,332.97
Donepezil+Memantine	1.935	$14,234.61	$9,505.56	$18,742.19
Dominated treatment options				
Memantine	1.714	$12,757.17	$18,478.73	Subject to extended dominance
Galantamine	1.827	$12,826.26	$7,428.08	Subject to extended dominance
Galantamine+Memantine	1.887	$14,197.57	$11,258.27	Subject to extended dominance
RivastigmineOral	1.845	$12,893.77	$7,090.57	Dominated
RivastigminePatch	1.888	$16,361.21	$20,038.95	Dominated
Rivastigmine+Memantine	1.549	$16,979.87	Dominated	Dominated

Table 12. Cost-effectiveness of Treatment Strategies in Severe AD in the community

	QALYs	Costs	Incremental cost per QALY gained vs. no treatment	Sequential incremental cost per QALY gained
Non-dominated treatment options				
No treatment	0.276	$9,329.96		
Donepezil	0.310	$9,843.47	$15,085.61	$15,085.61
Donepezil+Memantine	0.323	$10,367.73	$22,400.58	$42,664.32
Dominated treatment options				
Galantamine	0.305	$9,848.32	$18,173.59	Dominated
Memantine	0.287	$9,854.22	$48,610.68	Dominated
RivastigmineOral	0.308	$9,870.17	$17,131.88	Dominated
Galantamine+Memantine	0.314	$10,372.58	$27,220.30	Dominated
RivastigminePatch	0.315	$11,224.38	$49,136.87	Dominated
Rivastigmine+Memantine	0.262	$11,748.64	Dominated	Dominated

Table 13. Cost-effectiveness of Treatment Strategies in Mild AD in institutional care

	QALYs	Costs	Incremental cost per QALY gained vs. no treatment	Sequential incremental cost per QALY gained
Non-dominated treatment options				
No treatment	1.644	$118,938.33		
Donepezil	1.861	$125,632.13	$30,837.03	$30,837.03
Donepezil+Memantine	1.935	$128,635.37	$33,251.25	$40,279.93
Dominated treatment options				
Memantine	1.714	$122,028.11	$44,100.33	Subject to extended dominance
Galantamine	1.827	$124,900.20	$32,473.01	Subject to extended dominance
RivastigmineOral	1.845	$125,360.97	$31,818.25	Subject to extended dominance
Galantamine+Memantine	1.887	$127,549.62	$35,446.49	Subject to extended dominance
Rivastigmine+Memantine	1.549	$121,700.73	Dominated	Dominated
RivastigminePatch	1.888	$129,746.04	$44,210.67	Dominated

Table 14. Cost-effectiveness of Treatment Strategies in Moderate AD in institutional care

	QALYs	Costs	Incremental cost per QALY gained vs. no treatment	Sequential incremental cost per QALY gained
Non-dominated treatment options				
No treatment	0.692	$85,421.38		
Donepezil	0.784	$89,834.90	$48,226.59	$48,226.59
Donepezil+Memantine	0.818	$91,894.60	$51,720.96	$61,227.17
Dominated treatment options				
Memantine	0.721	$87,415.44	$69,294.20	Subject to extended dominance
Galantamine	0.769	$89,302.78	$50,795.38	Subject to extended dominance
RivastigmineOral	0.777	$89,632.43	$49,746.02	Subject to extended dominance
Galantamine+Memantine	0.796	$91,109.60	$55,125.06	Subject to extended dominance
Rivastigmine+Memantine	0.656	$87,427.50	Dominated	Dominated
RivastigminePatch	0.796	$92,515.23	$68,292.83	Dominated

Table 15. Cost-effectiveness of Treatment Strategies in Severe AD in institutional care

	QALYs	Costs	Incremental cost per QALY gained vs. no treatment	Sequential incremental cost per QALY gained
Non-dominated treatment options				
No treatment	0.276	$55,842.17		
Donepezil	0.310	$56,355.68	$15,085.61	$15,085.61
Donepezil+Memantine	0.323	$56,879.94	$22,400.58	$42,664.32
Dominated treatment options				
Galantamine	0.305	$56,360.53	$18,173.59	Dominated
Memantine	0.287	$56,366.43	$48,610.68	Dominated
RivastigmineOral	0.308	$56,382.37	$17,131.88	Dominated
Galantamine+Memantine	0.314	$56,884.79	$27,220.30	Dominated
RivastigminePatch	0.315	$57,736.58	$49,136.87	Dominated
Rivastigmine+Memantine	0.262	$58,260.84	Dominated	Dominated

Appendix B3: Results of Deterministic Sensitivity Analysis

Table 16. Deterministic Sensitivity Analysis: Moderate AD in the Community

Scenario	Finding
Base case: **Time horizon: 10 years**	If λ < $12,122 per QALY, no treatment is most cost-effective If $12,122 < λ < $28,882 per QALY, donepezil monotherapy is the most cost-effective strategy If λ > $28,882 per QALY, donepezil+memantine is most cost-effective
Time horizon: 3 years	If λ < $8,999 per QALY, no treatment is most cost-effective If $8,999 < λ < $26,873 per QALY, donepezil monotherapy is the most cost-effective strategy If λ > $26,873 per QALY, donepezil+memantine is most cost-effective
Time horizon: 5 years	If λ < $11,254 per QALY, no treatment is most cost-effective If $11,254 < λ < $27,867 per QALY, donepezil monotherapy is the most cost-effective strategy If λ > $27,867 per QALY, donepezil+memantine is most cost-effective
Discount rate: 0% per annum	If λ < $16,132 per QALY, no treatment is most cost-effective If $16,132 < λ < $31,253 per QALY, donepezil monotherapy is the most cost-effective strategy If λ > $31,253 per QALY, donepezil+memantine is most cost-effective
Discount rate: 3% per annum	If λ < $13,250 per QALY, no treatment is most cost-effective If $13,250 < λ < $29,308 per QALY, donepezil monotherapy is the most cost-effective strategy If λ > $29,308 per QALY, donepezil+memantine is most cost-effective
Alternative utilities	If λ < $23,053 per QALY, no treatment is most cost-effective If $23,053 < λ < $61,132 per QALY, donepezil monotherapy is the most cost-effective strategy If λ > $61,132 per QALY, donepezil+memantine is most cost-effective
Alternative transition probabilities (CERAD)	If λ < $18,868 per QALY, donepezil monotherapy is the most cost-effective strategy If λ > $18,868 per QALY, donepezil+memantine is most cost-effective

Table 17. Threshold Analysis: Necessary Price Reduction for the Rivastigmine Patch

	Price reduction for Rivastigmine Patch for it to be Cost Effective based on a Threshold Incremental cost per QALY gained of $50,000	
Disease Severity	**Community**	**Institutionalized**
Mild	45%	58%
Moderate	52%	68%
Severe	62%	62%

Appendix C – Budget Impact Analysis

Research Question

What is the budget impact of alternative policies for reimbursing cognitive enhancers versus placebo, other cognitive enhancers, or best supportive care for the treatment of Alzheimer's disease (AD)?

Methods Reimbursement Based Economic Assessment

An applied, policy-oriented economic model focusing on financial impact was developed to facilitate consideration of alternative reimbursement strategies for pharmacotherapies available to treat AD. Utilization data for cognitive enhancers, specifically acetylcholinesterase inhibitors (AChEIs), for AD (donepezil (DON), galantamine (GAL), and rivastigmine (RVS)) were provided by OPDP from January 1, 2000 to December 31, 2014.

The number of users of cognitive enhancers per quarter for the next three years, 2015-2017, were predicted using time series analysis. Four models were used to forecast the number of users of AChEIs.

1. A linear model whereby the number of users was assumed to increase by the same amount each year and also increase with each new AChEI covered under OPDP.
2. An exponential model where an exponential relationship between number of users and time and number of AChEIs covered was assumed.
3. A power model that allowed a non-linear relationship between time and number of users, and included the number of AChEIs covered by OPDP.
4. A constant growth model that assumed a constant percentage increase in the number of users, with additional coverage of new AChEIs also leading to a percentage increase.

Within all of the models the following covariates were considered: quarter (i.e., January 1-March 31, 2000 was quarter 1, April 1-June 30, 2000 was quarter 2, etc.), and the number of available AChEIs covered by OPDP. Each model was also examined for seasonal effects based on absolute and Winters seasonal effects calculations. For each model, the most suitable combination of independent variables and inclusion of seasonal effects were selected based on the Bayesian Information Criterion (BIC). Once the most functional form for each of the four models was chosen, the appropriate model including all users was determined using the smallest BIC. We also developed prediction models for each age category (65-74 years, 75-84 years, and 85+ years), but the models were not significantly different from the model for overall users. Based on this analysis, we elected to use one model including all age groups, rather than three distinct models separated by age. A linear model with quarter and number of drugs covered by OPDP as independent variables, and with no seasonal effects was chosen (See Appendix C1: Model Details for model details).

Once forecasts for number of users were obtained for 2015-2017, number of users was then converted to expenditure by multiplying the total users per year by average units per user per quarter in the last year and average cost per unit in the last year (Status Quo). For DON costs were based on the last two quarters of data instead of the full year because of the introduction of generic DON. Expenditures under alternative reimbursement strategies were estimated. The alternative strategies considered were:

1. No change to current limited use (LU) listing for AChEIs (status quo). This strategy uses current utilization trends to forecast costs for 2015-2017.

2. LU listing for AChEIs for mild and moderate AD and exceptional access program (EAP) criteria for Exelon patch (RVS patch formulation). For this strategy we assumed that a proportion of oral DON, GAL, and RVS users will switch to the patch.
3. LU listing for AChEIs for patients with mild, moderate, and severe AD. Including severe AD patients in the LU listing was assumed to increase the total number of users of DON, GAL, and RVS.
4. Strategy 2 + 3: LU listing for AChEIs for mild, moderate, and severe AD patients, and EAP criteria for the Exelon patch.
5. General benefit (GB) listing for DON and LU listing for oral GAL and RVS. The strategy assumes that a proportion of patients will switch from GAL and RVS to DON. As well, this strategy includes donepezil with a generic price that is 18% of the brand price.

Findings

Current Usage and Expenditure

Table 18. Average number of cognitive enhancer users, units and prescriptions, per quarter in 2014.

	Average number per quarter in 2014		
	Users N (%)	**Units N (%)**	**Prescriptions N (%)**
Total AChEIs	62,764 (100%)	6,039,011 (100%)	487,998 (100%)
DON	41,307 (66%)	3,694,640 (61%)	313,312 (64%)
GAL	17,060 (27%)	1,567,736 (26%)	137,358 (28%)
RVS	4,397 (7%)	776,635 (13%)	37,328 (8%)

Total number of AChEI users, units, and prescriptions per quarter was 62,764, 6,039,011, and 487,998, respectively. DON accounts for the majority in all three instances (61-66%).

Summary of average number of AChEI users, units, and prescriptions per quarter in 2014

- In all instances, DON accounted for the majority (61-66%) of AChEI use in 2014 and RVS accounted for the least (7-13%).
- The total average of AChEI users per quarter in 2014 was 62,764, ranging from 4,397 users of RVS (7%) to 41,307 users of DON (66%).
- The total average of AChEI units per quarter in 2014 was 6.0 million, ranging from 0.8 million units of RVS (13%) to 3.7 million units of DON (61%).
- The average number of AChEI prescriptions per quarter in 2014 was 487,998, ranging from 37,328 (8%) prescriptions for RVS to 313,312 for DON (64%).

Table 19 OPDP expenditure on cognitive enhancers used to treat AD in the elderly from January 1, 2000-March 31, 2014.

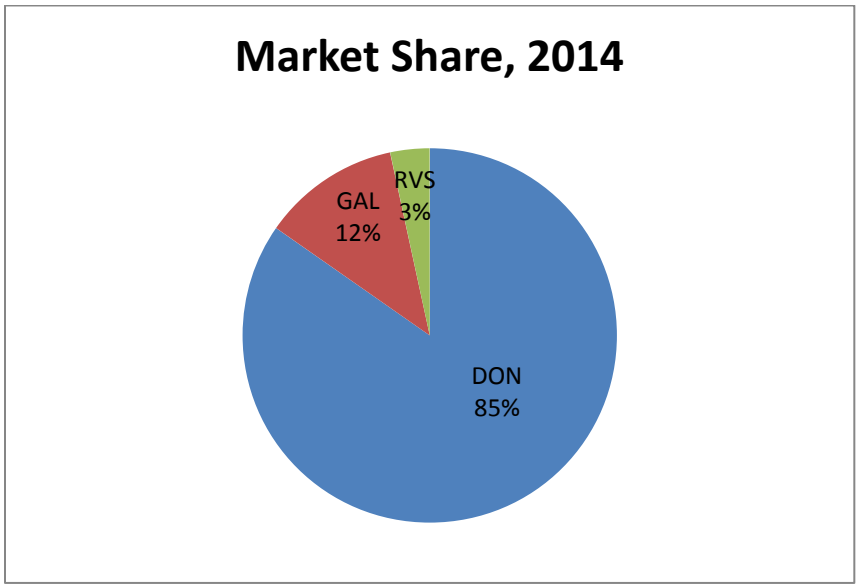
OPDP COGNITIVE ENHANCERS EXPENDITURE				
YEAR	**DON**	**GAL**	**RVS**	**TOTAL**
2000	$14,540,345.85	$0.00	$0.00	$14,540,345.85
2001	$24,065,616.47	$0.00	$1,040,719.19	$25,106,335.66
2002	$34,435,250.23	$1,839,664.66	$2,999,289.35	$39,274,204.24
2003	$40,365,570.35	$7,334,519.81	$6,385,344.92	$54,085,435.08
2004	$45,919,902.12	$13,801,020.42	$10,010,777.11	$69,731,699.65
2005	$50,107,740.61	$18,008,595.59	$11,678,330.42	$79,794,666.62
2006	$53,978,250.84	$22,357,496.93	$13,427,375.02	$89,763,122.79
2007	$58,364,574.74	$26,692,687.47	$15,246,990.29	$100,304,252.50
2008	$62,063,481.52	$32,110,476.45	$16,021,329.50	$110,195,287.47
2009	$65,574,554.21	$37,031,681.18	$14,995,103.61	$117,601,339.00
2010	$70,793,586.47	$42,047,579.29	$6,488,292.10	$119,329,457.86
2011	$76,020,666.67	$21,970,195.02	$4,193,298.73	$102,184,160.42
2012	$80,957,008.84	$12,599,522.16	$3,701,599.09	$97,258,130.09
2013	$84,736,461.51	$11,907,924.62	$3,393,932.08	$100,038,318.21
2014	$35,266,921.86	$11,150,979.40	$2,994,114.02	$49,412,015.28

Expenditure for AChEIs used to treat AD has increased from $14 million in 2000 to almost $120 million in 2010. Recently, there has been a reduction in the expenditure for AChEIs to $49 million in 2014 with the introduction of generic products.

Summary of OPDP expenditure for AChEIs used to treat AD from 2000-2014 (adjusted to 2014 $CAD)

- Expenditure for AChEIs among AD patients has risen over the last 14 years.
- In 2000, AChEI expenditure by OPDP was just over $14.5 million.
- By 2010, total AChEI expenditure by OPDP was almost $120 million.
- Over the last 5 years, there has been a decline in AChEI expenditure due to the introduction of generic products to the market. In 2014, total OPDP expenditure for AChEIs was $49.4 million.

Figure 5. Cognitive enhancers market share in 2014.



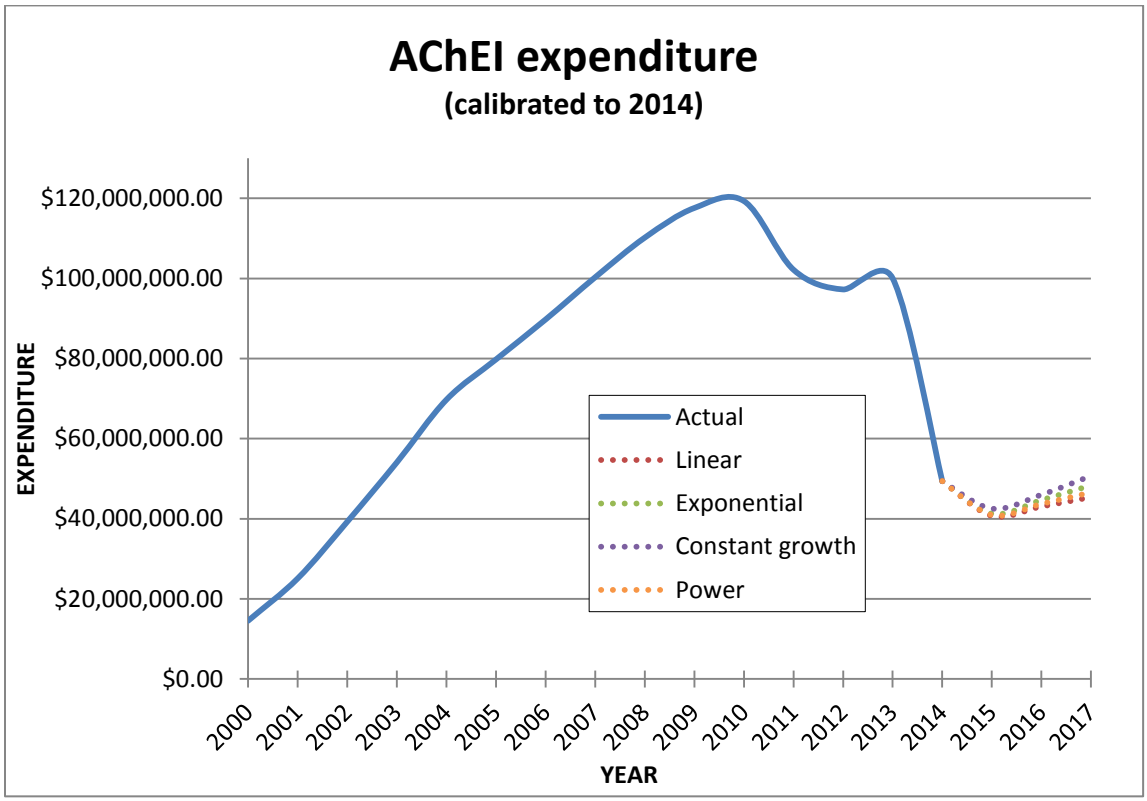
Based on expenditure in 2014, DON had the largest market share at 85%, while GAL had 12% and RVS had 3%.

Summary of AChEIs market share in 2014

- In 2014, DON had the largest market share (85%) of AChEIs, followed by GAL (12%) and RVS (3%).

Forecasting expenditure

Figure 6. Cognitive enhancer expenditure for AD patients (calibrated to actual data from 2014).

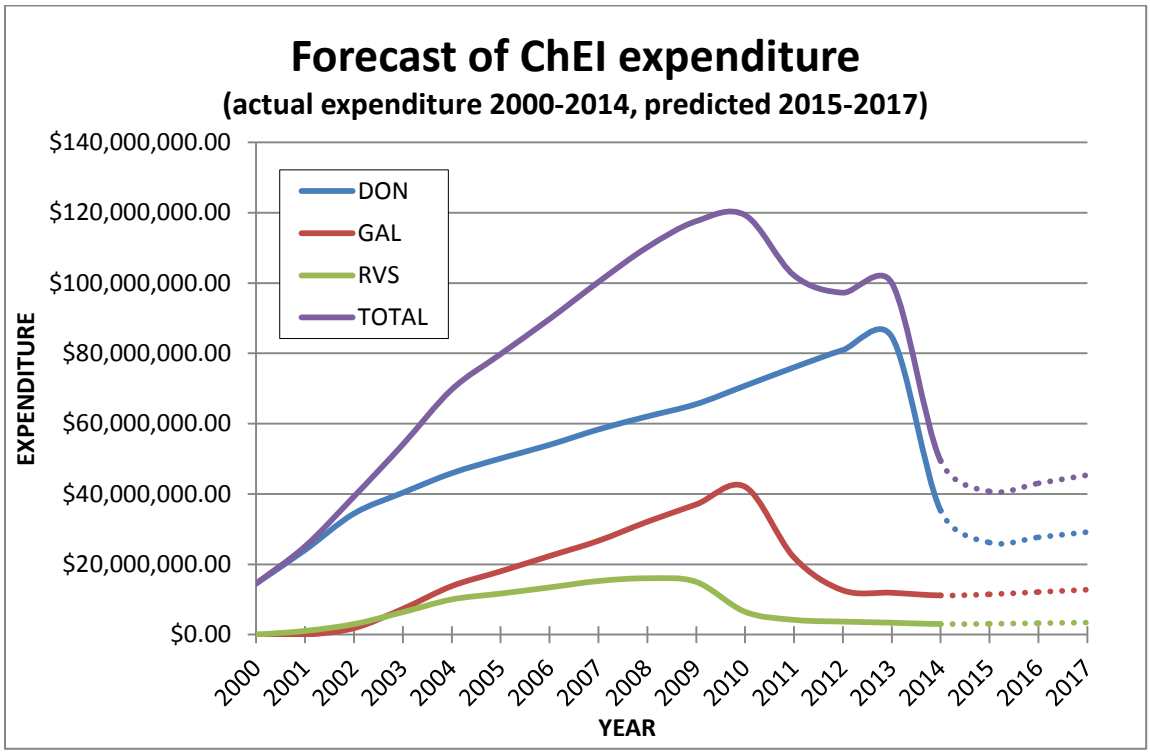


AChEI expenditure has risen consistently since 2000, peaking in 2010. It is expected that AChEI expenditure will rise slightly over the next three years.

Summary of AChEI expenditure

- AChEI expenditure is expected to rise slightly over the next three years.
- All four models follow an upward trend.
- The linear model is the most appropriate for forecasting future expenditure.

Figure 7. Forecast of individual cognitive enhancers based on linear model



DON is expected to have the greatest growth in expenditure over the next three years.

Summary of forecasted expenditure for individual AChEIs

- DON is expected to continue to contribute to the majority of AChEI expenditure over the next three years.
- No major increases are expected for GAL or RVS in the next three years.

Table 20. Forecasted AChEI expenditure

YEAR	AChEI EXPENDITURE			
ACTUAL	**DON**	**GAL**	**RVS**	**TOTAL**
2000	$14,540,345.85	$0.00	$0.00	$14,540,345.85
2001	$24,065,616.47	$0.00	$1,040,719.19	$25,106,335.66
2002	$34,435,250.23	$1,839,664.66	$2,999,289.35	$39,274,204.24
2003	$40,365,570.35	$7,334,519.81	$6,385,344.92	$54,085,435.08
2004	$45,919,902.12	$13,801,020.42	$10,010,777.11	$69,731,699.65
2005	$50,107,740.61	$18,008,595.59	$11,678,330.42	$79,794,666.62
2006	$53,978,250.84	$22,357,496.93	$13,427,375.02	$89,763,122.79
2007	$58,364,574.74	$26,692,687.47	$15,246,990.29	$100,304,252.50
2008	$62,063,481.52	$32,110,476.45	$16,021,329.50	$110,195,287.47
2009	$65,574,554.21	$37,031,681.18	$14,995,103.61	$117,601,339.00
2010	$70,793,586.47	$42,047,579.29	$6,488,292.10	$119,329,457.86
2011	$76,020,666.67	$21,970,195.02	$4,193,298.73	$102,184,160.42
2012	$80,957,008.84	$12,599,522.16	$3,701,599.09	$97,258,130.09
2013	$84,736,461.51	$11,907,924.62	$3,393,932.08	$100,038,318.21
2014	$35,266,921.86	$11,150,979.40	$2,994,114.02	$49,412,015.28
PREDICTED				
2015	$26,178,614.44	$11,466,104.17	$3,078,727.17	$40,723,445.79
2016	$27,675,202.45	$12,121,602.35	$3,254,732.90	$43,051,537.69
2017	$29,171,790.45	$12,777,100.52	$3,430,738.63	$45,379,629.60

Without any changes to current reimbursement for AChEIs, expenditure is expected to be $40.7 million for 2015 and $45.4 million for 2017

Impact of Alternative Approaches to Reimbursement

Table 21. Forecasted total costs (2017) under each reimbursement strategy

AVERAGE COST OF AChEIs PER QUARTER IN 2017						
REIMBURSEMENT STRATEGY	**DON**	**GAL**	**RVS***	**TOTAL**	**NET BUDGET IMPACT**	**%**
#1 Status quo (base case)						
	$29,171,790.45	$12,777,100.52	$3,430,738.63	$45,379,629.60	N/A	N/A
#2 EAP for Exelon patch						
1% of users switch to Exelon patch	$28,880,072.54	$12,649,329.51	$4,654,080.96	$46,183,483.01	$803,853.42	2%
5% of users switch to Exelon patch	$27,713,200.92	$12,138,245.49	$9,547,450.26	$49,398,896.68	$4,019,267.09	9%
10% of users switch to Exelon patch	$26,254,611.40	$11,499,390.47	$3,087,664.77	$53,418,163.77	$8,038,534.17	18%
#3 LU listing for AChEI in all severities of AD						
0% increase in usage	$29,171,790.45	$12,777,100.52	$3,430,738.63	$45,379,629.60	$0.00	0%
5% increase in usage	$30,630,379.97	$13,415,955.54	$3,602,275.56	$47,648,611.08	$2,268,981.48	5%
#4 LU listing for AChEI in all severities of AD, EAP for Exelon patch						
0% increase in usage, 1% of users switch to Exelon patch	$28,880,072.54	$12,649,329.51	$4,654,080.96	$46,183,483.01	$803,853.42	2%
0% increase in usage, 5% of users switch to Exelon patch	$27,713,200.92	$12,138,245.49	$9,547,450.26	$49,398,896.68	$4,019,267.09	9%
0% increase in usage, 10% of users switch to Exelon patch	$26,254,611.40	$11,499,390.47	$15,664,161.90	$53,418,163.77	$8,038,534.17	18%
5% increase in usage, 1% of users switch to Exelon patch	$30,324,076.17	$13,281,795.99	$4,886,785.01	$48,492,657.16	$3,113,027.57	7%
5% increase in usage, 5% of users switch to Exelon patch	$29,098,860.97	$12,745,157.77	$10,024,822.78	$51,868,841.52	$6,489,211.92	14%
5% increase in usage, 10% of users switch to Exelon patch	$27,567,341.97	$12,074,359.99	$16,447,369.99	$56,089,071.96	$10,709,442.36	24%
#5 GB for DON, LU for RVS (oral) and GAL (oral)						
1% of users switch to DON	$24,045,212.87	$12,649,329.51	$3,396,431.24	$40,090,973.63	-$5,288,655.97	-12%
5% of users switch to DON	$24,542,591.69	$12,138,245.49	$3,259,201.70	$39,940,038.88	-$5,439,590.72	-12%
10% of users switch to DON	$25,164,315.20	$11,499,390.47	$3,087,664.77	$39,751,370.44	-$5,628,259.16	-12%

* includes Exelon patch

If generic DON was listed under general benefit and between 1 and 10% percent of users switched, there would be a 12% reduction in overall expenditure by 2017.

Summary of forecasted total costs (2017) under each reimbursement strategy

- Without any changes to current AChEI reimbursement, expenditure is expected to be $45.4 million by 2017.
- Listing generic DON as general benefit would result in a 12% reduction in expenditure for AChEIs by 2017, assuming between 1% and 10% of users will switch to DON.
- All other alternative reimbursement strategies would result in an increased expenditure for AChEIs by 2017.

Conclusions

In conclusion, without any changes to the current reimbursement for AChEIs, expenditure is expected to reach $45.4 million in 2017. Listing generic donepezil as general benefit with a generic price that is 18% of the brand price is the only alternative reimbursement strategy resulting in a reduction (-12%) in AChEI expenditure by 2017. All other strategies would result in an increased expenditure.

Appendix C1: Model Details

Table 22. Model details for users of cognitive enhancers

	CONSTANT	QUARTER	NO. DRUGS IN CLASS
LINEAR MODEL			
Coefficient	-490.799	3687.81	10691.11091
Std. error	4583.552181	170.46	1802.166339
BIC	4455.735334		
	CONSTANT	**QUARTER**	**NO. DRUGS IN CLASS**
EXPONENTIAL MODEL			
Coefficient	2729.412596	1.08	2.075636398
Std. error	0.135241248	0.01	0.05317431
BIC	4479.842594		
	CONSTANT	**QUARTER**	**NO. DRUGS IN CLASS**
POWER MODEL			
Coefficient	-11541.5377	6189.42	8551.131027
Std. error	4174.322527	257.50	1684.2894
BIC	4453.200816		
	CONSTANT	**NEW TRT AVAILABLE**	
CONSTANT GROWTH MODEL			
Coefficient	0.02550155	0.402432464	
Std. error	0.00443455	0.050171204	
BIC	4513.608934		

Appendix D – Reimbursement Based Economic Assessment

Research Question

RQ4. Based on a de novo economic model, what is the cost-effectiveness of alternative policies for reimbursing cognitive enhancers for the treatment of AD?

Methods

Analysis considered the five reimbursement strategies introduced within the Budget Impact Analysis.

1. No change to current limited use (LU) listing for AChEIs (status quo).
2. LU listing for AChEIs for mild and moderate AD and exceptional access program (EAP) criteria for Exelon patch (RVS patch formulation).
3. LU listing for AChEIs for patients with mild, moderate, and severe AD.
4. Strategy 2 + 3: LU listing for AChEIs for mild, moderate, and severe AD patients, and EAP criteria for the Exelon patch.
5. General benefit (GB) listing for DON and LU listing for oral GAL and RVS.

The conclusions of Appendix C were that in terms of budget impact, strategy 5 would likely lead to a reduction in drug expenditure in comparison to strategy 1 whilst strategies 2, 3 and 4 would lead to an increase in drug expenditure. The focus of this analysis is to determine the cost effectiveness of the alternative reimbursement strategies.

To accurately assess the cost effectiveness of the alternative reimbursement strategies we would need data on the proportion of individuals taking each monotherapy and their disease severity at onset of treatment. As this was unavailable we made the following assumptions with respect to initiation of therapy.

1. 50% of patients will have mild disease at treatment onset whilst the other 50 % will have moderate disease.
2. All patients will be treated in the community at treatment onset.
3. The proportion taking donepezil, rivastigmine (oral) and galantamine monotherapy were based on the proportion of users in 2014 taking each of these therapies: 66.5%,6.8% and 26.7% respectively.

To assess the impact of each of the alternate reimbursement strategies the following assumptions were made:

- Under strategy 2, it is assumed that 5% of users of current monotherapies switch to the rivastigmine patch – usage will now be 63.2% for donepezil, 6.4% for rivastigmine (oral) and 25.4% for galantamine and 5% for rivastigmine (patch)
- Under strategy 3, it is assumed there will be a 5% increase in usage leading to the distribution of severities at onset being: 47.6%, 47.6%, 4.8% for mild, moderate and severe disease
- Under strategy 4, both assumptions under strategies 2 and 3 will apply
- Under strategy 5, it is assumed that 5% of galantamine and rivastigmine users with will switch to donepezil and there will be a 5% increase in overall usage due to patients initiating donepezil

monotherapy with severe disease. Thus the distribution of users with middle to moderate disease will now be 68.2% for donepezil, 6.4% for rivastigmine oral and 25.4% for galantamine. The distribution of severities at onset will be 47.6%, 47.6%, 4.8% for mild, moderate and severe disease.

Results

The estimated average costs and QALYs from the 5 reimbursement strategies are detailed in Table X.

Strategy 4 will lead to the greatest QALY gain over Strategy 1 and with the highest costs. The incremental cost per QALY gained for Strategy 5 over Strategy 1 is $12,572. The incremental cost per QALY gained for Strategy 4 over Strategy 5 is $208,528.

Table 23. Cost-effectiveness of Reimbursement Strategies for Cognitive Enhancers in the Treatment of Alzheimer's disease

	QALYs	Costs	Incremental cost per QALY gained vs. no treatment	Sequential incremental cost per QALY gained
Non-dominated treatment options				
Strategy 1	1.265	$12,133.27		
Strategy 5	1.267	$12,158.15	$12,572.01	$12,572.01
Strategy 4	1.268	$12,301.38	$63,074.01	$208,527.93
Dominated treatment options				
Strategy 3	1.267	$12,159.79	$19,642.52	Dominated by Strategy 5
Strategy 2	1.266	$12,271.65	$107,232.02	Dominated by Strategies 3&5

Strategy 1. No change to current limited use (LU) listing for AChEIs (status quo).
Strategy 2. LU listing for AChEIs for mild and moderate AD and exceptional access program (EAP) criteria for rivastigmine patch
Strategy 3. LU listing for AChEIs for patients with mild, moderate, and severe AD.
Strategy 4. Strategy 2 + 3
Strategy 5. General benefit (GB) listing for donepezil and LU listing for oral galantamine and rivastigmine.

If the generic price of donepezil was 18% of the brand price, the incremental cost per QALY gained for Strategy 5 over Strategy 1 would be $7,368; whilst the incremental cost per QALY gained for Strategy 4 over Strategy 5 would be $230,017.

Conclusions

Based on the results of the de novo modelling, strategy 5 (the listing of donepezil as general benefit) can be considered cost effective. Strategies relating to the reimbursement of rivastigmine patch were not cost effective.

Analysis did not consider the cost effectiveness of reimbursement strategies with respect to memantine.

References

1. Bond M, Rogers G, Peters J, Anderson R, Hoyle M, Miners A, et al. The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of technology appraisal no. 111): A systematic review and Economic model. Health Technology Assessment. 2012;16(21):1-469.

2. Loveman E, Green C, Kirby J, Takeda A, Picot J, Payne E, et al. The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease. Health Technology Assessment. 2006;10(1):iii-160.

3. Getsios D, Blume S, Ishak KJ, Maclaine GDH. Cost effectiveness of donepezil in the treatment of mild to moderate Alzheimer's disease: A UK evaluation using discrete-event simulation. PharmacoEconomics. 2010;28(5):411-27.

4. Guo S, Hernandez L, Wasiak R, Gaudig M. Modelling the clinical and economic implications of galantamine in the treatment of mild-to-moderate Alzheimer's disease in Germany. Journal of Medical Economics. 2010;13(4):641-54.

5. Hartz S, Getsios D, Tao S, Blume S, Maclaine G. Evaluating the cost effectiveness of donepezil in the treatment of Alzheimer's disease in Germany using discrete event simulation. BMC neurology. 2012;12.

6. Hoogveldt B, Rive B, Severens J, Maman K, Guilhaume C. Cost-effectiveness analysis of memantine for moderate-to-severe Alzheimer's disease in The Netherlands. Neuropsychiatric Disease and Treatment. 2011;7(1):313-7.

7. Nagy B, Brennan A, Brandtmuller A, Thomas SK, Sullivan SD, Akehurst R. Assessing the cost-effectiveness of the rivastigmine transdermal patch for Alzheimer's disease in the UK using MMSE- and ADL-based models. International Journal of Geriatric Psychiatry. 2011;26(5):483-94.

8. Pfeil AM, Kressig RW, Szucs TD. Alzheimer's dementia: budget impact and cost-utility analysis of a combination treatment of a cholinesterase inhibitor and memantine in Switzerland. Swiss medical weekly. 2012;142()(pp w13676), 2012. Date of Publication: 2012.):w13676.

9. Rive B, Aarsland D, Grishchenko M, Cochran J, Lamure M, Toumi M. Cost-effectiveness of memantine in moderate and severe Alzheimer's disease in Norway. International Journal of Geriatric Psychiatry. 2012;27(6):573-82.

10. Rive B, Grishchenko M, Guilhaumegoulant C, Katona C, Livingston G, Lamure M, et al. Cost effectiveness of memantine in Alzheimer's disease in the UK. Journal of Medical Economics. 2010;13(2):371-80.

11. Touchon J, Lachaine J, Beauchemin C, Granghaud A, Rive B, Bineau S. The impact of memantine in combination with acetylcholinesterase inhibitors on admission of patients with Alzheimer's disease to nursing homes: cost-effectiveness analysis in France. Eur J Health Econ. 2014

Nov;15(8):791-800. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4201748

12. Wimo A, Gaudig M, Schauble B, Jedenius E. The economic impact of galantamine vs placebo: An analysis based on functional capacity in a Swedish cohort study. Journal of Medical Economics. 2012;15(4):786-91.

13. Lachaine J, Beauchemin C, Legault M, Bineau S. Economic evaluation of the impact of memantine on time to nursing home admission in the treatment of Alzheimer disease. Canadian Journal of Psychiatry. 2011;56(10):596-604.

14. Garattini L, Koleva D, Casadei G. Modeling in pharmacoeconomic studies: funding sources and outcomes. Int J Technol Assess Health Care. 2010 Jul;26(3):330-3.

15. Howard R, Phillips P, Gray R. The authors reply. New England Journal of Medicine. 2012;366(23):2228.

16. Jones RW, McCrone P, Guilhaume C. Cost effectiveness of memantine in alzheimer's disease: An analysis based on a probabilistic Markov model from a UK perspective. Drugs and Aging. 2004;21(9):607-20.

17. Trabucchi M. An economic perspective on Alzheimer's disease. Journal of Geriatric Psychiatry and Neurology. 1999;12(1):29-38.

18. Nagy B, Brennan A, Brandtmuller A, Thomas SK, Sullivan SD, Akehurst R. Assessing the cost-effectiveness of the rivastigmine transdermal patch for Alzheimer's disease in the UK using MMSE- and ADL-based models. International Journal of Geriatric Psychiatry. 2011;26(5):483-94.

19. Mendiondo MS, Ashford JW, Kryscio RJ, Schmitt FA. Modelling mini mental state examination changes in Alzheimer's disease. Statistics in Medicine. 2000;19(11-12):1607-16.

20. Spackman DE, Kadiyala S, Neumann PJ, Veenstra DL, Sullivan SD. Measuring Alzheimer disease progression with transition probabilities: Estimates from NACC-UDS. Current Alzheimer Research. 2012;9(9):1050-8.

21. Neumann PJ, Araki SS, Arcelus A, Longo A, Papadopoulos G, Kosik KS, et al. Measuring Alzheimer's disease progression with transition probabilities: Estimates from CERAD. Neurology. 2001;57(6):957-64.

22. Brazier J. Quality of life evidence for patients with Alzheimer's disease: Use of existing quality of life evidence from the ADENA trials to estimate the utility impact of Exelon® (Appendix 1 - Utility evidence). Discussion paper. (Unpublished). 2001.

23. Bank of Canada. Bank of Canada Inflation Calculator. 2014. [cited 2015 Jun 9]. Available from: http://www.bankofcanada.ca/rates/related/inflation-calculator/

24. Wodchis W, Bushmeneva K, Nikitovic M, McKillop I. Guidelines on Person-level Costing Using

Administrative Databases in Ontario. Toronto, ON: 2013. 1 p.

25. Hux MJ, O'Brien BJ, Iskedjian M, Goeree R, Gagnon M, Gauthier S. Relation between severity of Alzheimer's disease and costs of caring. CMAJ. 1998;159(5):457-65.

26. Ontario Ministry of Health and Long-Term Care. Ontario Drug Benefit Formulary. Comparative Drug Index. 2015 May 28. [cited 2015 Jun 9]. Available from: https://www.healthinfo.moh.gov.on.ca/formulary/