



A Pharmacoeconomic Review of Cholinesterase Inhibitor Drugs for Alzheimer's Disease

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EXECUTIVE SUMMARY

A PHARMACOECONOMIC REVIEW OF CHOLINESTERASE INHIBITOR DRUGS FOR ALZHEIMER'S DISEASE

INTRODUCTION

The report provides a pharmacoeconomic review of the cost effectiveness of cholinesterase inhibitors, specifically donepezil, galantamine and rivastigmine, in the treatment of mild to moderate Alzheimer's disease (AD) including an assessment of the current literature, the measures used in assessing cost effectiveness of these agents and the evidence gaps.

RESEARCH QUESTIONS

Assessment of the Pharmacoeconomic Literature

1. What is the comparative cost-effectiveness of the cholinesterase inhibitors, donepezil, galantamine and rivastigmine, for all patients with mild to moderate Alzheimer's disease?
2. What is the comparative cost-effectiveness of the drugs under review for subpopulations of patients with mild to moderate Alzheimer's disease?
3. Based on cost-effectiveness, should one or more of the drugs under review be preferred for coverage?

Assessment of Methodological Considerations

1. What are the reliable measures that can be used to determine and delineate comparative cost-effectiveness? These may include health services utilization rates, including:
 - o time to institutionalization;
 - o quality of life;
 - o mortality;
 - o utilization / costs of physician services, drugs, hospital services, and other care (e.g., home support);
 - o caregiver impact.

Assessment of Evidence Gaps

- Based upon the findings from above, what are any important research questions or evidence "gaps" which may be used to assess the relative cost-effectiveness of the cholinesterase inhibitors?
- What evidence review strategy could the Ministry engage in that would fill the evidence gaps?

SEARCH STRATEGY AND FINDINGS

The National Institute for Health and Care Excellence (NICE), within the United Kingdom (UK), conducted a health technology assessment (HTA) of cholinesterase inhibitors for Alzheimer's disease in 2006 which was updated in 2012. The systematic reviews contained within both reports were used as the basis for examining the cost effectiveness literature as of February 2010. A further comprehensive

search of the medical literature was conducted from this time point onwards including the following databases: Medline, Embase, Cochrane and NHS EED. A review of studies conducted from a Canadian perspective is also provided.

OVERALL SUMMARY

Discussion of the Assessment of the Pharmacoeconomic Literature

There were three questions posed with respect to the pharmacoeconomic literature, each of which is discussed below.

1. What is the comparative cost-effectiveness of the cholinesterase inhibitors for all patients with mild to moderate Alzheimer's disease?

A search of the literature did not reveal any well-designed independent cost effectiveness studies examining the use of cholinesterase inhibitors in mild to moderate Alzheimer's disease from a Canadian perspective. If a funding decision must be made based on current evidence, the most recent independent analysis was conducted by NICE from a UK perspective. It provides an objective estimate of cost effectiveness; however, differences in healthcare systems between countries may significantly affect the results of these analyses. This is particularly true within this therapeutic area where the benefits of treatment are small and the long term impacts are assessed using modeling techniques which require assumptions regarding effects on institutionalization and mortality. Additionally, the usage and funding of institutionalization is inconsistent from one country to another, which highly influences the cost effectiveness estimates. The authors of the NICE analysis caution that there is a great deal of uncertainty both with respect to the structural modeling of AD and with the parameter estimates. Bearing this in mind, their report found cholinesterase inhibitors to be cost effective in the treatment of mild to moderate AD based on a willingness to pay of £30,000 per quality adjusted life year (QALY).

2. What is the comparative cost-effectiveness of the drugs under review for subpopulations of patients with mild to moderate Alzheimer's disease?

It is common throughout the literature to consider patients with mild to moderate AD as a single group; however, some analyses were conducted separately for mild and moderate patients. From the published literature there is varying evidence, some supporting greater cost effectiveness in mild patients and some supporting greater cost effectiveness in moderate patients. Further study would be required to answer this question.

3. Based on cost-effectiveness, should one or more of the drugs under review be preferred for coverage?

Review of the published literature does not provide support for coverage of one drug rather than another or for the cost effectiveness of the use of a specific agent as first line therapy. At present there is insufficient evidence to support assessing the drugs comparatively; therefore, they are considered as a class.

Assessment of Methodological Considerations

With respect to methodological considerations, the clinical evidence of efficacy with these drugs is primarily focused on measures of cognition, activities of daily living and, to a lesser extent, behavior. Given the lack of direct evidence of an impact of treatment on institutionalization, quality of life / utility or mortality, assumptions are made within the cost effectiveness analyses when modeling the long term impact of treatment. In general, cross sectional data is used to associate an improvement in cognition and/or activities of daily living with a delay in institutionalization, a reduction in resources and costs of management, and an improvement in quality of life. Although some studies have incorporated a benefit of treatment to caregivers both in terms of improved quality of life and reduced time spent in direct patient care, there is a need for better information to reduce the uncertainty within these estimates. Longer term randomized trials to assess the impact of treatment on the parameters which most significantly impact the cost effectiveness estimates including institutionalization and mortality are needed.

Assessment of Evidence Gaps

The results of the available cost effectiveness analyses are often conflicting; in particular, those conducted independently have often produced differing results from those supported by the pharmaceutical industry. In many cases, there is a high level of uncertainty surrounding the reported results. The main areas for concern include:

- The long term efficacy of treatment especially with respect to delays in institutionalization, effect on duration of institutionalization, impact on survival and quality of life
- The impact of treatment on caregivers with respect to health, quality of life and time spent in caring for the patient
- The current course of AD within the Canadian population and its associated costs

Although one could pursue an independent cost effectiveness analysis of cholinesterase inhibitors from a Canadian perspective, based on the lack of data to inform the creation of the model and the impact of treatments, it is likely that the results may not differ significantly from those arrived at by NICE. Depending on the assumptions made with respect to the input parameters, the results of studies vary from the treatments being cost ineffective to the treatments dominating no treatment. Regardless, the uncertainty surrounding the results is significant. Before entering into such a project it would be best to assess the availability of good quality current Canadian epidemiological data regarding Alzheimer's disease. In addition, further study to bridge the evidence gaps particularly with respect to the effect of treatment on institutionalization and mortality would be of great value.

CONCLUSIONS

Well designed, independent cost effectiveness analyses of cholinesterase inhibitors from a Canadian perspective are lacking. Evidence from NICE suggests that they may be cost effective in mild to moderate AD from a UK perspective. Caution should be exercised in applying these results within Canada both due to differences in care for AD patients between the two countries and due to the uncertainty surrounding the results of the NICE assessment.

There are a number of methodological gaps in our knowledge regarding both the course of AD within Canadian society and with respect to the impact of treatment on outcomes that are both important to caregivers and patients and may demonstrate a cost benefit specifically with respect to improved quality of life, time spent in institutions and mortality.

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LIST OF ABBREVIATIONS

AD – Alzheimer’s disease
ADL – activities of daily living
AHEAD – Assessment of Health Economics in Alzheimer’s Disease
BSC – best supportive care
CDR – Clinical Dementia Rating scale
ChEI – cholinesterase inhibitors
ER – emergency room
FTC – full time care
HTA – health technology assessment
HUI – Health Utilities Index
ICER – incremental cost effectiveness ratio
MMSE – Mini Mental State Examination
NHS EED – National Health Service economic evaluation database
NICE – National Institute for Health and Care Excellence
PSA – probabilistic sensitivity analysis
QALY – quality adjusted life years
QOL – quality of life
RCT – randomized controlled trial
SHTAC - Southampton Health Technology Assessments Centre
UK – United Kingdom
USA – United State of America

A PHARMACOECONOMICS REVIEW OF CHOLINESTERASE INHIBITOR DRUGS FOR ALZHEIMER'S DISEASE

1. REQUEST

To review the pharmacoeconomic literature examining the cost effectiveness of cholinesterase inhibitors in the treatment of mild to moderate Alzheimer's disease. Additionally, to assess the measures used to evaluate the comparative cost-effectiveness of these medications and identify evidence gaps within the literature to assist in developing a research strategy.

2. RESEARCH QUESTION(S)

Currently, the BC Ministry of Health provides special authority coverage for the three cholinesterase inhibitors, donepezil, galantamine and rivastigmine. This pharmacoeconomic review is divided into three sections. Firstly, a review and critique of the current literature examining the cost effectiveness of cholinesterase inhibitors, second an assessment of the methodological considerations in assessing their cost effectiveness and finally identification of evidence gaps. The specific questions addressed within each of these three areas are detailed below:

2.1 Assessment of the Pharmacoeconomic Literature

1. What is the comparative cost-effectiveness of the drugs under review (the cholinesterase inhibitors – ChEIs) for all patients with mild to moderate Alzheimer's disease?
2. What is the comparative cost-effectiveness of the drugs under review for subpopulations of patients with mild to moderate Alzheimer's disease?
3. Based on cost-effectiveness, should one or more of the drugs under review be preferred for coverage?

2.2 Assessment of Methodological Considerations

1. What are the reliable measures that can be used to determine and delineate comparative cost-effectiveness? These may include health services utilization rates, including:
 - a. time to institutionalization;
 - b. quality of life;
 - c. mortality;
 - d. utilization / costs of physician services, drugs, hospital services, and other care (e.g., home support);
 - e. caregiver impact.

2.3 Assessment of Evidence Gaps

1. Based upon the findings from above what are any important research questions or evidence “gaps” which may be used to assess the relative cost-effectiveness of the ChEIs?
2. What evidence review strategy could the Ministry engage in that would fill the evidence gaps?

3. ASSESSMENT OF PHARMACOLOGIC LITERATURE

3.1 Search Strategy

NICE conducted two health technology assessments (HTAs), one in 2006 and an update in 2012, both containing systematic reviews of the literature. (Loveman 2006, Bond 2012) The reviews within these HTAs were used as the basis for the assessment of the studies identified in the cost effectiveness literature prior to February 2010, when the last search was completed by NICE.

A further search of the medical literature from 2010 to present in Medline (indexed, in-process and other non-indexed), Embase, Cochrane database, NHS EED, based on the NHS EED recommended search strategy, was conducted in order to capture all relevant literature published subsequent to the most recent NICE review. In addition, the reference lists of retrieved studies were hand searched. Details of the search including the search strategy and a table of excluded studies and the rationale for exclusion are provided in Appendix 1 and Appendix 2.

3.2 Literature Review Based on NICE HTA

Over the past ten years NICE, in the UK, has conducted two health technology assessments of treatments for Alzheimer’s disease (AD). The first, published in 2006, contained a systematic review of the clinical and cost effectiveness literature, a review of industry submissions and a cost effectiveness analysis conducted by a group commissioned by NICE. (Loveman 2006) The results of this publication lead to the recommendation to only fund cholinesterase inhibitors for the treatment of patients with moderate AD as the estimates of cost effectiveness exceeded the generally accepted threshold value of £30,000 per QALY within the UK. There were a number of criticisms raised with respect to the modeling exercise conducted within this analysis, although a legal challenge to the results found in favour of NICE’s recommendations.

NICE conducted a more recent review in 2012 which provided an update of the reviews of clinical and cost effectiveness literature, further reviews of industry submissions and a new cost effectiveness modeling study which addressed some of the criticisms that were lodged against the original analysis. (Bond 2012) This assessment concluded that although there is still considerable uncertainty regarding the cost effectiveness estimates, the base case suggested that cholinesterase inhibitors may be cost effective in the treatment of mild to moderate AD. Below is a summary of the review of the cost effectiveness papers that were included within the two HTAs by NICE and a description of the two models used to assess the cost effectiveness of cholinesterase inhibitors in the two HTAs.

3.3.1 Prior Systematic Reviews Conducted by NICE UK

Review by NICE in 2006

The systematic review of the cost effectiveness literature focusing on cholinesterase inhibitors in the treatment of AD within the 2006 NICE HTA identified a total of 21 studies: 11 for donepezil, 5 for rivastigmine and 5 for galatamine. (Loveman 2006) The following summary is based on the NICE report.

For donepezil two of the studies were conducted from a Canadian perspective (Lanctôt 1999 (abstract only) and O'Brien 1999), 3 from a UK perspective (Stein 1997, Stewart 1998, AD2000 Collaboration Group 2004), two from Swedish (Jonsson 1999, Wimo 2003), and one each from USA (Neumann 1999), Japanese (Ikeda 2002), Polish (Sobolewski 2002) and French (Fagnani 2003). Two studies measured efficacy in terms of quality adjusted life years (Stein 1997 and Neumann 1999); whereas the others reported either a delay in disease progression or a reduced time in need of full-time care (Fagnani 2003). Six of the studies stated that they were from a societal perspective, four did not clearly identify the perspective and only one was stated to be from a payer perspective (Ikeda 2002). Donepezil treatment was found to be either cost saving or cost neutral in 6 of the studies, cost incurring in 4 and unclear in one published only in abstract form (Lanctôt 1999). The cost savings occurred typically in studies adopting a societal perspective which included costs to both patients and caregivers in addition to the healthcare sector. One study found donepezil to be more cost effective in moderate AD patients than in mild AD patients. (Stewart 1998)

With respect to rivastigmine, two of the studies were conducted from a UK perspective (Stein 1998, Fenn and Gray 1999), one from a Canadian perspective (Hauber 2000) and two from a USA perspective (Hauber 2000, Brooks and Deal 2000); however, one of the US studies was only available in abstract. All analyses were conducted in mild to moderate AD patients. Three of the studies did not state the perspective of the analysis, one was from a societal perspective (Hauber 2000) and one from both a societal and a HCS perspective (Fenn and Gray 1999). Three of the five studies were funded by the pharmaceutical industry. Only one study (Stein 1998) was a cost utility analysis, the rest were cost effectiveness analyses. All of the cost effectiveness analyses found that the delay in cognitive decline with rivastigmine, as measured using Mini Mental State Examination (MMSE) scores, was associated with cost savings. Most of the cost calculations excluded the cost of the drug. In the one cost utility analysis, the cost per QALY (based only on drug costs) ranged from £10,266 per QALY at one year to £73,320 per QALY at five years. The majority of subgroup analyses found treatment to be more cost effective in mild patients as compared with moderate patients.

In the published literature for galantamine, there was one study from each of the following perspectives: Canada, Sweden, Netherland, USA and UK. (Getsios 2001, Garfield 2002, Caro 2002, Migliaccio-Walle 2003, Ward 2003) Three of the studies were cost utility analyses whereas the others were cost effectiveness analyses which used time in full time care as an outcome measure. All analyses focused on mild to moderate AD patients. Four of the studies appeared to be from the perspective of the healthcare payer and the Dutch study was from a perspective broader than the healthcare payer. All received financial support from the pharmaceutical industry. Overall, all analyses found that treatment with galantamine reduced time in full time care versus no treatment, was associated with QALY gains relative to no treatment and was cost saving over time. Galantamine therefore dominated no treatment. In the three studies which conducted subgroup analyses (Getsios 2001, Garfield 2002, Ward 2003) galantamine was found to be more cost effective in moderate patients than in mild patients. Review by NICE in 2010

More recently in 2010 (published in 2012), NICE conducted a further HTA in which an updated review of the literature was conducted along with an updated cost effectiveness analysis. (Bond 2012) This subsequent review identified 12 additional studies; 8 relating to donepezil, 2 for rivastigmine and 2 for galantamine. Of the 8 new studies examining the cost effectiveness of donepezil, only 5 were specific to AD patients with mild to moderate disease. There was one study from each of a UK, Taiwan, Spain, Sweden and German perspective. (Getsios 2009, Fuh 2008, Lopez-Bastida 2009, Mesterton 2009, Teipel 2007) All five studies were conducted from a societal perspective; however, the UK study and the Spanish study also provided a health service perspective. The three studies, which were either funded by the pharmaceutical industry or listed industry employees as authors, found that donepezil was either cost saving or highly cost effective. The remaining two studies, from a Spanish and a German perspective were independently funded. The Spanish study by Lopez-Bastida found donepezil to be cost saving from a societal perspective and cost effective for patients with mild disease but not cost effective for those with moderate disease from the perspective of the healthcare system. The results of the second independent study by Teipel, from a German perspective, suggested that donepezil may be considered cost effective from a societal perspective; however, the authors state that considerable uncertainty remains regarding the findings.

The two new studies examining the cost effectiveness of rivastigmine were published only in abstract form at the time of the review; however, one has subsequently been published in full. (Brennan 2007 and Nagy 2011, Pattanaprteep 2005)

The abstract only study was conducted from the perspective of the Thai healthcare system comparing the cost effectiveness of donepezil versus high and low dose rivastigmine and versus no drug treatment in mild to moderate AD patients. (Pattanaprteep 2005) High dose rivastigmine was found to be more cost effective than donepezil 10 mg which was found to be more cost effective than low dose rivastigmine. The details of this study are scant, making the credibility of the conclusions questionable.

The second study was conducted from the perspective of the UK healthcare system examining the comparative cost effectiveness of rivastigmine patch versus best supportive care in moderate AD. (Brennan 2005) One of the authors is employed within the pharmaceutical industry. Rivastigmine

patch was associated with an incremental cost of £13,000 per QALY. (A more detailed review of this study published in full (Nagy 2011) is provided in the review of literature post the NICE reviews below.)

There were two new studies examining the cost effectiveness of galantamine in mild to moderate AD patients within Korea, one published in full and one only in abstract. (Suh 2008, Suh 2009) The study published in full was based on an economic evaluation alongside a clinical trial which compared different doses of galantamine. (Suh 2008) A community control was used to compare the costs of galantamine with no drug treatment over the course of a year from a societal perspective. The study was sponsored by the pharmaceutical industry. The authors found galantamine to be cost saving over the 1 year time period. In the second study galantamine was compared with usual care using a Markov model over the course of 5 years. Galantamine was found to be cost effective with an incremental cost of \$4,939 US per QALY. There is little information available to assess this evaluation given that it is only available in abstract form and therefore caution should be exercised in interpreting the results.

The only study within the review that was conducted from a Canadian perspective was by Feldman et al; however, it focused on patients with moderate to severe disease which were considered outside of the scope of the NICE review and this review. (Feldman 2004)

3.3.2 NICE Economic Analyses

As part of the 2006 NICE review a cost utility analysis was conducted examining the cost effectiveness of these drugs. The Southampton Health Technology Assessments Centre (SHTAC) group created a Markov model to simulate disease progression in mild to moderately severe AD patients. This model was used to compare the cost effectiveness of donepezil, rivastigmine and galatamine versus standard care over the course of 5 years, from the perspective of the UK healthcare system. Patients were assumed to enter into the model following 6 months of treatment in which they incurred the costs of the medications and monitoring, but did not accrue any benefit. Patients then transitioned through the three model states of pre-full time care (FTC), FTC and an absorbing state of death. The natural history of the disease was derived from a cohort of UK patients. Effectiveness of treatments was sourced from the clinical systematic review which estimated the effect of treatment on cognitive function. Each of the health states within the model were assigned utility values based on a mapping cognitive function to utility values found in the literature. Treatments were assumed to have no effect on survival. The costs for pre-FTC, FTC in the community and FTC in an institution were sourced from UK published literature. Galantamine was associated with the greatest increase in QALYs of 0.039 versus standard care, followed by rivastigmine with an increase of 0.037 and donepezil with an increase of 0.036. Donepezil was associated with the highest incremental cost versus standard care with a value of £2,895 per patient over 5 years as compared with £2,647 with galantamine and £2,121 with rivastigmine. This resulted in incremental cost effectiveness ratios ranging from £57,000 to £80,000 per QALY for cholinesterase inhibitors versus no drug treatment. Based on the probabilistic sensitivity analysis (PSA) at a willingness to pay of £30,000 per QALY, the probability that the treatments were cost effective was less than 10%. Results were sensitive to changes in assumptions within the deterministic sensitivity analyses; however, in no scenario did the estimated incremental cost effectiveness ratio (ICER) drop below £30,000 per QALY.

Within the 2010 NICE HTA, a new model was created which again examined the cost effectiveness of each of the cholinesterase inhibitors compared with standard care but also attempted to address a number of the criticisms of the SHTAC model. A new Markov model was developed which modeled three states defined as pre-institutionalization, institutionalization and death. A retrospective cohort analysis of people diagnosed with AD or vascular dementia within the UK was used to estimate the time to institutionalization and to death in order to inform the parameter values for the base case analysis. The proportion of patients who were institutionalized at different levels of cognitive impairment as assessed by Mini Mental State Examination (MMSE) scores was estimated from the UK literature. In the base case, treatments were assumed to have no effect on survival; however, this assumption was tested within sensitivity analyses. Unlike the previous model both treatment costs and utilities are accrued from the time treatment is initiated. Both MMSE and ADL (activities of daily living) scores are used to predict delay in institutionalization due to treatment. The model allows for treatment discontinuations and all treatments are assumed to stop once institutionalization occurs. Efficacy of treatment was based on 6 month trials, after which time, the benefits are assumed to decline at a rate parallel to those not receiving treatment. Utility values were mapped onto MMSE values based on the literature. Costs included within the model were for drugs, outpatient visits, hospitalizations, respite care, day care and home attendants, the non-self-funded portion of institution costs and the costs of medical devices. All treatments produced greater QALYs than best supportive care, which had an estimated gain of 1.584 QALYs, with the most QALYs associated with donepezil (1.619) followed by galantamine (1.617) and by rivastigmine capsules and patches (1.613 and 1.616, respectively). Costs of treatment were lower than the cost of best supportive care (BSC: £70,212; rivastigmine capsule: £69,678; donepezil £69,624; rivastigmine patch: £69,598; galantamine: £69,592). Best supportive care and rivastigmine were dominated by galantamine and donepezil resulted in an ICER of £17,900 per QALY versus galantamine. The probabilistic sensitivity analysis did not indicate that any treatment had a significantly greater chance of being cost effective. Assuming a survival effect for treatment results in all treatments producing an incremental cost effectiveness ratio of greater than £37,000 per QALY compared with best supportive care.

The results of this new model lead to the recommendation that cholinesterase inhibitors may be an appropriate treatment for patients with both mild and moderate Alzheimer's disease. A paper published in 2013 by Peters and colleagues provided a detailed explanation of the changes that occurred between the two NICE models. (Peters 2013) The paper is summarized below.

In the original model donepezil resulted in an ICER of £81,000 per QALY. In 2009 NICE conducted an updated review of treatments for AD. In the interim, additional information became available which lead to decisions that affected the structure of the model. The changes incorporated within the model include a new discount rate for costs and utilities of 3.5% (versus 6% for costs and 1.5% for effects in previous model), a 20 year time horizon (versus 5 years in previous model), a 4% per month discontinuation rate (not included in previous model), new parameter estimates for clinical effectiveness from an updated systematic review, incorporation of UK AD progression data (US data used in previous model), stratification into three age groups and stratification of pre-institutional care by severity. Incorporation of all of these changes results in donepezil dominating best supportive care.

3.3 Literature Review Post 2010

Two reviewers (KC and DC) independently reviewed the literature searches in order to identify potential articles for inclusion within the critical appraisal of the literature published subsequent to NICE's most recent review. Any disagreements were resolved through consensus. A total of 20 studies were identified for potential inclusion within the report.

3.3.1 Number of studies included and excluded

The 20 potential studies identified during the literature review were reviewed by two reviewers (KC and DC). Of the 20 studies, the eight studies which addressed the objectives of the review were selected for inclusion. Six of the studies were published in full and two were available only in abstract. (Table 1) Those studies that were not included within the review along with the reasons for exclusion are detailed in Appendix 2.

Table 1: INCLUDED STUDIES

Getsios D, Blume S, Ishak J et al. Cost effectiveness of donepezil in the treatment of mild to moderate Alzheimer's disease. *Pharmacoeconomics* 2010;28(5):411-427.

Guo S, Hernandez L, Wasiak R et al. Modelling the clinical and economic implications of galantamine in the treatment of mild-to-moderate Alzheimer's disease in Germany. *J Med Economics* 2010;13(4):641-654.

Hartz S, Getsios D, Tao S et al. Evaluating the cost effectiveness of donepezil in the treatment of Alzheimer's disease in Germany using discrete event simulation. *BMC Neurology* 2012;12:2.

Nagy B, Brennan A, Brandtmuller A et al. Assessing the cost-effectiveness of the rivastigmine transdermal patch for Alzheimer's disease in the UK using MMSE- and ADL-based model. *Int J Geriatr Psychiatry* 2011;26:483-494.

Peters JL, Anderson R, Hoyde M et al. Evolution of a cost-utility model of donepezil for Alzheimer's disease. *Intl J of Technology Assessment in Health Care* 2013;29(2):147-154.

Wimo A, Gaudig M, Schauble B et al. The economic impact of galantamine vs placebo: An analysis based on functional capacity in a Swedish cohort study. *J Medical Economics* 2012;12(5):1019-1024.

ABSTRACTS:

Turongkaravee S. Cost utility analysis of cholinesterase inhibitors in the treatment of mild to moderate Alzheimer's disease. *Value in Health* 2010;13(7):A502.

Permsuwan U, Niwatananun W, Pimkrai A. Cost-utility analysis of donepezil for the treatment of Alzheimer's disease in Thailand. *Value in Health* 2012;15:A648.

3.3.2 Assessment of Current Pharmacoeconomic Literature

The following is a summary and critique of the literature published subsequent to the latest NICE review divided by drug treatment. This review is followed by a detailed summary of all cost effectiveness studies of cholinesterase inhibitors that were conducted from a Canadian perspective.

Donepezil

There are only two new studies published in full, involving donepezil, that are relevant in answering the question: Getsios from a UK perspective and Hartz from a German perspective. (Getsios 2010, Hartz 2012) Both used the same discrete event simulation model, but incorporated country specific parameters where available. Both found donepezil dominated no treatment in mild to moderate patients. The design of these models makes it very difficult to evaluate their validity, without access to the original trial data on which they were based, as there is no way of assessing the appropriateness of the equations used to model an individual patients' progress through the model. One of the studies did provide one internal validity check. Hartz found that their model predicted a 1.92 point improvement in MMSE compared with a 1.88 point improvement seen within the clinical trial. More detailed information would be needed to fully assess the accuracy of the modeling exercise.

Getsios D, Blume S, Ishak J et al. Cost effectiveness of donepezil in the treatment of mild to moderate Alzheimer's disease. *Pharmacoeconomics* 2010;28(5):411-427.

A discrete event simulation model was developed to compare the cost effectiveness of donepezil versus no treatment in the treatment of mild to moderate AD from a UK perspective. The analysis was conducted from both a societal and a healthcare system perspective with patients modeled for a period of 10 years. Costs were adjusted to 2007 values and both costs and utilities were discounted at a rate of 3.5%. Progression through the model incorporated treatment effects on cognition, behavior and function. Both patient and caregiver utilities were considered within the analysis. Donepezil dominated no treatment in mild to moderate patients with AD. From a HCS perspective donepezil resulted in cost savings of £1,600 per patient in those with moderate disease and £4,000 per patient with mild disease. In probabilistic sensitivity analyses, the ICER for donepezil versus no treatment was below £30,000 per QALY in 78% of replications within mild patients and 74% of replications for moderate patients.

Factors which may limit the utility of this study in aiding in decision making include:

- the lack of transparency within the model.
- improvements in functioning were associated with delays in institutionalization which have not been directly demonstrated in clinical trials
- the study is conducted from a UK perspective

Hartz S, Getsios D, Tao S et al. Evaluating the cost effectiveness of donepezil in the treatment of Alzheimer's disease in Germany using discrete event simulation. *BMC Neurology* 2012;12:2.

This cost utility analysis compared treatment with donepezil versus no treatment in mild to moderate AD patients and donepezil versus memantine in moderate AD patients from both a German health care system and societal perspective. A discrete event simulation model was developed to model the progression of patients with AD with respect to cognition, behavior and function. The time line for the model was 10 years and a 3% discount rate applied to both costs and utilities. Utilities were derived from the literature for patients and from donepezil trials for caregivers. As there are no stopping rules in Germany, patients with severe AD were assumed to continue on treatment until death. In patients with mild to moderate AD donepezil treatment dominated no treatment and in moderate patients donepezil dominated memantine treatment. Sensitivity analysis found the results to be insensitive to changes in caregiver time, costs, utilities, institutionalization and treatment effects. Donepezil dominated no treatment in mild to moderate AD patients in 100% of the replications within the probabilistic sensitivity analysis.

Factors which may limit the utility of this study in aiding in decision making include:

- the lack of transparency within the model
- improvements in functioning were associated with delays in institutionalization which have not been directly demonstrated in clinical trials
- the assumptions that patients continued treatment with cholinesterase inhibitors until death is inconsistent with current Canadian recommendations
- the study is conducted from a German perspective

Rivastigmine

Nagy B, Brennan A, Brandtmuller A et al. Assessing the cost-effectiveness of the rivastigmine transdermal patch for Alzheimer's disease in the UK using MMSE- and ADL-based model. *Int J Geriatr Psychiatry* 2011;26:483-494.

This cost utility analysis compared the cost effectiveness of rivastigmine patches and capsules versus best supportive care in AD patients with mild to moderate disease. A model was created which followed patients over the course of 5 years estimating the costs and QALYs associated with the 3 treatment arms from the perspective of the UK healthcare and societal perspective. Disease progression was modeled using a published longitudinal study that followed untreated patients for 7 years. Costs included within the model were medications, monitoring, physician visits and institutionalization. It was assumed that all institutional costs were borne by the healthcare payer. Costs were adjusted to 2008 values and were discounted at a rate of 3.5% per annum, as were utility values. A sensitivity analysis incorporated caregiver time. Both one way deterministic and probabilistic sensitivity analyses were conducted. Two models were considered, one in which only the cognitive functioning of patients was mapped to utility values and a second in which both the cognitive and activities of daily living were mapped to utilities. In the first model the incremental cost per QALY was £10,579 for rivastigmine patch versus BSC and £15,154 for rivastigmine capsule versus BSC. In the second model which incorporated activities of daily living impacts the incremental cost per QALY was £9,114 for rivastigmine patch versus BSC and £13,758 for rivastigmine capsule versus BSC. Results were

relatively insensitive to changes in assumptions regarding the perspective of the analysis, probability of institutionalization and regression mapping of behavioral outcomes to utility values. At £20,000 per QALY 100% of replications were cost effective for the patch and 87.9% for the capsule.

Factors which may limit the utility of this study in aiding in decision making include:

- the institutional costs were all assumed to be borne by the HCS. Generally, within Canada, a portion of these costs are born by the patient and their family
- improvements in functioning were associated with delays in institutionalization which have not been directly demonstrated in clinical trials
- the study is conducted from a UK perspective

Galantamine

Wimo A, Gaudig M, Schauble B et al. The economic impact of galantamine vs placebo: An analysis based on functional capacity in a Swedish cohort study. *J Medical Economics* 2012;15(5):1019-1024.

This cost consequences analysis examined the cost implications of treatment of patients with mild to moderate AD with galantamine as compared with placebo based on a 6 month randomized clinical trial which included 80 patients. The analysis appears to have been conducted from a Swedish societal perspective with costs derived from a Swedish database of resource use and costs which included 162 dementia patients over 75 years of age. Activities of daily living scores (ADL) from the clinical trial were mapped to a second ADL scoring system (Katz) to allow linkage of the scores to costs within the database. A number of different approaches for categorizing the ADL scoring systems were examined including one which considered only those patients living at home within the database as compared with the total population of those living at home and in care. The study found no significant difference in costs between galantamine 79,774 SEK (51,605 SEK to 107,943 SEK) versus placebo 110,809 SEK (76,310 SEK to 145,309 SEK). Results were consistent throughout sensitivity analyses. The authors concluded that the addition of galantamine is cost neutral, while offering an improvement in treatment of AD based on clinical trial data.

Factors which may limit the utility of this study in aiding in decision making include:

- there were small numbers in both the randomized controlled trial (RCT) and the costing database. The costing database only included patients over 75 years of age with dementia and was not specific to those with AD
- the RCT was short term at only 6 months
- the linking of the data used only one measure, ADL (not cognition)
- the study received industry sponsorship
- the study is conducted from a Swedish perspective

Guo S, Hernandez L, Wasiak R et al. Modeling the clinical and economic implications of galantamine in the treatment of mild-to-moderate Alzheimer's disease in Germany. *J Med Economics* 2010;13(4):641-654.

This study used a discrete event simulation model derived from patient data from two large US galantamine clinical trials and adjusted for the age and sex distribution of German AD patients to compare the cost effectiveness of galantamine versus ginkgo biloba and no drug treatment. The population modeled had mild to moderate AD. The model estimated the efficacy of treatment with respect to effects on time spent in severe disease, time spent in institutional care and caregiver time as well as the costs of care over a course of 10 years. Costs and health benefits were discounted at a rate of 5% per annum. The model assumed no effect of treatment on survival, but did assume an impact on delayed institutionalization. Galantamine resulted in greater reductions in time spent in institutional care, time spent in a severe state and in caregiver time relative to the other two treatment arms. Galantamine was also associated with lower costs versus placebo (net savings of €3,978) and versus ginkgo biloba (net saving of €3,972). In one way deterministic sensitivity analyses results were insensitive to changes in efficacy assumptions, discontinuations, costs, discount rate, resource use and increased mortality for all AD patients relative to the general population.

Factors which may limit the utility of this study in aiding in decision making include:

- the lack of transparency within the model
- the benefits of treatment were primarily with respect to reduced time in institutions and severe disease. These benefits are assumed based on improvements in cognition, but have not been shown directly in clinical trials.
- the patient population reflected a clinical trial database which is likely to be a selective group of patients and although it was adjusted for the age and sex of the German AD population, it may not be representative of this population.
- This study received pharmaceutical industry sponsorship.
- The study was not conducted from a Canadian perspective.

3.3.3 Canadian Studies

There are five studies examining the cost effectiveness of cholinesterase inhibitors in the treatment of Alzheimer's disease from a Canadian perspective. A summary of each of the studies is provided below with an assessment of their limitations. Unfortunately, all of the studies are quite old, being published between 1999 and 2004.

O'Brien BJ, Goeree R, Hux M, Iskedjian M, Blackhouse G, Gagnon M, *et al.* Economic evaluation of donepezil for the treatment of Alzheimer's disease in Canada. *J Am Geriatr Soc* 1999;**47**:570–8.

In 1999 O'Brien and colleagues conducted a cost effectiveness analysis comparing donepezil versus no treatment in mild to moderate Alzheimer's patients. A decision analytic model was used to project the course of the disease over a 5 year time period and to estimate the benefit and costs of treatment. The analysis was conducted from the perspective of the Canadian society incorporating both medical costs and the value of unpaid caregiver time. Efficacy was measured as the increased number of years per patient in non-severe disease and costs were derived from Canadian sources including the Canadian Study of Health and Aging. The characteristics of the patients entered into the model are based on the donepezil clinical trial, weighted by the population in an Alberta based AD clinic. The study was funded

by the pharmaceutical industry. Treatment with donepezil increased the amount of time spent in a non-severe state to 2.41 years as compared with 2.21 years with no treatment. Donepezil was also associated with a cost savings over the five year time period (\$80,305 for donepezil versus \$81,187 for no treatment). This resulted in donepezil being the dominant treatment over no treatment from a Canadian societal perspective.

Factors which may limit the utility of this study in aiding in decision making include:

- The age of the study given that it was completed over 13 years ago.
- The inclusion of unpaid caregiver time within the costs, which are not born by the healthcare system
- The receipt of industry funding

Hauber AB, Gnanasakthy A, Mauskopf JA et al. Savings in the cost of caring for patients with Alzheimer's disease in Canada: An analysis of treatment with rivastigmine. *Clinical Therapeutics* 2000;22(4):439-451.

This study examined the potential cost savings associated with a delay in transition to more severe stages of AD over a 2 year time period. The analysis was conducted from a societal perspective incorporating healthcare costs, community support services and unpaid caregiver time. Resource use and costs were derived from the Canadian Study of Health and Aging. Deterioration in disease was modeled using a decision analytic model based on MMSE scores from two rivastigmine clinical trials. Rivastigmine was estimated to delay the transition of mild patients to more severe AD by 188 days, mild to moderate patients by 106 days and moderate patients by 44 days. These delays were associated with cost savings of \$6.44 per patient per day for mild patients and \$4.93 per patient per day for all patients combined. These estimates do not include the cost of the drug as it was not marketed at the time. This study was supported by the pharmaceutical industry.

Factors which may limit the utility of this study in aiding in decision making include:

- The age of the study, given that it was completed over 12 years ago
- The lack of inclusion of the price of rivastigmine, as it was not marketed at the time of the study
- The inclusion of unpaid caregiver time, as these costs are generally not borne by the Canadian healthcare system
- The limited duration of the analysis of only 2 years

Getsios D, Caro JJ, Caro G et al. Assessment of health economics in Alzheimer's disease (AHEAD). *Neurology* 2001; 57: 972-978.

This study used the AHEAD model to compare the cost effectiveness of galantamine with no treatment over a course of 10 years in patients with mild to moderate Alzheimer's disease from a Canadian societal perspective. The AHEAD model has three states, pre-full time care (pre-FTC), FTC and death. It is primarily US data that has been used to populate the AHEAD model. Efficacy data was derived from two six month placebo controlled clinical trials. The costs included within the model were medical

costs including doctor visits, emergency room (ER) visits, hospitalizations and medications, the costs of institutionalizations and paid home help. For the initial six month period of the model resource use was derived from the clinical trials and for the long term portion, the Canadian Study of Health and Aging was used. Costs were derived from the Quebec healthcare system resources. Effects and costs were discounted at a rate of 3% per annum.

For all mild to moderate patients, galantamine was associated with an increase in pre-FTC time by 5.3% and a decrease in time spent in FTC of 9.9%. For patients with moderate disease, time in pre-FTC care increase 10.1% and time in FTC decreased 11.2%. Costs were \$788 lower in the galantamine treatment group as compared with the no treatment group when considering all patients and \$3,718 dollars lower when considering only moderate patients. Although conflicts of interest were not cited within the published paper, the authors of this study are employees of a consulting firm which completed the two analyses summarized below, both sponsored by the pharmaceutical industry.

Factors which may limit the utility of this study in aiding in decision making include:

- The age of the study, given that it was completed over 11 years ago
- The inclusion of paid home help, the cost of which is generally not borne by the Canadian healthcare system
- Assumptions regarding a correlation between a slowed decline in cognitive function and both a delay in need for FTC and a reduced duration of FTC, which were not measured within the clinical trials

Caro J, Getsios D, Migliaccio-Walle K et al. Rational choice of cholinesterase inhibitor for the treatment of Alzheimer's disease in Canada: a comparative economic analysis. *BMC Geriatrics* 2003;3:6.

In a study by Caro and colleagues the AHEAD model was used to compare the cost effectiveness of donepezil 5 and 10 mg, rivastigmine 1-4 mg and 6-12 mg, galantamine 16mg and 24mg and no treatment over a course of 10 years. Efficacy was assessed based on changes in cognitive scores sourced from Cochrane meta-analyses which compared each of the treatments with placebo. Formal multiple treatment comparisons were not conducted. The perspective of the analysis was somewhat broader than the healthcare system as informal costs such as those for in-home personal care were included. Resource use was derived from the Canadian Study of Health and Aging and unit costs from the province of Quebec. Seventy three percent of patients requiring full time care were assumed to be in institutions. Costs and utilities were discounted at a rate of 3% per annum. All treatments were more efficacious than no drug therapy with the greatest improvements reported for galantamine followed by donepezil and then rivastigmine. Both doses of galantamine and donepezil 10 mg were associated with cost savings relative to no drug treatment. Overall galantamine 24 mg dominated all other treatments as it was both more efficacious and produced greater cost savings. The base case assumed no effect of treatment on mortality; however, sensitivity analyses incorporating a survival benefit of treatment resulted in all treatments costing more than no drug treatment, although the relative position of the medications cost effectiveness did not change.

Factors which may limit the utility of this study in aiding in decision making include:

- The age of the study, given that it was completed over 9 years ago
- The perspective of the study was somewhat greater than the healthcare system and therefore included costs outside of the healthcare system
- Efficacy measures were derived from separate systemic reviews for each of the three treatments rather than either head to head trials or a multiple treatment comparison. The patient populations included within the clinical trials may have differed significantly from one drug to another.
- Assumptions regarding a correlation between a slowed decline in cognitive function and both a delay in need for FTC and a reduced duration of FTC, which were not measured within the clinical trials
- Industry sponsorship

Caro J, Salas M, Ward D et al. Assessing the health and economic impact of galantamine treatment in patients with Alzheimer's disease in the health care systems of different countries. *Drugs Aging* 2004;21(10):677-686.

A second study by the same authors used the AHEAD model to assess the relative cost effectiveness of galantamine versus placebo in seven countries, including Canada over a 10 year time period for the treatment of mild to moderate Alzheimer's disease. Efficacy data were derived from three clinical trials comparing galantamine 16 mg/day with placebo. Efficacy was measured as both a delay in need for full time care and quality adjusted life years. A societal perspective was adopted for the analysis which included the costs of medical services (doctors, physical and occupational therapists, psychotherapists, nurses, ER, nursing home, drug, hospital) and social services costs (respite care, home help, day care, home meals etc.) Costs and effects were discounted at a rate of 3% per annum. In Canada over 70% of patients in FTC were assumed to be in institutions. The improvement in cognition scores seen with galantamine are assumed to delay entrance into full time care and are therefore associated with cost savings. Time until full time care is predicted to increase by 6.8% from the non-treatment average time of 3.2 years. Assuming no survival benefit for treatment resulted in a net saving of €1,227 from a Canadian perspective.

Factors which may limit the utility of this study in aiding in decision making include:

- The age of the study, given that it was completed over 8 years ago
- The societal perspective of the study which includes costs not borne by the Canadian healthcare system
- Assumptions regarding a correlation between a slowed decline in cognitive function and both a delay in need for FTC and a reduced duration of FTC, which were not measured within the clinical trials
- Industry sponsorship

Discussion of Canadian Studies

The majority of literature is quite old, with none of the studies being conducted subsequent to 2004. This is of particular concern given that both galantamine and rivastigmine are available in generic formulations at lower costs than the original branded products considered within these analyses. None of the cost effectiveness analyses conducted from a Canadian perspective may be considered independent as all appeared to receive pharmaceutical industry funding. All were conducted from a societal perspective incorporating costs which are outside the scope of the healthcare system. Three of the studies are based on the AHEAD model, which uses US data to inform the base transition probabilities within the model and may not reflect the natural history of AD in Canada given the differences in the healthcare systems. The use of the single comparative study by Caro to establish the relative cost effectiveness of treatments should be cautioned against as the efficacy data is based on three separate Cochrane reviews that compared each treatment to placebo. The populations within the trials may differ substantially leading to differences in results which are, in fact, an artifact of trial inclusion/exclusion criteria. These studies also suffer from many of the drawbacks of the previously reviewed pharmacoeconomic literature in that they require assumptions regarding the relationship between decline in cognitive function and quality of life, costs and institutionalization.

3.4 Discussion of the Assessment of the Pharmacoeconomic Literature

1. What is the comparative cost-effectiveness of the drugs under review (the cholinesterase inhibitors – ChEIs) for all patients with mild to moderate Alzheimer’s disease?

A search of the literature did not reveal any well-designed independent cost effectiveness studies examining cholinesterase inhibitors in mild to moderate Alzheimer’s disease from a Canadian perspective. If a decision must be made based on current evidence the most recent analysis conducted by NICE within the UK provides an objective estimate of cost effectiveness; however, differences in healthcare systems may significantly affect the results of these analyses. This is particularly true within this area where the benefits of treatment are small and the long term benefits are assessed using modeling techniques which require assumptions regarding effects on institutionalization and mortality. Additionally, the rate and funding for institutionalization varies greatly between countries which is a large component within the cost effectiveness estimates. The authors of the NICE analysis caution that there is a great deal of uncertainty both with respect to the structural modeling of AD and with the parameter estimates. Bearing this in mind, their report found the cholinesterase inhibitors to be cost effective in the treatment of mild to moderate AD based on a willingness to pay of £30,000 per QALY.

2. What is the comparative cost-effectiveness of the drugs under review for subpopulations of patients with mild to moderate Alzheimer’s disease?

It is common throughout the literature to consider mild and moderate AD as both a single group, but also to consider the cost effectiveness of treatment in these two groups separately. The two NICE HTAs did not appear to conduct subgroup analysis based on severity of AD, although the first

publication led to a recommendation for funding in moderate patients; whereas, the second recommended funding in mild and moderate patients. From the published literature there is varying evidence, some supporting greater cost effectiveness in mild patients and some supporting greater in moderate patients. Further study would be required to answer this question.

Although there is an interest in addressing the impact of genetic testing on targeted AD treatment and its cost effectiveness, studies in this area, thus far, have been mainly based on hypothetical data.

3. Based on cost-effectiveness, should one or more of the drugs under review be preferred for coverage?

A review of the published literature does not provide support for coverage of one drug rather than another or for the cost effectiveness of the use of a specific agent as first line therapy. The comparative clinical data from head to head randomized controlled trials is sparse therefore limiting conclusions regarding comparative efficacy. Although in the deterministic analysis of the NICE report, donepezil and galantamine appeared more cost effective than rivastigmine capsules and patch, the probabilistic sensitivity analysis did not indicate that any therapy had a significantly greater chance of being cost effective than another. This is primarily due to the large degree of uncertainty within the analysis. At present there is insufficient evidence to support assessing the drugs comparatively; therefore, they are considered as a class.

4. Assessment of Methodological Considerations

There are a large number of possible measures which may be used to assess both the natural course of Alzheimer's disease and the impact of treatment. These include measures of cognitive function, functional capacity (e.g. activities of daily living), behavior symptoms, psychological symptoms, quality of life, health resource utilization, impacts on institutionalization and impacts on mortality.

4.1 Cognitive Function, Functional Capacity, Behavioural symptoms, Psychological Symptoms

The most common measure used in modeling the natural history of AD and the treatment effect of cholinesterase inhibitors is MMSE. Many of the clinical trials used the ADAS-cog as an assessment tool for cognitive function, requiring a conversion between the two scales in order to enable modeling. MMSE has an advantage in that it has been mapped to both utility values and to the probability of institutionalization based on both US and UK epidemiological data. MMSE is also a well validated instrument for the diagnosis of dementia related diseases.

Older cost effectiveness analyses tended to model based solely on cognitive decline; however newer studies such as the HTA by NICE have attempted to incorporate functional capacity through measures such as activities of daily living. In general the clinical data regarding effects on behavioural or psychological symptoms are lacking and therefore are not incorporated within the models.

Concerns have been raised that the decline in cognitive function and/or in the activities of daily living do not represent the most important factors for caregivers and patients when addressing the progression of Alzheimer's disease.

The majority of clinical studies measuring MMSE do so at approximately a 6 month time point. There is only limited evidence of longer term efficacy based on well controlled trials. Therefore, in developing an economic model, assumptions must be made with regards to the long term efficacy of treatments after the 6 month timeframe. In most models it is assumed that from this time point on, patients decline at a level parallel to that of placebo. This means that the disease is progressing at the same rate; however, due to the benefits in the first six months of treatment the time for patients to decline to a severe MMSE is extended by the treatment.

Cross sectional studies have been used to establish a relationship between MMSE and utility values and probability of institutionalization. Based on these studies, the proportion of patients institutionalized is greater in patients who have lower MMSE scores indicating poorer cognitive function. Similarly, average utility values tend to be lower in groups of patients with lower MMSE scores. Fuller discussion of both the effect on institutionalization and on patient's quality of life is provided in the next two sections. There is also heavy reliance on MMSE scores with respect to estimating the costs of AD management.

4.2 Time to institutionalization

A large portion of the costs associated with Alzheimer's disease are due to institutionalization which occurs predominantly in the later, more severe stages of the disease. As institutionalized care is very expensive, treatments which delay and reduce the time spent in institutions are more likely to be cost effective. Unfortunately, evidence regarding the impact of cholinesterase inhibitors on either a delay in institutionalization or a reduction in time spent in an institution is lacking.

Clinical studies have demonstrated an improvement in cognitive function with cholinesterase inhibitors, but they are generally of too short a duration to demonstrate an impact on institutionalization or survival. Most economic models assume that the improvement in cognitive function is associated with a delay in institutionalization. This is based on cross functional epidemiological data which shows that with lower MMSE scores, there is a higher portion of the Alzheimer's population within institutions. There is, however, no direct evidence that an improvement in cognitive function with treatment is associated with a delay in institutionalization. As there is also no evidence of an effect of treatment on mortality, most studies assume no survival benefit with treatment. Together, these assumptions manifest as a reduced time in an institution with cholinesterase inhibitors. As institutionalization is very expensive, these costs are a significant portion of the cost calculation within the cost effectiveness analyses. This leads to a dominant result, although the evidence supporting the result is weak.

4.3 Quality of Life:

There are very few randomized controlled trials involving cholinesterase inhibitors in the treatment of Alzheimer's disease which examined the impact of treatment on quality of life.

There are three published short term donepezil studies which provided a patient rating of quality of life and one also provided a caregiver rating of quality of life. (Rogers 1996, Rogers 1998, Rogers 1998) The rating scales used have not been validated in AD and were general health questionnaires. The studies showed varied results with some reporting an improvement relative to no treatment and some reporting no difference. This may be due to the instruments used or to the small number of studies in this area. The results have not been converted to utility values for use in economic analyses. We are not aware of any studies for galantamine or rivastigmine incorporating quality of life measures.

As discussed in the section regarding clinical measures, to model the long term impact of cholinesterase treatments on quality of life the MMSE scores of patients within the trials have been mapped onto utility values from the literature. There are a number of papers within the literature which use either the EQ-5D, the Health Utilities Index (HUI) 2 or 3 in a cross sectional population of Alzheimer's patients or their caregivers to measure quality of life in addition to MMSE scores, thereby providing a relationship between the two measures within a cohort of patients. As expected, lower MMSE values are associated with lower utilities. Whether this relationship holds true with respect to an individual's variation in MMSE over time, while on treatment is unclear. The benefits seen with these drugs are generally small and the minimal clinically significant effect required to impact a patients' quality of life is uncertain.

One of the difficulties in measuring quality of life in AD is in determining who is best able to assess the patients' quality of life given the nature of the disease. In milder stages of the disease the patient may be able to do so; however, in more severe stages a caregiver proxy is usually more appropriate. There are some studies which have assessed quality of life of AD patients by both the patient themselves and by caregiver proxy. These lead to quite different results with caregiver's generally providing lower utility values than patients.

With respect to economic modeling, some studies consider only the AD patient's quality of life (QOL), whereas others also incorporate the impact of treatment of the patient on the caregiver's quality of life. There is, however, only limited evidence regarding the effect of treatment on caregiver's QOL.

4.4 Mortality

There are no studies that have demonstrated an effect of cholinesterase inhibitors on survival of patients with AD. In general, most modeling studies assume no effect on survival of treatment. Although this may be viewed as a conservative assumption in most analyses, assuming a delay in institutionalization with no survival benefit results in the implication that cholinesterase inhibitors significantly reduce the time patients spend in institutions. As institutionalization is a large portion of

the costs associated with AD, this assumption will optimize the cost effectiveness estimates of the treatments. The most recent HTA by NICE assumed no survival benefit of treatment in the base case; however, within a sensitivity analysis, they tested this assumption assuming that the delay in decline in MMSE was also associated with a delay in mortality. This significantly increased the ICERs for the cholinesterase inhibitors resulting in them no longer being considered cost effective at the generally accepted UK threshold of £30,000 per QALY.

4.5 Utilization / costs of physician services, drugs, hospital services and other care (home support)

There are very few studies which have examined the effects of treatment with cholinesterase inhibitors on resource use and costs within AD clinical trials. One study by Feldman and one by Wimo, both involving donepezil conducted economic analyses based on this type of data from randomized clinical trials. (Feldman 2001, Wimo 2003)

The study by Wimo assessed the resource utilization and costs for donepezil versus placebo over a 12 month period based on a RCT. Patient costs were slightly higher within the donepezil group at 137,752 SEK as compared with the placebo group at 135,314 SEK. The costs for hospitalizations and emergency room visits were higher within the donepezil group; whereas, the costs of social services and accommodation were higher within the placebo group. None of the differences reached statistical significance.

Feldman assessed the resource use and costs for donepezil versus placebo over a 24 week study period based on a RCT; however, the patient population included only moderate and severe Alzheimer's patients and the results may not apply to the population of interest within this review. The baseline adjusted total patient costs were numerically slightly higher for donepezil; whereas the total costs, including caregiver time and caregiver healthcare were numerically slightly higher for placebo. The confidence intervals of the estimates showed substantial overlap.

Other modeling studies are based on costs from cross sectional studies examining the average cost of treating patients at a certain stage of disease, generally with respect to measurement of MMSE. One factor which is often not considered within modeling studies, but should be if the study is conducted from the perspective of the healthcare system is with respect to who bears the cost of institutionalization. In many countries, a portion of this cost is borne by patients which influences the cost effectiveness of treatments from the perspective of the healthcare system.

4.6 Caregiver impact

There is a dearth of literature examining the effects of treatment with cholinesterase inhibitors on both the well-being and the costs of care for caregivers of patients with AD. In 2009 Schoenmakers conducted a meta-analysis examining whether pharmacological treatment of behavioral disturbance of patients with dementia lowered the burden and time spent by the family caregiver. (Schoenmakers

2009) Treatment of behavioral disturbances in patients with AD was associated with lower caregiver burden and reduced time spent in caregiving (41.65 minutes). It is difficult to draw conclusions from this study, however, as the effects of all pharmacological treatments were combined. Of the eight studies in this area, only five focused on cholinesterase inhibitors (3 on donepezil and 2 galantamine). The remaining studies examined antipsychotics and antidepressants.

A systematic review by Levy was published in 2012 which examined if the treatment of neuropsychiatric symptoms with cholinesterase inhibitors in AD relieved caregiver burden. (Levy 2012) Overall results were mixed with some studies reporting reduced caregiver burden and others reporting similar effects on caregiver burden with treatment as compared with placebo. The authors concluded that although cholinesterase inhibitors may be somewhat effective in reducing caregiver burden, it is difficult to quantify the true treatment effect.

4.7 Discussion of the Assessment of Methodological Considerations

The question posed for the review was:

What are the reliable measures that can be used to determine and delineate comparative cost-effectiveness? These may include health services utilization rates, including:

- time to institutionalization;
- quality of life;
- mortality;
- utilization / costs of physician services, drugs, hospital services, and other care (e.g., home support);
- caregiver impact.

Time to institutionalization and mortality are both very important outcome measures which have been shown to contribute significantly to the uncertainty with respect to the cost effectiveness of these medications; however, there is currently no good quality evidence that treatments affect these outcomes.

Quality of life is also a relevant measure, as it would serve to better understand the impact of the improvements in clinical measures with respect to cognition and behavior scales on the burden faced by patients and caregivers. It would allow one to answer the question: does an improvement in cognition with treatment transfer into a meaningful improvement in the disease from the standpoint of the patient and caregiver? To date, however, there is little direct evidence from clinical trials on the effect of treatment on quality of life. A contributing factor may be the difficulties face in assessing patient's with this disease.

There is also little information regarding the effect of treatment on utilization and cost of medical services. The few small trials that have examined resource use and costs in treated patients have not shown significant differences between treated and untreated groups. The short term nature of the

trials and high level of variability in costs may contribute to the difficulty in demonstrating differences between treatment arms. As the costs of institutionalization are a main cost driver in many of the cost effectiveness analyses, long term studies examining this endpoint may be useful in assessing differences in resource use with treatment.

Lastly, with respect to caregiver impact, there is some evidence to support that treatment with cholinesterase inhibitors may reduce caregiver burden through reducing the amount of time spent in direct patient care; however, further well-designed trials are needed to validate this finding.

Overall, the most common approach used in modeling cost effectiveness of these treatments is to use measures of cognition and activities of daily living and, less frequently, behavior, from clinical trials. These results are then linked to cross sectional data regarding resources, costs, utilities and the need for institutionalization to provide inputs to the cost effectiveness models. The validity of such linkages with respect to disease progression has not been validated.

5. Assessment of Evidence Gaps

The review of the literature and the assessment of methodological considerations provide a window to the significant number of areas for which increasing our knowledge of the impact of cholinesterase inhibitors would provide better estimates of their cost effectiveness. As cited by NICE within their most recent health technology assessment, there is a great deal of structural uncertainty within their disease model in addition to the uncertainty regarding the impact of treatments. This is in part due to the limited information available regarding the natural progression of Alzheimer's within the population and the fact that much of the data used to populate the model is dated. This may be of particular concern within this disease area as treatment patterns, particularly with respect to institutionalization of patients, have changed substantially in the past 20 years.

There are a number of uncertainties with respect to the cost effectiveness of cholinesterase inhibitors in the treatment of Alzheimer's disease from a Canadian perspective. The most relevant of these are:

- The lack of independent cost effectiveness analyses conducted from a Canadian perspective
- The lack of clinical evidence regarding the effect of treatment on delay in institutionalization, time spent within an institution and mortality
- A lack of understanding of the impact of treatment, if any, on the behavioural and psychological components of the disease
- A lack of evidence of long term benefits of treatment in addition to an understanding of the course of the disease after discontinuing therapy
- The lack of a direct assessment of the impact of treatment on the quality of life of patients and caregivers and the need for further elucidation as to what a clinically meaningful change is with respect to clinical outcomes

- The lack of an assessment of resource use and costs directly from long term trials
- A paucity of information regarding the course of the disease and its management within current Canadian society. This includes an understanding of the extent of institutionalization of patients with Alzheimer's, the factors that influence the need for institutionalization and current Canadian costs of management.
- Little information regarding the effect of the duration of the analysis on the results of cost effectiveness analyses. Generally, shorter durations tend to result in treatments appearing less cost effective as fewer institutional costs are accounted for. However, as the clinical trials are of short duration, extended models rely much more heavily on assumptions in order to provide longer term estimates. Most of the long term benefits have not been directly demonstrated within clinical trials.

Although one could pursue an independent cost effectiveness analysis of cholinesterase inhibitors from a Canadian perspective, based on the uncertainty in the data to inform the creation of the model and the impact of treatments, it is likely that the results may not differ significantly from those arrived at by NICE. Depending on which assumptions are made with respect to the input parameters, the results of studies vary from the treatments being cost ineffective to the treatments dominating no treatment. Regardless, the uncertainty surrounding the results is significant. Before entering into such a project it would be best to assess the availability of good quality current Canadian epidemiological data regarding Alzheimer's disease. In addition, further study to bridge the evidence gaps particularly with respect to the effect of treatment on institutionalization and mortality, would be of great value.

6. Conclusions

Well designed, independent cost effectiveness analyses of cholinesterase inhibitors from a Canadian perspective are lacking. Evidence from NICE suggests that they may be cost effective in mild to moderate AD from a UK perspective. Caution should be exercised in applying these results within Canada both due to differences in care for AD patients between the two countries and due to the uncertainty surrounding the results of the NICE assessment.

There are a number of methodological gaps in our knowledge regarding both the course of AD within Canadian society and with respect to the impact of treatment on outcomes that are both important to caregivers and patients and may demonstrate a cost benefit specifically with respect to improved quality of life, time spent in institutions and mortality.

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APPENDIX 1: SEARCH STRATEGY

A search of the medical literature from 2010 to present in Medline (indexed, in-process and other non-indexed), Embase, Cochrane database, NHS EED was conducted in order to capture all relevant literature based on the NHS EED recommended search strategy published subsequent to the most recent NICE review. Key search words included, "economics", "costs", "cost", "costly", "price", "pricing", "pharmacoeconomics", "expenditure", "value", "budget", "donepezil", "aricept", "galantamine", "reminy", "razadyne", "rivastigmine", "exelon", "alzheimer's disease" and "dementia". In addition, the reference lists of retrieved studies were hand searched.

APPENDIX 2: EXCLUDED STUDIES

The following table lists the studies which were excluded from the literature review with the reason for exclusion.

Table 2: EXCLUDED STUDIES

Reference	Reason for Exclusion
Budd D, Burns LC, Guo Z et al. Impact of early intervention and disease modification in patients with predementia Alzheimer's disease: a Markov model simulation. <i>ClinicoEconomics and Outcomes research</i> 2011;3:189-195.	Evaluation of early assessment
Djalalov S, Yong J, Beca J et al. Genetic testing in combination with preventive donepezil treatment for patients with amnesic mild cognitive impairment. <i>Mol Diagn Ther</i> 2012;16:389-399.	Not mild to moderate AD patients
Getsios D, Blume S, Ishak KJ et al. An economic evaluation of early assessment for Alzheimer's disease in the United Kingdom. <i>Alzheimer's & Dementia</i> 2012;8:22-30.	Evaluation of early assessment
Gustavsson A, Van Der Putt R, Jonsson L et al. Economic evaluation of cholinesterase inhibitor therapy for dementia: comparison of Alzheimer's disease and dementia with Lewy bodies. <i>Int J Geriatr Psychiatry</i> 2009;24:1072-1078.	Not focused on AD
Hyde C, Peters J, Bond M 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. <i>Age and Ageing</i> 2013;42:14-20.	Review article
Knapp M, Lemmi V, Romeo R. Dementia care costs and outcomes: a systematic review. <i>In J Geriatr Psychiatry</i> 2013;28:551-561.	Review article
Knoth R, Bentley T, Richardson S et al. Cost-effectiveness of donepezil 23 mg in the treatment of moderate to severe Alzheimer's disease from a US payor perspective. <i>Alzheimer's & Dementia</i> 2011;7(4):S797.	Moderate to severe AD
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. <i>Arch Geront and Geriatr</i> 2010;50:295-299.	Mild cognitive impairment
Lachaine J, Beauchemin C, Legault M et al. Economic evaluation of the impact of memantine on time to nursing home admission in the treatment of Alzheimer disease. <i>Can J Psychiatry</i> 2011;56(10):596-604.	Memantine
Pfeil Am, Kressig RW, Szucs TD. Alzheimer's dementia: budget impact and cost-utility analysis of a combination treatment with a cholinesterase inhibitor and memantine in Switzerland. <i>Swiss Med Wkly</i> 2012;142:w13676.	Combination therapy with memantine

<p>Pouryamout L, Dams J, Wasem J et al. Economic evaluation of treatment options in patients with Alzheimer's disease. A systematic review of cost-effectiveness analysis. <i>Drugs</i> 2012;72(6):789-802.</p>	<p>Review article</p>
<p>Rive B, Grishchenko M, Guilhaume-Goulant C et al. Cost effectiveness of memantine of Alzheimer's disease in the UK. <i>J Medical Economics</i> 2010;13(2):371-380.</p>	<p>Memantine</p>
<p>Versijpt J. Pharmacoeconomics of Alzheimer's disease (AD) treatment with cholinesterase inhibitors. <i>Acta Neurol Belg</i> 2012;112:141-145.</p>	<p>Review article</p>
<p>Wong CL, Bansback N, Lee PE et al. Cost-effectiveness: Cholinesterase inhibitors and memantine in vascular dementia. <i>Can J Neurol Sci</i> 2009;36:735-739.</p>	<p>Combination therapy with memantine</p>