A Meta-Analysis of Efficacy and Safety of Cholinesterase Inhibitors in Mild to Moderate Alzheimer's Disease with a Systemic Review of Quality of Life, Cost Effectiveness and Dose Delivery Preference

Evaluation of the effect of the three Cholinesterase Inhibitors (ChEIs), donepezil (Aricept®), galantamine (Reminyl®) and rivastigmine (Exelon® oral and transdermal) on patient outcomes compared with placebo and to each other in patients with mild to moderate stages of Alzheimer's disease.

ReVue Drug Evaluation Group and the Programs for Assessment of Technology in Health (PATH) Research Institute
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Title	A Meta-Analysis of Efficacy and Safety of Cholinesterase Inhibitors in Mild to Moderate Alzheimer's Disease with a Systemic Review of Quality of Life, Cost Effectiveness and Dose Delivery Preference
Review Question Requested	Evaluate the effect of the three Cholinesterase Inhibitors (ChEIs), donepezil (Aricept®), galantamine (Reminyl®) and rivastigmine (Exelon® oral and transdermal) on patient outcomes compared with placebo and to each other in patients with mild to moderate stages of Alzheimer's disease. The following are the patient outcomes to be included in the review protocol and the requested search strategy to be incorporated: <u>Efficacy outcomes</u>: • Cognitive function as assessed by any valid method • Daily function as assessed by any valid method • Clinician's global impression of change as assessed by any valid method • Behavioural disturbance (e.g. agitation, psychosis, depression) as assessed by any valid method <u>Harm outcomes</u>: Safety as measured by the incidence of adverse events (including side-effects) leading to withdrawal Evaluate by systematic review the following outcomes: • Quality of Life as assessed by any valid method • Health Care Resource Utilization (e.g. hospital services, physician services) as assessed by any valid method Any clinical efficacy/safety differences between the patch and capsules.
Drug	donepezil (Aricept®), galantamine (Reminyl®) and rivastigmine (Exelon® oral and transdermal)

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ABBREVIATIONS/GLOSSARY

Cholinesterase inhibitors (ChEIs)

Alzheimer's Disease (AD)

Randomized controlled trials (RCTs)

Activities of daily living (ADL)

Mini-mental state examination (MMSE)

AD Assessment Scale – cognitive subscale (ADAS-cog)

Clinician's Interview-Based Impression of Change scale (CIBIC-Plus)

Gottfries, Brane and Steen scale (GBS)

Global Deterioration Scale (GDS)

Severe Impairment Battery (SIB)

Progressive Deterioration Scale (PDS)

Disability Assessment for Dementia (DAD)

Activities of Daily Living (ADCS)

Neuropsychiatric Instrument (NPI)

Quality of Life (QoL)

National Institute for Health and Clinical Excellence (NICE)

Minimal Clinically Important Difference (MCID)

Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Programs for Assessment of Technology in Health (PATH)

EXECUTIVE SUMMARY

1. Background:

Alzheimer's disease is a fatal, progressive and degenerative disease that destroys brain cells. It is the most common form of dementia, accounting for 64 per cent of all dementias in Canada. Alzheimer's disease is not a normal part of aging. Symptoms include having difficulty remembering things, making decisions and performing everyday activities. These changes can affect the way a person feels and acts. There is currently no way to stop the progression of the disease. An estimated 500,000 Canadians have Alzheimer's disease or a related dementia. Over 70,000 of them are under 65 and approximately 50,000 are under the age of 60. It is estimated that 1 in 11 Canadians over the age of 65 has Alzheimer's disease or a related dementia.

Neurotransmitter enhancement therapy with cholinesterase inhibitors (ChEIs) is a treatment approach for patients with mild to moderate Alzheimer's Disease (AD). Cholinesterase inhibitors increase cholinergic synaptic transmission by inhibiting acetylcholinesterase in the synaptic cleft, thereby decreasing the hydrolysis of acetylcholine released from the presynaptic neurons. Donepezil, rivastigmine and galantamine are the three currently approved ChEIs for treating mild to moderate AD symptoms.

To evaluate the potential benefits of ChEIs, two large systematic reviews of the literature have been conducted by NICE (Bond et al. 2012 Technology Appraisal No. 111) and the Cochrane Collaboration (Birks 2006). From their respective reports the overall conclusions regarding a comparison of donepezil, rivastigmine and galantamine suggest that that there is insufficient evidence to indicate that one treatment is better than another. The three drugs appear to show similar benefit for cognitive function and global assessment. Therefore it has been suggested that the ChEIs are taken as a class of drugs. The important question remains whether the differences seen between these agents and placebo are clinically meaningful in the short and long term. This report, in addition to providing an update from the two reviews, will apply the concept of minimal clinically important differences (MCID) which may help to determine the impact of therapy with the ChEIs. Minimal clinically important differences (MCID) are patient derived scores that reflect changes in a clinical intervention that are meaningful for the patient (Cook 2008).

Very little work has been done on the impact of ChEIs on Quality of Life (QoL) and caregiver burden. Also, there have been very few economic assessments that assess the cost effectiveness of the three agents compared to each other.

2. Requested Research Question:

The objective of this study was to evaluate the effect of the three ChEIs, donepezil (Aricept®), galantamine (Reminyl®) and rivastigmine (Exelon® oral and transdermal), on patient outcomes compared with placebo and to each other in patients with mild to moderate stages of Alzheimer's disease. Patient outcomes of interest for the review included the following:

Efficacy outcomes:

- Cognitive function as assessed by any valid method

- Daily function as assessed by any valid method
- Clinician's global impression of change as assessed by any valid method
- Behavioural disturbance (e.g. agitation, psychosis, depression) as assessed by any valid method

Harm outcomes:

- Safety as measured by the incidence of adverse events (including side-effects) leading to withdrawal

Other outcomes:

- Quality of Life as assessed by any valid method
- Health Care Resource Utilization (e.g. hospital services, physician services) as assessed by any valid method
- Clinical efficacy/safety differences between the patch and capsules.

3. Methods:

A systematic literature review was conducted to identify randomized controlled trials (RCTs) evaluating the clinical efficacy and safety of the selected drugs for AD. The search was limited to studies published since 2010, which is the date of the literature search conducted by Bond 2012 for NICE. The data from the relevant studies was combined with previously reported RCTs to update the previous meta-analysis.

A separate literature review was conducted to identify studies that assessed quality of life, health care resource utilization, and cost effectiveness analysis from January 2006 to present date and where RCTs are not identified, observational evidence have been included. A descriptive summary is presented to outline important results.

Additional steps were conducted after updating the previous meta-analysis of the selected drugs versus placebo. First, an indirect comparison (network meta-analysis) was conducted to estimate the relative efficacy and safety between each of the drugs. Second, an assessment of the clinical benefit of achieving a clinically meaningful difference was estimated for the primary outcome of the studies, ADAS-cog at 24 weeks. Third, an assessment of the risk of bias was conducted using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for each new RCT identified to quality the level of evidence. Fourth, a separate exploration was conducted for the relative efficacy, safety, quality of life, resource utilization and caregiver impact for rivastigmine patches versus oral capsules.

4. Results and Interpretation:

a. Meta-analyses

Cognitive Function:

For ADAS-cog, the evidence for the effect of the relevant AD drugs versus placebo was available at the time points 12, 16, 21, 24 and 26 weeks. New RCT evidence was combined for donepezil at 24 weeks. The difference in the mean change from baseline of ADAS-cog for

donepezil versus placebo was -2.27 (95%CI: -2.76 to -1.79). The difference in the mean change from baseline of ADAS-cog for galantamine versus placebo was -2.96 (95%CI: -3.37 to -2.55).

For MMSE, the evidence for the effect of the included drugs versus placebo was available at the time points of 12-13 weeks, and 24-26 weeks. The only new evidence was for donepezil at 24 weeks. The mean difference for MMSE was 1.25 (95%CI: 0.87 to 1.62).

Clinical Global Impression:

For CIBIC-plus, the evidence for the effect of the included drugs versus placebo was available at the time points of 12, 13, 16, 24 and 26 weeks. The only new evidence was for donepezil at 24 weeks. The difference in the mean change from baseline of CIBIC-plus for donepezil versus placebo was -0.39 (95%CI: -0.49 to -0.29).

For ADCS-CGIC, there was newly reported evidence for donepezil but not for the other drugs. The mean change in ADCS-CGIC at 12 weeks was a reduction -0.2 (95%CI: -0.4 to -0.02).

Activities of Daily Living:

The activities of daily living were reported differently for donepezil and galantamine, which limits their comparison. For donepezil, the difference in activities of daily living was reported as a standardized mean difference from a mixture of different scales. For galantamine, the activities of daily living were reported with the ADCS-ADL scale. For both drugs there was an improvement in ADL versus placebo.

Behavioural Disturbance:

Change in behavioural disturbance was a newly reported outcome that had only evidence for donepezil. For donepezil versus placebo, the relative increase in NPI at 12 weeks was 8.0 (95%CI: -0.8 to 16.8), but this was not significant.

Safety:

For withdrawals due to adverse events, the evidence for the effect of the included drugs versus placebo was available at the time points of 24 and 26 weeks. There was new evidence was for all three AD drugs. The odds ratio for withdrawal due to adverse events was 1.48 (95%CI: 0.93 to 2.38) for donepezil, 2.91 (95%CI: 1.50 to 5.66) for rivastigmine, and 1.95 (95%CI: 1.31 to 2.89) for galantamine.

Clinically meaningful differences:

We have demonstrated that the differences in efficacy between the included AD drugs versus placebo are statistically significant, but the magnitude of the differences does not exceed the MCID for the outcomes evaluated, and may not be clinically important. Therefore, based upon the data evaluated, the overall clinical benefit of the AD drugs is disappointing.

Heterogeneity:

For each of the outcomes that were updated, there was an absence of heterogeneity due to a small number of similar studies. This precludes the need for exploration of the source of heterogeneity such as removing outliers or subgroup analysis.

b. Indirect meta-analysis

Indirect meta-analyses were conducted for the outcome of ADAS-cog for weeks 12-16 and weeks 21-26; the outcome of MMSE at weeks 12-13 and weeks 24-26, the outcome of CIBIC-plus for weeks 24-26; and lastly, the outcome of withdrawals due to an adverse event at weeks 24-26.

There were only 2 outcomes that had rates of outcomes that were different from another drug, ADAS-cog at 21-26 weeks, and CIBIC-plus at 24-26 weeks. For ADAS-cog, galantamine had a small but improved rate of ADAS-cog reduction versus donepezil, WMD=0.69 (95%CI: 0.055 to 1.325), p=0.033.

For CIBIC-plus, donepezil had a preferable higher rate of reduction versus galantamine, WMD = -0.168 (95%CI: -0.305 to -0.031), p=0.016. Both differences are small and probably not clinically meaningful.

c. Rivastigmine patch versus capsules

The literature review provided a direct comparison for the outcomes for patients that received rivastigmine. The IDEAL study by Winblad et al in 2007 randomized patients to low dose patches, high dose patches and capsules. There were no differences in efficacy between the 3 treatments, while low dose patches had fewer adverse events. This effect may be dose related since high dose patches had similar safety risk as capsules.

Previous cost effectiveness analysis indicated that differences patches versus oral were not meaningful, such as a difference of costs of £20.8/year, and a difference in quality of life of 0.001 QALYs per year. This analysis was also based on similar prices of the two modalities, suggesting any difference in price is not based on economic benefit. One benefit for patches versus oral is a higher level of satisfaction for caregivers. Patch therapy also appears to improve adherence to therapy, to reduce discontinuation rate and improve ease of administration.

d. Cost Effectiveness

The most recent cost effectiveness evidence by Hyde et al in 2013 has been consistent with previous estimates. There appears to be favourable cost effectiveness for each drug versus placebo, such as cost neutrality or small cost savings and small differences in quality of life. Based on the evidence, there is an absence of differences in costs and quality of life between drugs.

e. Resource Utilization and Quality of Life

The scope of this project was to assess any new economic information from March 2010 (the cut off date for data capture for the NICE review) to December 2013. If there were few high quality publications the search was extended back to 2006 to uncover any reports that may not have been included in the NICE review. The literature from 2006 until December 2013, yielded only one new high quality report on the economics of treatment with the cholinesterase inhibitors (Hyde 2013) and this was a follow up to an earlier report included in the Cochrane review. There are some savings in resource utilization that offsets the cost of the medications. There is a small improvement in the quality of life as well, measured in QALYs. Both the net resource savings and the incremental QALYs are extremely small. In light of the limitation of the precision of

these estimates, one cannot conclude with certainty that there are improvements in quality of life with net resource savings.

All other economic assessments were included in the NICE report and can be reviewed therein or in Appendix 2. Though assessment of the economics of these agents was summarized in the Cochrane and NICE reviews, neither included Canadian sourced information. There have been several older reports, prior to the year 2000 that were Canadian based but these were not included in the NICE and Cochrane reports.

There were no new high quality studies addressing quality of life published after the NICE review. One study (Ward 2008) assessed the impact of cholinesterase therapy on unmet needs in both patients and caregivers. The needs and quality of life of patients attending an outpatient dementia care service were assessed using the Camberwell Assessment of Need for the Elderly (CANE) and Quality of Life in Alzheimer's Disease: Patient and Caregiver report. Other tools used were the Problems Checklist and Carer Strain, the Minimental State Examination (MMSE) and a proforma to obtain sociodemographic details.

It was found that there was reduction in the number of CANE unmet needs and increased combined Quality of Life in Alzheimer's Dementia scores in the first three months amongst the newly referred patients and their caregivers. This study showed that the outpatient prescribing of cholinesterase inhibitors helped to meet the needs of patients and improve patients' quality of life in the first three months. Those patients who were still on cholinesterase inhibitors and being seen in the outpatient dementia care service for nearly two years had low number of unmet needs along with severity of carer strain (distress) and quality of life similar to newly referred patients.

5. Strengths of Review

The strength of this report is the systematic approach to identifying the available RCT evidence to compare each of the drugs versus placebo. In addition, this is the first report that we are aware of that compared the relative safety and efficacy of drugs versus each other. Overall, the final analysis is consistent with the findings of earlier reports.

6. Limitation of Review

The main limitation of the overall findings of this report was the weak inference that can be applied to a lifelong disease. Most trials were for a short duration of 6 months, and the short term finding must be compared to lifelong annual rapid decline in health. In addition, a gap identified in the literature was that there are no new cost effectiveness studies with a Canadian perspective using Canadian drug prices, although all past economic evaluations had similar findings of small cost differences between drugs and small differences in effectiveness between drugs.

7. Conclusions

Overall the meta-analyses of the safety and efficacy of the three agents did not show a change in clinical impact compared to the two recent large reviews (NICE and Cochrane) of these agents. Although the differences in several of the efficacy outcome measures showed improvements compared to placebo at several time points, the differences were not deemed to be clinically

meaningful. There does not appear to be significant efficacy and/or safety differences between the three agents.

Overall, the evidence suggest that all of the 3 drugs provide benefit versus placebo in improvement in cognitive function, clinical global impression, activities of daily living, and behaviour. However, there were also the risk of withdrawal from therapy at 24 weeks, which was estimated as the ratio of the rate of withdrawal for patients receiving active therapy divided by the rate of withdrawal for patients who received placebo to generate an odds ratios relative to placebo of 1.48 for donepezil (p=0.06), 2.91 for rivastigmine (p=0.11), and 1.74 for galantamine (p=0.39). There is no long term evidence on the rates of withdrawals, but there is at least a 48% increase in the odds of withdrawal for the short time period at 24 weeks (i.e, for donepezil). Longer term follow up studies, such as extensions studies or observational data, may be useful to quantify the long term safety.

Comparisons of the transdermal patch delivery of rivastigmine to oral therapy appear to demonstrate equivalent efficacy, with preference for the transdermal patch being indicated by both patients and caregivers due to better adherence to the dosing regimen. One study indicated that both the patch and oral therapy may be cost effective compared to best supportive care but the data is not Canadian based.

There has been no new information on cost utilization outside of the follow up Hyde 2013 report. This reinforced that there are some savings in resource utilization that offsets the cost of the medications. There is a small improvement in the quality of life as well, measured in QALYs. Both the net resource savings and the incremental QALYs are extremely small. In light of the limitation of the precision of these estimates, one cannot conclude with certainty that there are improvements in quality of life with net resource savings. There has been nothing in the recent literature that captures costs in the Canadian situation.

In terms of quality of life there were no new high quality studies published after the NICE review. One study by Ward 2008 demonstrated that treatment with cholinesterase inhibitors resulted in a reduction in the number of CANE unmet needs and increased combined Quality of Life in Alzheimer's Dementia scores in the first three months amongst the newly referred patients and their caregivers. It was further shown that those patients who were still on cholinesterase inhibitors for nearly two years had a low number of unmet needs along with severity of carer strain (distress) and quality of life similar to newly referred patients.

Title: A Meta-Analysis of Efficacy and Safety of Cholinesterase Inhibitors in Mild to Moderate Alzheimer's Disease with a Systemic Review of Quality of Life, Cost Effectiveness and Dose Delivery Preference

1. INTRODUCTION

1.1. Disease Prevalence and Incidence

Alzheimer's disease is a fatal, progressive and degenerative disease that destroys brain cells. It is the most common form of dementia, accounting for 64 per cent of all dementias in Canada. (Alzheimer Society of Canada website)

Alzheimer's disease is not a normal part of aging. Symptoms include having difficulty remembering things, making decisions and performing everyday activities. These changes can affect the way a person feels and acts. There is currently no way to stop the progression of the disease.

An estimated 500,000 Canadians have Alzheimer's disease or a related dementia. (Alzheimer Society of Canada website) Over 70,000 of them are under 65 and approximately 50,000 are under the age of 60. It is estimated that 1 in 11 Canadians over the age of 65 has Alzheimer's disease or a related dementia. Women constitute almost three-quarters of Canadians with Alzheimer's disease. In just 5 years, as much as 50% more Canadians and their families could be facing Alzheimer's disease or a related dementia. Within a generation, the number of Canadians with Alzheimer's disease or a related dementia will more than double, ranging between 1 and 1.3 million people. (Alzheimer Society of Canada website)

1.2. Standard of Therapy

Neurotransmitter enhancement therapy with cholinesterase inhibitors (ChEIs) is a treatment approach for patients with mild to moderate Alzheimer's Disease (AD). Cholinesterase inhibitors increase cholinergic synaptic transmission by inhibiting acetylcholinesterase in the synaptic cleft, thereby decreasing the hydrolysis of acetylcholine released from the presynaptic neurons. Donepezil, rivastigmine and galantamine are the three currently approved ChEIs for treating mild to moderate AD symptoms.

There have been many randomized controlled trials (RCTs) that have studied the use of ChEIs in patients across the AD severity spectrum. These RCTs provide Level I evidence for 24 to 28 week treatment efficacy and safety in patients with mild to moderate AD. Systemic reviews including many double-blind, randomized, placebo-controlled trials (RCTs) of the three ChEIs have all shown benefit on cognitive functions, activities of daily living (ADL), and global function for patients with mild to moderate AD compared to placebo and no significant difference of efficacy between individual ChEIs has been shown. Up to 60% of AD patients respond to ChEI treatment, defined as 4 points or more benefit in the ADAS-cog and a mini-mental state examination (MMSE) score improvement of 2 or more points from baseline compared to placebo treatments (Qaseem 2008). Reviews and meta-analyses of ChEI use recently published have showed that they delay the decline in cognitive function as measured by the AD Assessment Scale – cognitive subscale (ADAS-cog), global clinical rating, behavior and

ADL over 6–12-month periods. These benefits seem to be applicable to mild, moderate and severe AD. Compared with those on placebo treatment, patients on ChEIs generally show an initial mild improvement in cognitive functions over the first 3 months and the mean decline in cognitive functions is less rapid over the subsequent 3–9 months.

Primary and secondary efficacy measures in the RCTs to date consist of change from baseline in domain-specific functions such as global function/severity, cognitive function, activities of daily living and behavioural disturbance. There are several tools/scales used to assess these functions. The most commonly used tools assessing global function are: the Clinician's Interview-Based Impression of Change scale (CIBIC-Plus), the Gottfries, Brane and Steen scale (GBS) and the Global Deterioration Scale (GDS). Cognitive function is measured with the following: the cognitive part of the Alzheimer's Disease Assessment Scale (ADAS-Cog), the MiniMental State Examination (MMSE) and Severe Impairment Battery (SIB.) Activities of daily living can be measured by: the Progressive Deterioration Scale (PDS), the Disability Assessment for Dementia (DAD) and Activities of Daily Living (ADCS). Finally the Neuropsychiatric Instrument (NPI) has been used to measure behavioural disturbance.

The safety of these agents has been assessed in terms of the incidence of adverse events, the acceptability of treatment measured by withdrawal from clinical trials and the incidence and severity of adverse events leading to discontinuation of study drug and withdrawal from studies. In terms of adverse events, systemic reviews have shown that the incidence of adverse effects is associated with a higher therapeutic dose of the ChEIs. In terms of comparative safety of the available agents the incidence of gastrointestinal adverse effects, such as nausea, vomiting, diarrhea and abdominal cramping, has been shown to be lower with donepezil than with rivastigmine and galantamine. It has been suggested that galantamine and rivastigmine may be equal to donepezil in tolerability if a careful and gradual titration routine of more than 3 months is used. The dermal form of rivastigmine provides a lower dose with fewer adverse effects but comparable efficacy, and has been shown to be preferred by some caregivers.

Very little work has been done on the impact of ChEIs on Quality of Life (QoL) and caregiver burden. One of the issues around the body of data available to date is that the clinical trials provide information on the performance of ChEIs under idealized trial conditions and in highly selective patient populations. Further to this, many of the trials of ChEIs are of short durations relative to the long course of illness in AD and are therefore unable to provide evidence on the long term effects of therapy.

In the last few years both NICE and the Cochrane Collaboration have published update reviews on the use of ChEIs. The Cochrane review included RCT's up to the end of 2006. The NICE Guidance 111 published in March 2011, included RCTs published to the end of March 2010.

1.3. Drugs

In Canada, rivastigmine and galantamine are indicated for the symptomatic treatment of patients with mild to moderate dementia of the Alzheimer's type. The Health Canada-approved indication for donepezil includes patients with mild, moderate and severe AD.

ChEIs used in Alzheimer's disease are presented below:

Drug	Class	Dose (mg/day)	Frequency (times/day)	Absorption affected by food	Metabolism
Donepezil (Aricept)	Cholinesterase inhibitor	5-10†	1	No	CYP2D6 CYP3A4
Rivastigmine (Exelon)	Cholinesterase inhibitor	3-12	2	Yes	Non-hepatic
Galantamine (Reminyl; Reminyl PR)	Cholinesterase inhibitor	8-32	2 1 (PR)	Yes	CYP2D6 CYP3A4
Memantine (Ebixa)	NMDA-receptor antagonist	5-20	2 (one)	No	Non-hepatic

* PR denotes prolonged release, and NMDA N-methyl D-aspartate
† Donepezil 23 mg not available yet in Hong Kong

Source: Chu, Hong Kong Med J 2012;18(3).

The cost of ChEIs in BC are presented in Table 1. Dosing of ChEIs are presented in Table 2.

1.4. Goals of Therapy

Primary and secondary efficacy measures in the RCTs to date consist of change from baseline in domain-specific functions such as global function/severity, cognitive function, activities of daily living and behavioural disturbance.

The safety of these agents has been assessed in terms of the incidence of adverse events, the acceptability of treatment measured by withdrawal from clinical trials and the incidence and severity of adverse events leading to discontinuation of study drug and withdrawal from studies.

1.5. Guidelines

All of the Canadian provincial drug programs cover the use of the three cholinesterase inhibitors. These drugs are accessed via "Limited Use", "Special Access" or "Exceptional Access" mechanisms. A summary of the criteria for use in each province is given in Appendix 1.

2. OBJECTIVES AND METHODS

2.1. Objectives requested

The objective of this study was to evaluate the effect of the three Cholinesterase Inhibitors (ChEIs), donepezil (Aricept®), galantamine (Reminyl®) and rivastigmine (Exelon® oral and transdermal) on patient outcomes compared with placebo and to each other in patients with mild to moderate stages of Alzheimer's disease. Patient outcomes of interest for the review included the following:

Efficacy outcomes:

- Cognitive function as assessed by any valid method
- Daily function as assessed by any valid method
- Clinician's global impression of change as assessed by any valid method
- Behavioural disturbance (e.g. agitation, psychosis, depression) as assessed by any valid method

Harm outcomes:

- Safety as measured by the incidence of adverse events (AE) (including side-effects) leading to withdrawal

Other outcomes:

- Quality of Life as assessed by any valid method
- Health Care Resource Utilization (e.g. hospital services, physician services) as assessed by any valid method

2.2. Methods

A systematic literature review was conducted to identify RCTs evaluating donepezil, galantamine, or rivastigmine for AD that have been published since the time of two recent systematic literature reviews by Bond 2012 and Birks 2012. The data from any new RCTs identified from the search were used to update the meta-analysis results from the two previous reviews.

2.2.1. Previous Reviews Cited by the Ministry

Both NICE in the UK and The Cochrane Collaboration have published updated reviews on the use of ChEIs. These comprehensive systematic reviews were used as a starting point for this review.

Bond et al. evaluated the effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of AD. The review clinical effectiveness included RCTs and systematic reviews of RCTs published to the end of March 2010. In addition, economic model was developed to determine the cost effectiveness of donepezil, galantamine, and rivastigmine for the treatment of mild-to-moderate AD. Selected results reported by Bond 2012 are shown in the Appendix 2.

The effectiveness of donepezil, galantamine, and rivastigmine in AD was also evaluated in a 2006 Cochrane Review by Birks et al. This review included all unconfounded, blinded RCTs of at least 6 months duration. Results from the 10 RCTs included in the review suggested that ChEIs offer improvements in cognitive function, clinician's global impression, activities of daily living, and behavior. Selected results reported by Birks 2006 are shown in the Appendix 3.

In 2005, the Canadian Agency for Drug and Technologies in Health (CADTH) conducted an assessment of the cholinesterase inhibitors. (Technology report no 58, Perras et.al.) The benefit and harm of ChEIs to manage mild to moderate AD was determined by examining changes in functional performance, global improvement, QoL, AE and serious AE. The effect of using ChEIs on the rates of institutionalization and persistence with therapy, was also examined. Selected results reported by CADTH (Technology report no 58, Perras et. al.)) are shown in Appendix 4.

2.2.2. Eligibility Criteria

Studies were selected for inclusion in the systematic review based on the following selection criteria:

Patient Population	Patients with mild to moderate stages of Alzheimer's disease.
Interventions	donepezil (Aricept®) galantamine (Reminyl®) rivastigmine (Exelon® oral and transdermal)
Comparators	Three agents listed above compared with placebo and to each other
Outcomes	***Key Efficacy Outcomes:*** • Cognitive function as assessed by any valid method • Daily function as assessed by any valid method • Clinician's global impression of change as assessed by any valid method • Behavioural disturbance (e.g. agitation, psychosis, depression) as assessed by any valid method ***Harms Outcomes:*** • Safety as measured by the incidence of adverse events (including side-effects) leading to withdrawal ***Other Outcomes:*** • Quality of Life as assessed by any valid method • Health Care Resource Utilization (e.g. hospital services, physician services) as assessed by any valid method
Study Design	Randomized Controlled Trials (RCTs) from the end search date of the two systematic reviews to present date (Bond, Birks). For the review of quality of life and health care resource utilization, observational evidence was included if insufficient RCTs were identified.

2.2.3. Search Strategy and Findings

The search strategy was developed by an information specialist in consultation with the review team. The bibliographic database search included a search of PubMed and hand searches of references retrieved. All searches were limited to the human population, the time period from March 2010 to December 31, 2013 and studies published in English, where possible.

Appendix 5 presented the detailed search strategy.

The results of the search yielded 245 distinct references.

Another search was conducted to cross reference the citations used in the two most recent large meta-analyses (Birks, Bond) with all other meta analyses (2006 – Dec 2013) to identify any studies that may not have been included in the Bond assessment. The summary of that analysis is contained in Appendix 6.

2.2.4. Study Selection

The initial search strategy generated 245 citations. From this initial list of 245 studies, each citation was screened using the inclusion criteria by two reviewers. Any discrepancy was resolved by a third reviewer in conjunction with discussion by the reviewers. Following the elimination of trials that did not meet the inclusion criteria based on the initial screening of the abstract, a list of 64 trials that warranted further review was generated. Full text versions of the 64 studies identified were reviewed and studies that were not within the scope of the project were eliminated.

This analysis generated 31 studies that were then subjected to the full GRADE review. Within this population of trials, 23 were RCT's and 8 were observational studies. The 31 papers were adjudicated based on the GRADE criteria. Any trials that not meet the level of rigour required for the meta-analysis were eliminated. After the GRADE analysis was conducted, 13 publications were identified that met the criteria for inclusion. (See Table 3). An explanation of the reason for exclusion is provided in Appendix 7.

2.2.5. Data Extraction

An assessment was conducted to identify whether there were new publications which provided additional information that was not already incorporated in previous meta-analyses by Bond 2012. The previous meta-analyses included the National Institute for Health and Clinical Excellence (NICE) Health Technology Assessments for each of the 3 cholinesterase inhibitors. This evidence was updated by NICE by Bond in 2012. Another recent systematic review and meta-analysis was conducted by Birks 2006 with The Cochrane Collaboration. After reviewing the reports of Bond 2012 and Birks 2006, it was determined that the Bond 2012 report was the most recent and comprehensive report including all the evidence of the Cochrane review. The focus for the analysis was then to identify any new evidence that was subsequent to the NICE report by Bond 2012.

The data was extracted into either a Microsoft Excel workbook for the later creation of summary tables, or outcome data for meta-analysis was extracted directly into Review Manager software.

2.2.6. Quality Assessment

The studies that provided outcomes for the meta-analysis were assessed with Grading of Recommendations Assessment, Development and Evaluation (GRADE) risk of bias tool. (Guyatt 2011)

2.2.7. Data Synthesis

Following data extraction, the next step was to identify the evidence that was available for drug dosages that are approved in Canada. For donepezil, the approved dosages are 5 mg/24hr and 10 mg/24hr. For galantamine, the approved dosages in Canada are 8 mg/24hr, 16 mg/24hr and 24 mg/24hr.

The final step prior to conducting the meta-analysis was to determine the outcome and time points for the outcome for which new or updated evidence was available. To summarize the

evidence for each outcome where there was new evidence, we provided the accumulated evidence from Bond 2012 and the subsequent evidence for all time points for any outcome that had new evidence.

Meta-analysis was conducted with the Cochrane based meta-analysis software, Review Manager version 5.2. The difference in response between each drug and placebo was pooled as mean difference. Differences between drug and placebo for the rate of withdrawal due to adverse events were estimated as an overall odds ratio (OR) with weights based on inverse variance.

The analysis was conducted under the assumption of a DerSimonian and Laird random effects model. This model assumed that any differences between studies were the result of random variation in the true effect size.

Heterogeneity was assessed using I^2 as the measure of between-study heterogeneity, using a random effects model. We followed the Cochrane Handbook to identify levels of heterogeneity as absent, low, moderate or substantial.

2.2.7.1. Minimal Clinical Important Difference (MCID)

In addition to evaluating differences in efficacy between the included AD drugs versus placebo in terms of statistical significance, the clinical importance of the differences were assessed by taking into consideration the MCID for the outcomes evaluated. ADAS-cog is a scale that ranges from 0 to 70 (higher score is clinically worse) and a MCID has been proposed as a difference of 4. The CIBIC-plus is a Likert scale that ranges from 1 to 7 (higher score is clinically worse) and the MCID has been proposed as a difference of 1. MMSE is a scale that can range from 0 to 30 (lower score is clinically worse), and a MCID has been estimated by survey to be 3.72. (See Table 4)

For the primary outcome of ADAS-cog at 24 weeks we first evaluated the overall meta-analytic weighted mean difference (WMD) for drug versus placebo to assess if the confidence intervals of the WMD included the MCID value. Second, we re-analyzed the trial data for each study included versus placebo to generate the percentage of patients that may have achieved an MCID level of improvement. The percentages achieving MCID was estimated separately for drug and for placebo, assuming a normal distribution around the mean effect. From these two percentages, the risk differences were estimated for each drug versus placebo, and finally a number needed to treat was estimated (1/Risk Difference). The number needed to treat represents the number of patients that are required to be treated by the drug to generate 1 patient that achieves the MCID clinical benefit, if they were otherwise treated with placebo

2.2.8. Additional Analyses

2.2.8.1. Indirect Treatment Comparison

An indirect treatment comparison between drugs was conducted, for which there were a sufficient number of studies. Indirect treatment comparison was conducted with CADTH software using the Bucher method. The Bucher method is the simplest method to conduct the indirect analysis (also often referred to as a network meta-analysis). The Bucher method compares the overall effect for one drug versus placebo, against the overall effect for a second drug versus placebo.

2.2.8.2. Patch versus Oral Administration of Rivastigmine

An additional analysis was requested to evaluate if there are any clinical efficacy or safety differences between the patch and capsule routes of administration for rivastigmine.

2.2.8.3. Cost effectiveness of ChEIs for AD

A systematic review of economic analyses related to the use of ChEIs for AD was not part of the scope of this project, however any information on the cost effectiveness of ChEIs from the included studies was identified and reviewed.

2.2.8.4. Resource Utilization and Quality of Life

For quality of life and health care resource utilization, RCTs from January 2006 to 2014 were assessed. However, observational evidence was also included. An additional search was conducted to determine whether there were any further studies outside of the scope of the timeline stipulated in the original search that addressed the issues of resource utilization and quality of life.

A search yielded 53 references using the search criteria outlined in Appendix 8. These 53 studies were screened for relevance and it was determined that of the studies that might have been of interest, 8 were already included in the above screening or were included in the Bond analysis. Five articles were sourced for a closer examination. (Appendix 9)

3. RESULTS

3.1. Findings from the Literature

After reviewing 245 citations identified through database searching, 13 RCTs evaluating donepezil, galantamine, or rivastigmine for AD were included in the analysis. The full screening process is documented in a PRISMA Flow Diagram in Figure 1.

3.2. Included Studies

Of the 13 new studies identified in the review, 5 new RCTs were published for donepezil, 6 new studies were published for rivastigmine, and 2 new studies were published for galantamine. It was then assessed whether the new trials overlapped with previous publications reported in the Bond 2012 analysis. It was identified that all of the evidence from the 6 new studies for rivastigmine came from the IDEAL trial, and all studies were post hoc subgroup analysis of the main trial evidence that was previously reported by Bond. Thus, it was determined that there was subsequent evidence for donepezil and galantamine, but not rivastigmine.

3.3. Critical Appraisal

There were 8 studies that provided updated comparative outcomes for the 3 drugs, 5 studies for donepezil, 1 for rivastigmine, and 2 studies for galantamine, listed in Table 5. The study that provided the most new information was Frolich 2011, which provided updates for the 2 outcomes of ADAS-Cog and MMSE. This study had 3 important limitations: unclear lack of

allocation concealment, unbalanced rates of dropout between drug and placebo, and was funded by industry.

Overall, there were a few items that consistently lead to an increased risk of bias, with most studies reporting a median of 3 items (mean 3.9, range 1 to 6). A very common concern was that 7/8 (88%) of the studies were industry sponsored fully or in part with provision of the active drug. There were concerns of lack of allocation of concealment with 6/8 (75%) of studies, and more concerning was the incomplete accounting of patients in 6/8 (75%) of the studies. Few studies were analyzed with intention to treat, which might have been appropriate given the unequal rates of dropouts between the treatment arms of drug versus placebo, and that the level of disease was different for the patients that dropped out compared to the patients that remained within the analysis when reported on a per protocol basis. This latter prognostic imbalance may be the factor that leads to the most important impact on risk of bias. Similar to the lack of accounting for patients was the incomplete accounting of outcome events in 4/8 (50%) of studies.

Overall, the risk of bias tool suggests that the evidence should be considered as having serious limitations being downgraded at least 1 step from high quality evidence to moderate quality evidence. The most serious limitation is the high rates of dropout (10 to 30%), which were not equally distributed between drug versus placebo, and where patients that dropped out were different than the remaining patients which introduced prognostic imbalance. No strict cutoff has been stated for an acceptable rate of drop-out before bias is introduced, but the different rates of dropouts is problematic.

3.4. Synthesis of Results

The evidence that was available for drug dosages that are approved in Canada was identified (see Table 6).

The outcome and time points for the outcome for which new or updated evidence was available was determined. We identified only 3 outcomes and time points that had more than 1 new trial: ADAS-Cog at 21 and 24 weeks, MMSE at 24 weeks, CIBIC at 24 weeks, and withdrawals due to adverse events at 24 and 26 weeks. There were also outcomes that were not previously reported; ADAS-CGIC at 12 weeks, DAD at 12 weeks, and NPI at 4 and 12 weeks. The accumulated evidence from Bond 2012 and the subsequent evidence for all time points for any outcome that had new evidence were included in the meta-analysis.

3.4.1. Cognitive Function

The results for ADAS-cog are reported in Table 7. For ADAS-cog, the evidence for the effect of the relevant AD drugs versus placebo was available at the time points 12, 16, 21, 24 and 26 weeks. The new evidence was for donepezil at 24 weeks. The difference in the mean change from baseline of ADAS-cog for donepezil versus placebo was -2.27 (95%CI: -2.76 to -1.79), and this difference was significant (see Figure 2). The difference in the mean change from baseline of ADAS-cog for galantamine versus placebo was -2.96 (95%CI: -3.37 to -2.55), and this difference was significant (see Figure 3).

The results for MMSE are reported in Table 8. For MMSE, the evidence for the effect of the included drugs versus placebo was available at the time points of 12-13 weeks, and 24-26 weeks. The only new evidence was for donepezil at 24 weeks. The mean difference for MMSE was 1.25 (95%CI: 0.87 to 1.62), and this difference was significant (see Figure 4).

3.4.2. Clinical Global Impression

The results for CIBIC-plus are reported in Table 9. For CIBIC-plus, the evidence for the effect of the included drugs versus placebo was available at the time points of 12, 13, 16, 24 and 26 weeks. The only new evidence was for donepezil at 24 weeks. The difference in the mean change from baseline of CIBIC-plus for donepezil versus placebo was -0.39 (95%CI: -0.49 to -0.29), and this difference was significant.(see Figure 5).

The results for ADCS-CGIC are reported in Table 10. For ADCS-CGIC, there was newly reported evidence for donepezil but not for the other drugs. The mean change in ADCS-CGIC at 12 weeks was a reduction -0.2 (95%CI: -0.4 to -0.02).

3.4.3. Activities of Daily Living

The activities of daily living were reported differently for donepezil and galantamine, which limits their comparison. For donepezil, the difference in activities of daily living was reported as a standardized mean difference from a mixture of different scales. For galantamine, the activities of daily living were reported as the ADCS-ADL scale. For both drugs there was a significant improvement in ADL versus placebo. (See Table 11 and 12)

3.4.4. Behavioural Disturbance

Change in behavioural disturbance was a newly reported outcome that had only evidence for donepezil, listed in Table 13. For donepezil versus placebo, there a relative increase in NPI at 12 weeks of 8.0 (95%CI: -0.8 to 16.8), which was not significant.

3.4.5. Safety

The results for withdrawals due to adverse events are reported in Table 14. For withdrawals due to adverse events, the evidence for the effect of the included drugs versus placebo was available at the time points of 24 and 26 weeks. There was new evidence for all three AD drugs. The odds ratio for withdrawal due to adverse events was 1.48 (95%CI: 0.93 to 2.38) for donepezil, 2.91 (95%CI: 1.50 to 5.66) for rivastigmine, and 1.95 (95%CI: 1.31 to 2.89) for galantamine (see Figure 6), and these differences were significant.

3.4.6. Clinically meaningful differences

We have demonstrated that the differences in efficacy between the included AD drugs versus placebo are statistically significant, but the confidence intervals of any of the drugs do not exceed the MCID for the ADAS-cog, and may not be clinically important. When we estimated the percentage of confidence interval for the mean difference that was greater than the MCID for each study, and then pooled the percentages across the studies, there were detectable improvements versus the MCID. The estimated percentage of patients that achieved the MCID

for ADAS-cog at 24 weeks was 29.7% of patients treated with donepezil, 32.3% treated with rivastigmine, and 25.9% with galantamine. In balance, these percentages need to be compared to the 16.6% of patients who received placebo who also achieved MCID of >4. The incremental percentage of patients who were able to achieve ADAS-cog improvement of >4 were 14% for donepezil, 14% for rivastigmine, and 9% for galantamine.

The respective estimated number of patients needed to be treated with the drug to achieve a benefit that exceeds the MCID threshold was 7, 7 and 10. That is, for every 7 patients treated with donepezil only one patient will achieve a clinically important improvement that is the direct result of the treatment. The other 6 patients would not obtain such a benefit from the treatment. A similar number of patients would need to receive rivastigmine for one patient to achieve the benefit, while 10 patients would have to be treated with galantamine in order for one patient to achieve an MCID benefit from the galantamine. In addition, the difference between drugs was not statistically different.

Heterogeneity

For each of the outcomes that were updated, there was an absence of heterogeneity, which precludes the need for exploration of the source of heterogeneity such as removing outliers or subgroup analysis.

3.5. Results of Additional Analyses

3.5.1. Indirect comparisons

Indirect meta-analyses were conducted for the outcome of ADAS-cog for weeks 12-16 and weeks 21-26 (Table 15 and Table 16); the outcome of MMSE at weeks 12-13 and weeks 24-26 (Table 17 and Table 18), the outcome of CIBIC-plus for weeks 24-26 (Table 19); and lastly, the outcome of withdrawals due to an adverse event at weeks 24-26 (Table 20).

There were only 2 outcomes that had rates of outcomes that were significantly different from another drug, ADAS-cog at 21-26 weeks (Table 16), and CIBIC-plus at 24-26 weeks (Table 19). For ADAS-cog, galantamine had a small but improved rate of ADAS-cog reduction versus donepezil, WMD=0.69 (95%CI: 0.055 to 1.325), p=0.033.

For CIBIC-plus, donepezil had a preferable higher rate of reduction versus galantamine, WMD = -0.168 (95%CI: -0.305 to -0.031), p=0.016. Both differences are small and probably not clinically meaningful.

3.5.2. Rivastigmine Patch versus Capsule

The highest quality of evidence that compares the outcomes for patients that received patches versus capsules for rivastigmine comes from the IDEAL study (Winblad 2007). In the IDEAL study, the comparator groups were low dose patches (9.5 mg/day), high dose patches (17.4mg/day), capsules (12mg/day) and placebo.

The main findings were no statistical differences in efficacy between dosages for patches, or between patches and capsule (see Table 21). However, high dose patches and capsules had

higher rates of adverse events than low dose patches. The low dose patches relative to capsule had fewer events for: nausea, vomiting, weight loss, dizziness, decreased appetite, and headaches but higher rates of diarrhea.

There were also non important differences in the costs and quality of life between patients that received patches and capsules (Bond 2012). The cost effectiveness model was based on a cohort with average age of 77 years and predicted average survival of 3.84 years. The analysis assumed a daily cost for the patch was £2.60 and the daily cost of the capsule was £2.38. The model predicted that the cohort of patients who received the patch would incur a cumulative cost of £69,598 compared to capsule of £69,678 for a difference of £80 lower (0.1% lower), or £80/3.84 = £20.8/year. In addition, the differences in quality of life was almost zero, with patients who received the patch experiencing 1.616 QALYs and 1.613 QALYs for capsule resulting in a difference of 0.003 (0.2% lower), or 0.001 QALYs per year. (See Table 22)

The cost effectiveness analysis included the impact on quality of life for the patient but did not include the impact on caregivers. In a separate sub-study of the IDEAL trial, 72% of caregivers preferred the patches to capsules and 64% of caregivers preferred the patches to capsules for ease of use. The higher satisfaction of caregivers for patch versus capsule was driven by the factors of: easy to follow schedule, easy to administer, does not interfere with daily life, and satisfaction with administration. All factors had small but statistically significant benefit.

3.5.3. Summary of Cost Effectiveness

An economic analysis by Hyde et al 2013 assessed the cost effectiveness of the 3 included AD drugs versus best supportive care. This analysis updated the previous cost effectiveness analysis of the HTA report by Bond 2012. The results estimated the cost effectiveness versus placebo, but did not report the cost effectiveness between drugs. The data was abstracted and cost effectiveness between drugs was estimated. (see Table 23)

The cost effectiveness results suggest that there are very small differences in costs and quality of life between the drugs. The cumulative cost differences between donepezil and rivastigmine were £54 or £86 over a 20 year time horizon. Similarly, there was a difference of 0.006 or 0.004 QALYs over a 20 year time horizon, which is not clinically important given that a meaningful difference of QALY has been reported to be no smaller than 0.030.

3.5.4. Resource Utilization and Quality of Life

Thirteen studies (observational or RCT) were identified with possible relevance for assessing resource utilization and quality of life. Eight studies were identified in the initial literature search and an additional five studies were identified when a search was conducted specifically with a focus on resource utilization and quality of life assessments (and not limited to RCT data). These 13 studies are summarized in Table 24 and their relevance to the evaluation conducted in this review is indicated. Additional details about each study are presented in Appendix 6.

No additional conclusions can be drawn regarding resource utilization or quality of life from these 13 papers that were not already presented in the Hyde et al 2013 analysis (which is one of the 13 papers). There are some savings in resource utilization that offsets the cost of the medications. There is a small improvement in the quality of life as well, measured in QALYs.

Both the net resource savings and the incremental QALYs are extremely small. In light of the limitation of the precision of these estimates, one cannot conclude with certainty that there are improvements in quality of life with net resource savings. Having said that, it is also true that one cannot conclude that the use of these medications will lead to a drain on resources while providing inadequate benefit.

All other economic assessments were included in the NICE report and can be reviewed therein. Though assessment of the economics of these agents was summarized in the Cochrane and NICE reviews, neither included Canadian sourced information. There have been several older reports, prior to the year 2000 that were Canadian based but these were not included in the NICE and Cochrane reports.

There were no new high quality studies addressing quality of life published after the NICE review. One study (Ward 2008) assessed the impact of cholinesterase therapy on unmet needs in both patients and caregivers. The needs and quality of life of patients attending an outpatient dementia care service were assessed using the Camberwell Assessment of Need for the Elderly (CANE) and Quality of Life in Alzheimer's Disease: Patient and Caregiver report. It was found that there was reduction in the number of CANE unmet needs and increased combined Quality of Life in Alzheimer's Dementia scores in the first three months amongst the newly referred patients and their caregivers. This study showed that the outpatient prescribing of cholinesterase inhibitors helped to meet the needs of patients and improve patients' quality of life in the first three months. Those patients who were still on cholinesterase inhibitors and being seen in the outpatient dementia care service for nearly two years had low number of unmet needs along with severity of carer strain (distress) and quality of life similar to newly referred patients.

4. DISCUSSION

Neurotransmitter enhancement therapy with ChEIs is a treatment approach for patients with mild to moderate AD. The treatment is not to prevent the deterioration of the patient with the disease, but instead to improve cognitive functions (such as memory loss), clinical global impression, activities of daily living, and behaviour. In the class of ChEIs, there are 3 drugs that have shown benefit versus placebo: donepezil, galantamine and rivastigmine.

To assess the safety and efficacy tradeoff, numerous trials have been conducted with each drug versus placebo with the first trial for donepezil published in the year 1998, rivastigmine published in 1999, and galantamine in published in 2000. Since the first trials, subsequent trials have been conducted on different doses and patient characteristics. To synthesize the available evidence, a number of systematic reviews and meta-analysis have been conducted. The reviews were first conducted separately for each drug versus placebo, and then a Cochrane review that combined all of the evidence was conducted by Birks 2006. Subsequent to the Birks review, another review was conducted by Bond in 2012 as part of a NICE Technology Appraisal. Our report provides an update to the Bond 2012 report.

This report was designed to search and assess any new trial data that may have been published following the cut off of March 2010 in the NICE report. A literature search found 13 new RCTs that were of sufficient quality. Five new RCTs were published for donepezil, 6 new studies were published for rivastigmine, and 3 new studies were published for galantamine. It was then

assessed whether the new trials overlapped with previous publications reported in the Bond 2012 analysis. It was identified that all of the evidence from the 6 new studies for rivastigmine came from the IDEAL trial, and all studies were post hoc subgroup analysis of the main trial evidence that was previously reported by Bond. Thus, it was determined that there was subsequent evidence for donepezil and galantamine, but not rivastigmine.

Overall, the evidence suggest that all of the 3 drugs provide benefit versus placebo in improvement in cognitive function, clinical global impression, activities of daily living, and behaviour. However, there were also the risk of withdrawal from therapy at 24 weeks, with odds ratios 1.48 for donepezil (p=0.06), 2.91 for rivastigmine (p=0.11), and 1.74 for galantamine (p=0.39). There is no long term evidence on the rates of withdrawals, but there is a 48% increase in the odds of withdrawal for the short time period at 24 weeks. Longer term follow up studies, such as extensions studies or observational data, may be useful to quantify the long term safety.

The review identified new studies for donepezil and galantamine but not rivastigmine. The outcomes that were updated are presented in the forest plots, figures 1 to 5. The outcomes that were updated as part of our review included: ADAS-cog at 24 weeks for donepezil, ADAS-cog at 21 to 26 weeks for galantamine, CIBIC-plus at 24 weeks for donepezil, MMSE at 24 weeks for donepezil, and withdrawals for adverse events for galantamine. The overall pattern was consistent, with the new evidence providing results of similar magnitude and direction as the previous results, and when combined with the previous results produced similar rates of outcomes with smaller confidence intervals due to the inclusion of further evidence. For all outcomes, the updated results were similar to the previous Bond 2012 conclusions. The key differences between this report and the previous report are that we assessed the relative safety and efficacy between the drugs, and we conducted an assessment of the clinical benefit versus a measure of clinically important differences.

The results of the indirect analysis between drugs indicated that were very small differences in efficacy, such as for ADAS-cog at 24 weeks. The extent of the clinical benefit was evaluated versus the MCID for ADAS-cog which is considered the primary outcome for the Alzheimer drugs. The suggested clinically important difference for ADAS-cog has been stated by the FDA to be 4 points, the differences of drugs versus placebo were all 2 to 3 points, and the differences between drugs were 1 point or less. However, the MCID has been suggested by the FDA as being 4 for all patients. Thus, the specific level of MCID that is desirable for mild or moderate severity has not been explicitly stated. Other than ADAS-cog, only MMSE has a peer reviewed estimate of MCID which was estimated by a survey of specialists in neurology and geriatric medicine (n=161), which was estimated to be 3.72 (95% CI: 3.50–3.95). The survey question was, "From your experience following demented patients, what are the smallest changes in the Folstein Mini-Mental State Examination (MMSE) scores that are compatible with a noticeable change in the patient's overall condition?" One drawback of this estimate is that the MCID was determined for all patients with dementia, and may not be representative of the MCID specifically for mild to moderate severity of Alzheimer disease. Based on the MCID analysis of our report, only 9 to 14% of patients being treated with a drug would be predicted to achieve the MCID difference of 4 on the ADAS-cog scale.

Limitations

This systematic review and meta-analysis was limited by a number of factors. First, the GRADE assessment of the trials indicated a potential for risk of bias on the overall body of evidence. Overall, the risk of bias tool suggests that the evidence should be considered as having serious limitations being downgraded at least 1 step from high quality evidence to moderate quality evidence. There were concerns of lack of allocation of concealment with 88% of the new studies, and more concerning was the incomplete accounting of patients in 75% of the new studies. The most serious limitation is the high rates of dropout (10 to 30%), which were not equally distributed between drug versus placebo, and where patients that dropped out were different than the remaining patients which introduced prognostic imbalance.

Another limitation is created from the meta-analysis by the short duration of the trials, where the most time points for assessment were 24 weeks (or 6 months). Given the significant rates of dropout due to adverse events, and that the disease produces further decline in function, the long term clinical benefit of the drug to manage symptoms while continuing therapy is uncertain.

One limitation exists for the comparisons between drugs, which was analyzed with indirect methods. Recent reviews of indirect methods versus head-to-head trials suggest that the indirect methods tend to overstate the difference, with weaker statistical significance. Based on those previous reviews, the differences between drugs that were estimated with indirect methods will likely be smaller and possibly statistically significant. Given that the differences are already small, any head-to-head evidence, such as RCTs that included 2 or 3 of the active drugs, is predicted to produce even smaller differences than are already considered to be not clinically meaningful.

Another limitation of the meta-analysis is the establishment of the MCID for patients with AD. The MCID has been suggested to be based on the primary outcome of ADAS-cog with a value of 4. It is unclear if this difference applies to patients with mild, moderate, severe patients or to all AD patients. It is possible that the MCID may have an anchor such that the MCID may be different for different severities of the disease. In addition, the improvement in ADAS-cog observed in the meta-analysis versus placebo must be considered against the annual decline in ADAS-cog that exists with the progressive disease. For patients with mild disease, the annual decline in ADAS-cog is less than 5 points per year. (Boustani 2003) For patients with moderate disease, the annual decline in ADAS-cog can be 7 to 11 points per year. Thus, the meta-analysis results indicated a benefit of 2 to 3 points at the duration of 6 months versus placebo, which is equivalent to arresting the disease for only a few months. Beyond the duration of the trial, it is unclear if the treatment will provide continued maintenance of ADAS-cog, a reduction in the rate of decline, or the rate of decline will resume the previous high rate.

A further limitation is that all of the RCTs have combined patients with mild and moderate AD, and there was a lack of studies that looked specifically at mild cases or moderates cases. Similarly, it is uncertain based on our review whether the drugs have important efficacy in patients with severe disease. Without this evidence, it is uncertain if the drugs should be started in patients with severe disease, or whether therapy should continue for patients with moderate disease who progress to severe disease.

Besides the clinical evidence, there is an absence of Canadian economic evidence that compares drugs to each other. There have been previous cost effectiveness analyses of drugs versus

placebo or usual care which suggested small cost savings or cost neutrality with little change in generic quality of life. (O'Brien 1999; Husereau 2001) The most recent Bond 2012 report indicated little differences in costs between treatment, and the most recent cost effectiveness analysis by Hyde 2013 also suggested little differences in costs or generic quality of life between drugs. In addition, a cost effectiveness analysis between the drugs and between patch versus capsule for rivastigmine was also considered economically neutral for costs and quality of life, although the low dose patches relative to capsule had fewer adverse events and patches are generally favoured by caregivers. (Winblad 2007)

There were not sufficient data to conduct a meta-analytical assessment of the impact of ChEIs on quality of life. Therefore a descriptive assessment was made. One study assessed the impact of cholinesterase therapy on unmet needs in both patients and caregivers. (Ward 2008) This study assessed the impact of outpatients' care and cholinesterase inhibitors in patients being treated for Alzheimer's dementia. The needs and quality of life of patients attending an outpatient dementia care service were assessed using the Camberwell Assessment of Need for the Elderly (CANE) and Quality of Life in Alzheimer's Disease: Patient and Caregiver report. Other tools used were the Problems Checklist and Carer Strain, the Minimental State Examination (MMSE) and a proforma to obtain sociodemographic details. The study demonstrated that there was reduction in the number of CANE unmet needs and increased combined Quality of Life in Alzheimer's Dementia scores in the first three months amongst the newly referred patients. The outpatient prescribing of cholinesterase inhibitors was shown to help meet the needs of patients and improve patients' quality of life in the first three months. Those patients who were still on cholinesterase inhibitors and being seen in the outpatient dementia care service for nearly two years had low number of unmet needs along with severity of carer strain (distress) and quality of life similar to newly referred patients.

Overall, this report supports the findings of the NICE and Cochrane reports. There does not appear to be any significant differences in safety and efficacy between the three agents, while there are small benefits versus placebo. One differentiating factor is for rivastigmine, where the lower dose patch appears to demonstrate comparable efficacy to capsule, with improved tolerability leading to adherence to therapy compared to oral therapy. However the beneficial effect may be dose related because the dosages of the low dose patches are less than the dose of the capsule, and the tolerability of the high dose patches is similar to the capsule. However, the patch is currently more expensive and previous cost effectiveness estimates which were cost neutral included similar cost of drugs for patches and capsules. One important feature of the patches indicates that caregivers prefer the patch to capsules.

5. CONCLUSIONS

Overall, the meta-analyses of the safety and efficacy of the three agents did not show meaningful differences from the two recent large reviews (NICE and Cochrane) of these agents. Overall, there were statistical benefits in efficacy with an offsetting increased risk of tolerability of all 3 drugs versus placebo. However, the clinical benefit is small and may not be clinically meaningful. Indirect evidence suggests very little differences between the drugs in efficacy or safety. In addition, cost effectiveness analyses indicate small differences in costs and quality of life between the 3 drugs.

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TABLES

Table 1: Cost of ChEIs (BC Pharmacare)

Rivastigmine

Products found: 31

DIN/PIN/NPN	Generic Name	Brand Name, Strength & Dosage Form	Manufacturer	RDP	Max. Day Supply per fill	Maximum PharmaCare Covers	Unit	Special Authority Needed
02302845	RIVASTIGMINE	Exelon Patch 5 -(4.6 Mg/24 H) 4.6MG/24HR PATCH TD24	NOVARTIS PHARM	No	35	4.8632	Each	Yes
02302853	RIVASTIGMINE	Exelon Patch 10 -(9.5 Mg/24 H) 9.5MG/24HR PATCH TD24	NOVARTIS PHARM	No	35	4.8632	Each	Yes
02242115	RIVASTIGMINE TARTRATE	Exelon 1.5 Mg 1.5 MG CAPSULE	NOVARTIS PHARM	No	35	0.7035	Each	Yes
02242116	RIVASTIGMINE TARTRATE	Exelon 3 MG CAPSULE	NOVARTIS PHARM	No	35	0.7035	Each	Yes
02242117	RIVASTIGMINE TARTRATE	Exelon 4.5 MG CAPSULE	NOVARTIS PHARM	No	35	0.7035	Each	Yes
02242118	RIVASTIGMINE TARTRATE	Exelon 6 MG CAPSULE	NOVARTIS PHARM	No	35	0.7035	Each	Yes
02245240	RIVASTIGMINE TARTRATE	Exelon 2 MG/ML SOLUTION	NOVARTIS PHARM	No	35	1.4796	Milliliters	Yes
02305984	RIVASTIGMINE TARTRATE	Novo-Rivastigmine 1.5 MG CAPSULE	NOVOPHARM LTD	No	35	0.7035	Each	Yes
02305992	RIVASTIGMINE TARTRATE	Novo-Rivastigmine 3 MG CAPSULE	NOVOPHARM LTD	No	35	0.7035	Each	Yes
02306018	RIVASTIGMINE TARTRATE	Novo-Rivastigmine 4.5 MG CAPSULE	NOVOPHARM LTD	No	35	0.7035	Each	Yes

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Galantamine

Products found: 12

DIN/PIN/NPN	Generic Name	Brand Name, Strength & Dosage Form	Manufacturer	RDP	Max. Day Supply per fill	Maximum PharmaCare Covers	Unit	Special Authority Needed
02266717	GALANTAMINE HBR	Reminyl Er 8 MG CAP24H PEL	JANSSEN-ORTHO	No	35	1.3462	Each	Yes
02266725	GALANTAMINE HBR	Reminyl Er 16 MG CAP24H PEL	JANSSEN-ORTHO	No	35	1.3462	Each	Yes
02266733	GALANTAMINE HBR	Reminyl Er 24 MG CAP24H PEL	JANSSEN-ORTHO	No	35	1.3462	Each	Yes
02316943	GALANTAMINE HBR	Pat-Galantamine Er 8 MG CAP24H PEL	PATRIOT, A DIV	No	35	1.3462	Each	Yes
02316951	GALANTAMINE HBR	Pat-Galantamine Er 16 MG CAP24H PEL	PATRIOT, A DIV	No	35	1.3462	Each	Yes
02316978	GALANTAMINE HBR	Pat-Galantamine Er 24 MG CAP24H PEL	PATRIOT, A DIV	No	35	1.3462	Each	Yes
02339439	GALANTAMINE HBR	Mylan-Galantamine Er 8 MG CAP24H PEL	MYLAN PHARMACE	No	35	1.3462	Each	Yes
02339447	GALANTAMINE HBR	Mylan-Galantamine Er 16 MG CAP24H PEL	MYLAN PHARMACE	No	35	1.3462	Each	Yes
02339455	GALANTAMINE HBR	Mylan-Galantamine Er 24 MG CAP24H PEL	MYLAN PHARMACE	No	35	1.3462	Each	Yes
02377950	GALANTAMINE HBR	Teva-Galantamine Er 8 MG CAP24H PEL	TEVA CANADA LI	No	35	1.3462	Each	Yes

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Donepezil

Products found: 26								
DIN/PIN/NPN ÷	Generic Name ÷	Brand Name, Strength & Dosage Form ÷	Manufacturer ÷	RDP	Max. Day Supply per fill	Maximum PharmaCare Covers ÷	Unit	Special Authority Needed
02232043	DONEPEZIL HCL	Aricept 5 MG TABLET	PFIZER CANADA	No	35	1.2750	Each	Yes
02232044	DONEPEZIL HCL	Aricept 10 MG TABLET	PFIZER CANADA	No	35	1.2750	Each	Yes
02269457	DONEPEZIL HCL	Aricept Rdt 5 MG TAB RAPDIS	PFIZER CANADA	Yes	0			No
02269465	DONEPEZIL HCL	Aricept Rdt 10 MG TAB RAPDIS	PFIZER CANADA	Yes	0			No
02322331	DONEPEZIL HCL	Pms-Donepezil 5 MG TABLET	PHARMASCIENCE	No	35	1.2750	Each	Yes
02322358	DONEPEZIL HCL	Pms-Donepezil 10 MG TABLET	PHARMASCIENCE	No	35	1.2750	Each	Yes
02328666	DONEPEZIL HCL	Sandoz Donepezil 5 MG TABLET	SANDOZ CANADA	No	35	1.2750	Each	Yes
02328682	DONEPEZIL HCL	Sandoz Donepezil 10 MG TABLET	SANDOZ CANADA	No	35	1.2750	Each	Yes
02340607	DONEPEZIL HCL	Teva-Donepezil 5 MG TABLET	TEVA CANADA LI	No	35	1.2750	Each	Yes
02340615	DONEPEZIL HCL	Teva-Donepezil 10 MG TABLET	TEVA CANADA LI	No	35	1.2750	Each	Yes
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(Source: BC Pharmacare)

Table 2: Dosing of the Cholinesterase Inhibitors (BC Pharmacare)

Drug	Dosage Forms	Daily Dose	Maximum Daily Dose	Cost of Maximum Daily Dose
Rivastigmine oral	1.5 mg, 3 mg, 4.5 mg, 6 mg, 2mg/mL	6 – 12 mg	12 mg	$1.4070
Rivastigmine patch	4.6 mg/24 h, 9.5/24 h	4.6 – 9.5 mg/24 h	9.5 mg/24 h	$4.8632
Donepezil	5 mg, 10 mg	5 – 10 mg	10 mg	$1.2750
Galantamine	8 mg, 16 mg, 24 mg	8 – 24 mg	24 mg	$1.3462

(Source: BC Pharmacare)

Table 3: Study characteristics of new included studies

Author (publication date) Journal	Study design, Trial name	Aim of the study	Study duration	Sample size	Active treatment	Comparator
Donepezil Studies						
Andersen F (2012) BMC Neurol	RCT	To estimate the effect of stimulation therapy and donepezil on cognitive function in early AD	52 weeks	185	Donepezil	Placebo
Burns A (2011) Dement Geriatr Cogn Disord	RCT	To assess the efficacy of melissa aromatherapy in the treatment of agitation in people with AD in an adequately powered and robustly blinded RCT comparing it with donepezil	12 weeks	114	Donepezil, melissa oil	Placebo
Frolich L (2011) J Alzheimers Dis	RCT, Phase IIb	To estimate effects of ADZ3480 on cognition in patients with mild-to-moderate AD relative to donepezil and placebo	12 weeks	659	Donepezil, AZD3480	Placebo
Gold M (2010) Dement Geriatr Cogn Disord	RCT, Phase III, REFLECT-1	To estimate the treatment effects of rosiglitazone monotherapy in mild-to-moderate AD	24 weeks	639	Donepezil, Rosiglitazone XR	Placebo
Maher-Edwards G (2011) Int J Geriatr Psychiatry	RCT, Phase II	To estimate the treatment effects of SB-742457 and donepezil in Alzheimer disease (AD)	24 weeks	226	Donepezil	Placebo
Rivastigmine Studies						
Alva G (2011) Int J Geriatr Psychiatry	Post hoc analysis of IDEAL RCT	To further evaluate the treatment effects of rivastigmine on individual ADL items	24 weeks	535	Rivastigmine	Placebo
Cummings JL (2010) Dement Geriatr Cogn Disord	Post hoc analysis of IDEAL RCT	This analysis investigated the ability of each domain of the ADCS-CGIC scale to measure change.	24 weeks	1039	Rivastigmine	Placebo

Farlow MR (2011) Int J Geriatr Psychiatry	Post hoc analysis of IDEAL RCT	This exploratory, hypothesis-forming analysis assessed response to rivastigmine according to severity of dementia at baseline	24 weeks	1039	Rivastigmine	Placebo
Grossberg G (2011) Am J Alzheimers Dis Other Demen	Post hoc analysis of IDEAL RCT	To assess the comparative effects of the rivastigmine transdermal patch and capsule formulations on specific aspects of ADLs	24 weeks	892	Rivastigmine	Placebo
Grossberg GT (2011) Int J Clin Pract	Post hoc analysis of IDEAL RCT	To investigate the effect of dose on the efficacy of the rivastigmine transdermal patch in mild-to-moderate AD	24 weeks	1052	Rivastigmine	Placebo
Lee JH (2011) Alzheimer Dis Assoc Disord	Post hoc analysis of IDEAL RCT	This analysis compared the effect of body weight on tolerability in AD patients receiving rivastigmine capsules or patch	24 weeks	887	Rivastigmine	Placebo
Galantamine Studies						
Gaudig M (2011) Curr Alzheimer Res	2 withdrawal trials	To evaluate the effects of galantamine withdrawal, and compare this with uninterrupted therapy. Two 6-week withdrawal studies were performed which enrolled individuals who completed one of two 3-or 5-month RCTs.	up to 26 weeks	Study 1 723; Study 2 118	Galantamine	Placebo
Scarpini E (2011) J Alzheimers Dis	RCT Withdrawal Trial	To assess if continuing galantamine treatment beyond 12 months delayed further cognitive deterioration associated with AD	Up to 24 months	133	Galantamine	Placebo

Table 4: Outcomes used in meta-analysis

Outcome	Range	MCID	Reference
Cognitive Function			
ADAS-cog (severity scale) Clinician administered patient evaluation	0 (better) to 70 (worse)	4	FDA- Rockwood 2007
MMSE (severity scale) Clinician administered patient evaluation	0 (worse) to 30 (better)	3.72	Burback 1999
Clinical Global Impression			
CIBIC-plus (change scale) Clinician rated (with caregiver input)	1 to 3 (improvement) 4: no change 5 to 7 (worsen)	1	By assumption (not published)
ADCS-CGIC (change scale) Clinician rated	1 to 3 (improvement) 4: no change 5 to 7 (worsen)	1	By assumption (not published)
Activities of Daily Living			
ADCS-ADL - Informant rated interview	0 (worse) to 54 (better)	Not available	-
DAD - Informant rated interview	0 to 40 raw scale (converted to percentage 0 (worse) to 100 (better)	Not available	-
Behavioural Differences			
NPI-total caregiver interview	0 (better) to 144 (worse)	8	Howard 2012

Table 5: GRADE assessment of new studies included in review

Author First, Year	RCT randomization	Lack of allocation concealment	Lack of blinding	Incomplete accounting of patients	Incomplete accounting of outcome events	Selective outcome reporting bias	Stopping early for benefit	Use of un-validated outcome measures	Funding
Donepezil studies									
Andersen 2012	Community randomization	Unclear	Blinding not explained	No limitation	dropouts had low MMSE	Limitation	No Limitation	No Limitation	Industry provided drug
Burns 2011	No limitation	Unclear	Blinding not explained	Unbalanced dropout rates	18% dropouts	No Limitation	No Limitation	QOL scale validated?	Industry provided drug
Frolich 2011	No limitation	Unclear	No limitation	Unbalanced dropout rates	No Limitation	No Limitation	No Limitation	No Limitation	Industry sponsored
Gold 2010	No limitation	Permuted block randomization	No limitation	Unbalanced dropout rates	No limitation	No limitation	No limitation	No limitation	Industry sponsored
Maher-Edwards 2011	No limitation	Unclear	Blinding not explained	Unbalanced dropout rates	No limitation	No limitation	No limitation	No limitation	Industry sponsored
Rivastigmine studies*									
Alva 2011	No limitation	Unclear	No limitation	Possible limitation	Unclear	No limitation	No limitation	No limitation	Industry sponsored
Galantamine studies									
Gaudig 2011	No limitation	Unclear	Unclear outcome assessment	No limitation	Dropouts unaccounted	No limitation	Dropouts unaccounted	No limitation	Industry sponsored
Scarpini 2011	No limitation	No limitation	No limitation	Low completion, withdrawals for other reasons	No limitation	No limitation	No limitation	No limitation	Industry sponsored
Limitations (% of studies)	**1/8 (12.5%)**	**7/8 (88%)**	**4/8 (50%)**	**6/8 (75%)**	**4/8 (50%)**	**1/8 (13%)**	**1/8 (13%)**	**1/8 (13%)**	**8/8 (100%)**

GRADE: Grading of Recommendations Assessment, Development and Evaluation
Not applicable assessments: Carryover Effects of Crossover Trial, Recruitment Bias in Cluster-randomized Trials
*Only one rivastigmine study presented here, as all new studies were came from the same RCT (IDEAL trial)

Table 6: Summary of included studies by drug and dosage

Drug	New Included Studies													Existing Studies	
	Andersen 2012	Burns 2011	Frolich 2011	Gold 2010	Maher-Edwards 2011	Alva 2011	Cummings 2010	Farlow 2011	Grossberg G 2011	Grossberg 2011	Lee 2011	Gaudig 2011	Scarpini 2011	Birks 2006 Cochrane	Bond 2012 NICE
Donepezil															
5 mg/ 24h*	x	x	x	x	x										x
10 mg/24h*	x	x	x	x	x										x
Rivastigmine															
2 mg/ 24h															
3 mg/ 24h*															x
4.6 mg/ 24h (patch)										x					x
9.5 mg/ 24h (patch)*						x	x	x	x	x	x				x
13.3 mg/ 24h (patch)										x					
12 mg/ 24h* (capsule)						x	x	x	x	x	x				x
17.4 mg/ 24h (patch)*							x	x		x					x
Galantamine															
4 mg															x
8 mg/ 24h*												x	x		x
16 mg/ 24h*												x	x		x
24 mg/ 24h*												x			x
32 mg/ 24h												x			

*Approved dosages

Table 7: ADAS-cog (mean change from baseline): donepezil, rivastigmine or galantamine (all dosages) vs placebo

Time point of assessment (weeks)	Weighted Mean Difference (95%CI) p-value		
	Donepezil (all dosages)	Rivastigmine (all dosages)	Galantamine (all dosages)
12	-1.992 (-2.87 to -1.11) p<0.001[2]	-1.567 (-2.877 to -0.256) p=0.019[3]	-2.344 (-2.721 to -1.966) p<0.001[4]
16			
21			-2.96 (-3.37 to -2.55) p<0.001[1]
24	-2.27 (-2.76 to – 1.79) p<0.001[1]	- 1.957 (-2.770 to -1.145) p<0.001[5]	
26			

[1] Updated with new results
[2] Bond, 2012, Figure 106
[3] Bond, 2012, Figure 122
[4] Bond, 2012, Figure 117
[5] Bond, 2012, Figure 123

Table 8: MMSE (mean change from baseline): donepezil, rivastigmine or galantamine (all dosages) vs placebo

Time point of assessment (weeks)	Weighted Mean Difference (95%CI) p-value		
	Donepezil (all dosages)	Rivastigmine (all dosages)	Galantamine (all dosages)
12	1.138 (0.864 to 1.411) p<0.001[2]	0.886 (-0.540 to 2.312) p=0.223[3]	
13			
16			
24	1.25 (0.87 to 1.62) p<0.001[1]	1.058 (0.693 to 1.424) p<0.001[4]	
26			

[1] Updated with new results
[2] Bond, 2012, Figure 108
[3] Bond, 2012, Figure 124
[4] Bond, 2012, Figure 125

MMSE (Mini Mental State Examination)

Table 9: CIBIC-plus (mean change from baseline): donepezil, rivastigmine or galantamine (all dosages) vs placebo

Time point of assessment (weeks)	Weighted Mean Difference (95%CI) p-value		
	Donepezil (all dosages)	Rivastigmine (all dosages)	Galantamine (all dosages)
12	-0.326 (-0.433 to -0.220) p<0.001[2]		
13			-0.361 (-0.527 to -0.196) p<0.001[3]
16			
24	-0.39 (-0.49 to – 0.29) p<0.001[1]		
26		-0.356 (-0.496 to -0.216) p<0.001[4]	-0.222 (-0.316 to -0.128) p<0.001[5]

[1] Updated with new results
[2] Bond, 2012, Figure 110
[3] Bond, 2012, Figure 115
[4] Bond, 2012, Figure 127
[5] Bond, 2012, Figure 116

CIBIC-plus (Clinician Interview-Based Impression of Change, plus carer interview)

Table 10: ADCS-CGIC (mean change from baseline): donepezil, rivastigmine or galantamine (all dosages) vs placebo

Time point of assessment (weeks)	Weighted Mean Difference (95%CI) p-value		
	Donepezil (all dosages)	Rivastigmine (all dosages)	Galantamine (all dosages)
12	-0.2 (-0.4 to 0.02)[1] P=0.036		
24			

[1] Updated with new results

ADCS-CGIC (Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change)

Table 11: ADCS-ADL (mean change from baseline): donepezil, rivastigmine or galantamine (all dosages) vs placebo

Time point of assessment (weeks)	Weighted Mean Difference (95%CI) p-value		
	Donepezil (all dosages)	Rivastigmine (all dosages)	Galantamine (all dosages)
12			1.394 (0.590 to 2.198) p<0.001[2]
13			
21			2.234 (1.328 to 3.141) p<0.001[3]
24	0.298 (0.144 to 0.452) p=<0.001[1]		
26			

[1] Bond, 2012, Figure 12, Multiple functional outcome measures pooled using standard mean difference
[2] Bond, 2012, Figure 25, results for galantamine ≤ 24mg/day
[3] Bond, 2012, Figure 26, results for galantamine ≤ 24mg/day

ADCS-ADL (Alzheimer's Disease Co-operative Study - Activities of Daily Living Inventory)

Table 12: DAD (mean change from baseline): donepezil, rivastigmine or galantamine (all dosages) vs placebo

Time point of assessment (weeks)	Weighted Mean Difference (95%CI) p-value		
	Donepezil (all dosages)	Rivastigmine (all dosages)	Galantamine (all dosages)
12	1.8 (-1.8 to 5.46)[1] P=0.164		
21			3.761 (1.661 to 5.861) p<0.001[2]
26			

[1] Updated with new results
[2] Bond, 2012, Figure 27, results for galantamine ≤ 24mg/day

DAD (Disability Assessment for Dementia)

Table 13: NPI (mean change from baseline): donepezil, rivastigmine or galantamine (all dosages) vs placebo

Time point of assessment (weeks)	Weighted Mean Difference (95%CI) p-value		
	Donepezil (all dosages)	Rivastigmine (all dosages)	Galantamine (all dosages)
4	8.1 (-5.51 to 21.71)[1] P=0.24		
12	8.0 (-0.8 to 16.8)[1] P=0.07		
13			-0.746 (-1.835 to 0.342) p=0.179[2]
21			-1.455 (-2.585 to -0.324) p=0.012[3]
26			

[1] Updated with new results
[2] Bond, 2012, Figure 29
[3] Bond, 2012, Figure 30

NPI (Neuropsychiatric Inventory)

Table 14: Withdrawals due to adverse events before end of treatment at 24 weeks or later: donepezil, rivastigmine or galantamine (all dosages) vs placebo

Time point of assessment (weeks)	Odds Ratio (95%CI) p-value		
	Donepezil (all dosages)	Rivastigmine (all dosages)	Galantamine (all dosages)
24	1.48 (0.93 to 2.38)[1] P=0.06		
26		2.91 (1.50 to 5.66)[1] P=0.11	1.74 (0.50 to 6.06)[1] P= 0.39

[1] Updated with new results

Table 15: ADAS-cog at 12-16 weeks (mean change from baseline): indirect meta-analysis between donepezil, rivastigmine and galantamine (WMD (95% CI) p-value)

	Donepezil	Rivastigmine	Galantamine
Donepezil		-0.425 (-2.004 to 1.154) P=0.5978[1]	0.352 (-0.606 to 1.31) P=0.4714[2]
Rivastigmine			0.777 (-0.587 to 2.141) P=0.2642[2]
Galantamine			

[1] Rivastigmine is the reference drug (donepezil minus Rivastigmine). [2]Galantamine is the reference drug

Table 16: ADAS-cog at 21-26 weeks (mean change from baseline): indirect meta-analysis between donepezil, rivastigmine and galantamine (WMD (95% CI) p-value)

	Donepezil	Rivastigmine	Galantamine
Donepezil		-0.313 (-1.259 to 0.633) P= 0.5167[1]	0.69 (0.055 to 1.325) P=0.033[2]
Rivastigmine			1.003 (0.093 to 1.913) P=0.0307[2]
Galantamine			

[1] Rivastigmine is the reference drug [2]Galantamine is the reference drug

Table 17: MMSE at 12-13 weeks (mean change from baseline): indirect meta-analysis between donepezil and rivastigmine (WMD (95% CI) p-value)

	Donepezil	Rivastigmine
Donepezil		0.252 (-1.2 to 1.704) P=0.7337[1]
Rivastigmine		

[1] Rivastigmine is the reference drug

Table 18: MMSE at 24-26 weeks (mean change from baseline): indirect meta-analysis between donepezil and rivastigmine (WMD (95% CI) p-value)

Drug	Donepezil	Rivastigmine
Donepezil		0.192 (-0.332 to 0.716) P=0.4727[1]
Rivastigmine		

[1] Rivastigmine is the reference drug

Table 19: CIBIC-plus at 24-26 weeks (mean change from baseline): indirect meta-analysis between donepezil, rivastigmine and galantamine (WMD (95% CI) p-value)

Drug	Donepezil	Rivastigmine	Galantamine
Donepezil		-0.034 (-0.206 to 0.138) P=0.6984[1]	-0.168 (-0.305 to -0.031) P=0.016[2]
Rivastigmine			-0.134 (-0.303 to 0.035) P=0.1202[2]
Galantamine			

[1] Rivastigmine is the reference drug [2]Galantamine is the reference drug

Table 20: Withdrawals due to an adverse event before end of treatment at 24 weeks or later (odds ratio): indirect meta-analysis between donepezil, rivastigmine and galantamine (OR (95% CI) p-value)

Drug	Donepezil	Rivastigmine	Galantamine
Donepezil		0.509 (0.225 to 1.147) P=0.105[1]	0.759 (0.411 to 1.403) P=0.378[2]
Rivastigmine			1.492 (0.689 to 3.232) P=0.155[3]
Galantamine			

[1] Rivastigmine is the reference drug [2]Galantamine is the reference drug

Table 21: Rivastigmine low dose patches, high dose patches and capsules

Efficacy Outcomes:

Comparison	Group 1		Group 2		Group 1 minus Group 2	
	Mean (SD)	N	Mean (SD)	N	Mean Difference (95% CI)	P value
ADAS-cog at 24 weeks						
low dose patch vs. high dose patch	-0.6 (6.4)	248	-1.6 (6.5)	262	1.00 (-0.12 to 2.12)	0.08
low dose patch vs. capsule	-0.6 (6.4)	248	-0.6 (6.2)	253	0.00 (-1.10 to 1.10)	1.00
high dose patch vs. capsule	-1.6 (6.5)	262	-0.6 (6.2)	253	-1.00 (-2.10 to 0.10)	0.07
ADCS-CGIC at 24 weeks						
low dose patch vs. high dose patch	3.9 (1.2)	248	4.0 (1.3)	260	-0.10 (-0.32 to 0.12)	0.37
low dose patch vs. capsule	3.9 (1.2)	248	3.9 (1.3)	253	0.00 (-0.22 to 0.22)	1.00
high dose patch vs. capsule	4.0 (1.3)	260	3.9 (1.3)	253	0.10 (-0.13 to 0.33)	0.38
ADCS-ADL at 24 weeks						
low dose patch vs. high dose patch	-0.1 (9.1)	247	0.0 (11.6)	263	-0.10 (-1.90 to 1.70)	0.91
low dose patch vs. capsule	-0.1 (9.1)	247	-0.5 (9.5)	254	0.40 (-1.23 to 2.03)	0.63
high dose patch vs. capsule	0.0 (11.6)	263	-0.5 (9.5)	254	0.50 (-1.32 to 2.32)	0.59
MMSE at 24 weeks						
low dose patch vs. high dose patch	1.1 (3.3)	250	0.9 (3.4)	262	0.20 (-0.38 to 0.78)	0.50
low dose patch vs. capsule	1.1 (3.3)	250	0.8 (3.2)	256	0.30 (-0.27 to 0.87)	0.30
high dose patch vs. capsule	0.9 (3.4)	262	0.8 (3.2)	256	0.10 (-0.47 to 0.67)	0.73

Safety Outcomes:

Comparison	Group 1	Group 2	Group 1/ Group 1	
	Events/N (%)	Events/N (%)	Relative Risk (95%CI)	P value
Adverse Events				
low dose patch vs. high dose patch	147/291 (51%)	200/303 (66%)	0.77 (0.67 to 0.88)	<0.01
low dose patch vs. capsule	147/291(51%)	186/294 (63%)	0.80 (0.69 to 0.92)	<0.01
high dose patch vs. capsule	200/303 (66%)	186/294 (63%)	1.04 (0.93 to 1.17)	0.48

Data abstracted for Winblad 2007 and re-analyzed for comparisons between treatments.

Table 22: Results of the deterministic base-case incremental Cost Utility Analysis for people with mild-to-moderate Alzheimer Disease (MMSE 10 to 26)

Drug	Lifetime costs	QALYS
Galantamine (16–24 mg)	£69,592	1.617
Rivastigmine patch (9.5 mg/day)	£69,598	1.616
Donepezil (10 mg)	£69,624	1.619
Rivastigmine capsules (9–12 mg)	£69,678	1.613
Best Standard Care	£70,212	1.584

Source: Table 116. Bond 2012.

Table 23: Calculation of incremental cost effectiveness ratios based on data presented in Hyde 2013

	Donepezil	Rivastigmine	Galantamine
Cost difference versus best supportive care	- £588	-£620	- £534
Quality of life difference versus best supportive care (QALYs)	0.035	0.033	0.029
Incremental cost vs. Galantamine	-£54	-£86	Reference
Incremental Quality of life vs. Galantamine	0.006	0.004	Reference

Source: Hyde et al. Age and Aging; 42. 2013

Table 24: Studies with data on resource utilization or quality of life., with a search extended back to 2006

Citation	Drugs	Outcomes	Relevance to BC ADTI
Articus K et al. A 24-week, multicentre, open evaluation of the clinical effectiveness of the rivastigmine patch in patients with probable Alzheimer's disease. Int J Clin Pract. 2011 Jul;65(7):790-6.	Rivastigmine oral vs. patch	Proportion of patients who reached and maintained the target rivastigmine patch dose compared with the target rivastigmine capsule dose	Low - Demonstrates adherence to the patch with good efficacy but due to non-randomized format may be due to other confounding factors that were not assessed. Importantly, the question still remains whether this adherence to treatment improves clinical outcomes and this was not addressed.
Molinuevo JL, Arranz FJ. Impact of transdermal drug delivery on treatment adherence in patients with Alzheimer's disease. Expert Rev Neurother. 2012 Jan;12(1):31-7	Transdermal patch	Adherence to patch in previous non compliant patients	Low - Demonstrates good adherence to therapy but once again the question still remains whether this adherence to treatment improves clinical outcomes and this was not addressed.
Gadzhanova S, Roughead L, Mackson J Anticholinesterase duration in the Australian veteran population. Aust N Z J Psychiatry. 2010 May;44(5):469-74.	Donepezil, rivastigmine, galantamine	Adherence to drugs for initial AD treatment	Low - Demonstrated discontinuation rates in Australian veterans but reasons for discontinuation were not given. Patients in community settings were more likely to discontinue therapy than those in care facilities.
Gauthier S, et al. Effects of rivastigmine on common symptomatology of Alzheimer's disease (EXPLORE). Curr Med Res Opin. 2010 May;26(5):1149-60.	rivastigmine	impact on six symptoms: attention, apathy, anxiety, agitation, irritability and sleep disturbance using Clinical Global Impression of Change (CGI-C) scale	Low - Physician assessment of CGI-C and was non-randomized. Does not add to the body of evidence derived from RCTs.
Kroger E, van Marum R, Souverein P, Egberts T. Discontinuation of cholinesterase inhibitor treatment and determinants thereof in the Netherlands: A retrospective cohort study. Drugs Aging. 2010 Aug 1;27(8):663-75	rivastigmine, galantamine	Discontinuation rates and determinants	Low - Quantified discontinuation rates but reasons for discontinuation were not assessed. It appeared that fewer patients taking rivastigmine than those taking galantamine reached recommended doses. Once again, importance of adherence to therapy remains questionable when the level of clinical improvement may be minimal.
Wattmo et al. Risk factors for nursing home placement in Alzheimer's disease: a longitudinal study of cognition, ADL, service utilization, and cholinesterase inhibitor treatment. Gerontologist. 2011 Feb;51(1):17-27.	Donepezil, rivastigmine, galantamine	Factors contributing to nursing home placement, increases in home help service, home day care	Low - Is not within the scope of the outlined project. This study may however give hints to reasons for increased risk for NHP. This could have cost implications to the BC government but there were no data to substantiate this.
Van Puyvelde K, Mets T; RODOS Study Group. Galantamine (Reminyl) once daily outcome and satisfaction	Once daily prolonged release galantamine	Adherence, AEs and satisfaction of patients, caregivers and clinicians	Low - Does not fall into the scope of the project. Once a day galantamine is preferred but that is the preparation that is routinely used now.

survey (RODOS) in mild to moderate Alzheimer's disease: a study in a real life population. Geriatr Gerontol Int. 2011 Jul;11(3):256-61			
Wimo et al The economic impact of galantamine vs. placebo: an analysis based on functional capacity in a Swedish cohort study. J Med Econ. 2012;15(5):1019-24.	Galantamine	Economics – direct medical, non direct medical costs, informal care	Low - results for the Swedish healthcare system. No actual resource utilization breakdown or assessment was provided.
Nagy B et al Assessing the cost-effectiveness of the rivastigmine transdermal patch for Alzheimer's disease in the UK using MMSE- and ADL-based models Int J Geriatr Psychiatry 2011; 26: 483–494.	Patch vs. oral rivastigmine	Incremental costs and Quality Adjusted Life Years (QALYs)	Moderate. Demonstrates that both oral and transdermal patch therapy with rivastigmine is cost effective compared to BSC in the UK. This analysis suggests that the patch may be more cost effective than oral therapy.
Hyde C 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: 14–20	Included in the PATH assessment.		
Winblad B et al Caregiver preference for rivastigmine patch relative to capsules for treatment of probable Alzheimer's disease Int J Geriatr Psychiatry 2007; 22: 485–491.1	Included in the PATH assessment		
Blesa R et al. Caregiver preference for rivastigmine patches versus capsules for the treatment of Alzheimer disease Neurology 2007;69;S23-S28	Duplicate report of the Winblad 2007 report above.		
Ward W and Kunle A. An Observational Study of the Needs and Quality of Life Amongst Patients in the Treatment of Alzheimer's Dementia with Cholinesterase Inhibitors Current Aging Science, 2008, 1, 140-143	No drugs identified, included patients on ChEI therapy	Patient and Caregiver satisfaction	Moderate - Describes impact of therapy on unmet needs in patients and caregivers. Did not identify drugs or therapies and no comparisons or conclusions on type of drug therapy were made.

FIGURES

Figure 1: PRISMA Flow Diagram of Included Studies

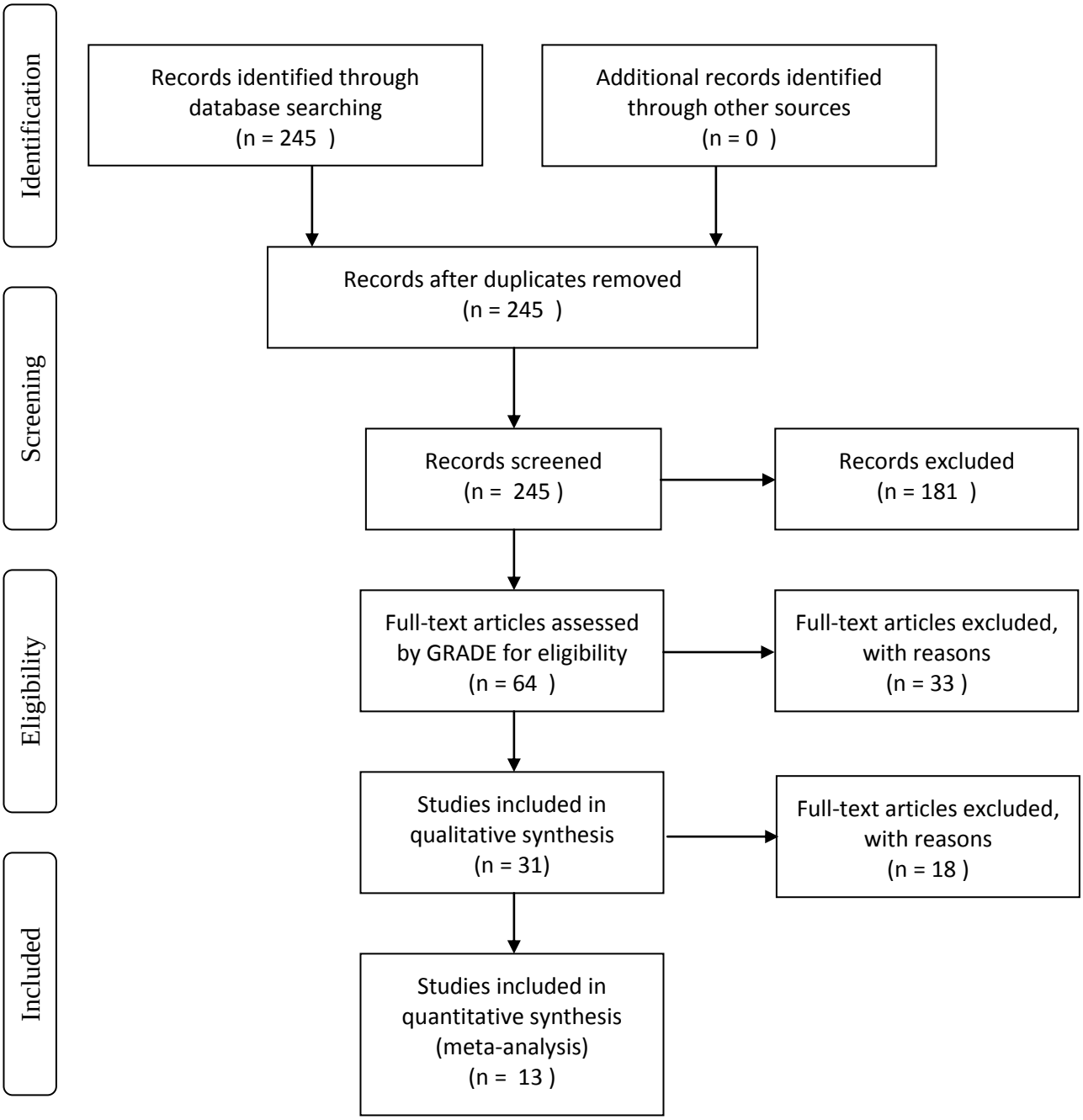


Figure 2: Random-effect meta-analysis-ADAS-cog at 24 weeks (mean change from baseline): donepezil (all dosages) vs placebo

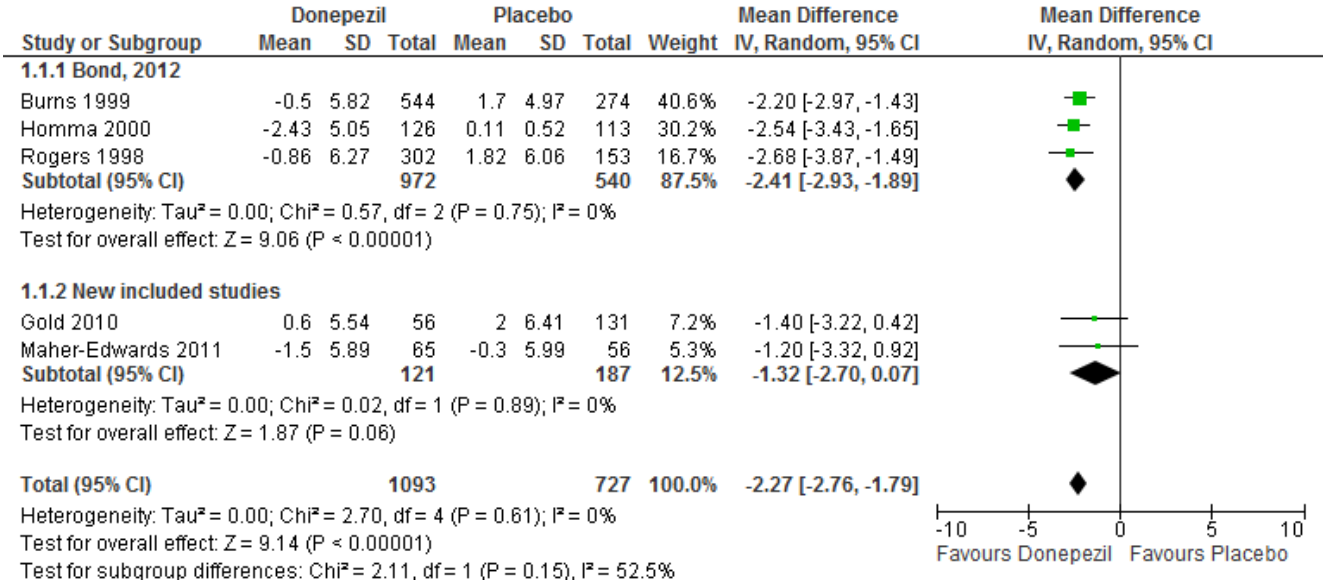


Figure 3: Random-effects meta-analysis – ADAS-cog at 21-26 weeks (mean change from baseline): galantamine (all dosages) vs placebo

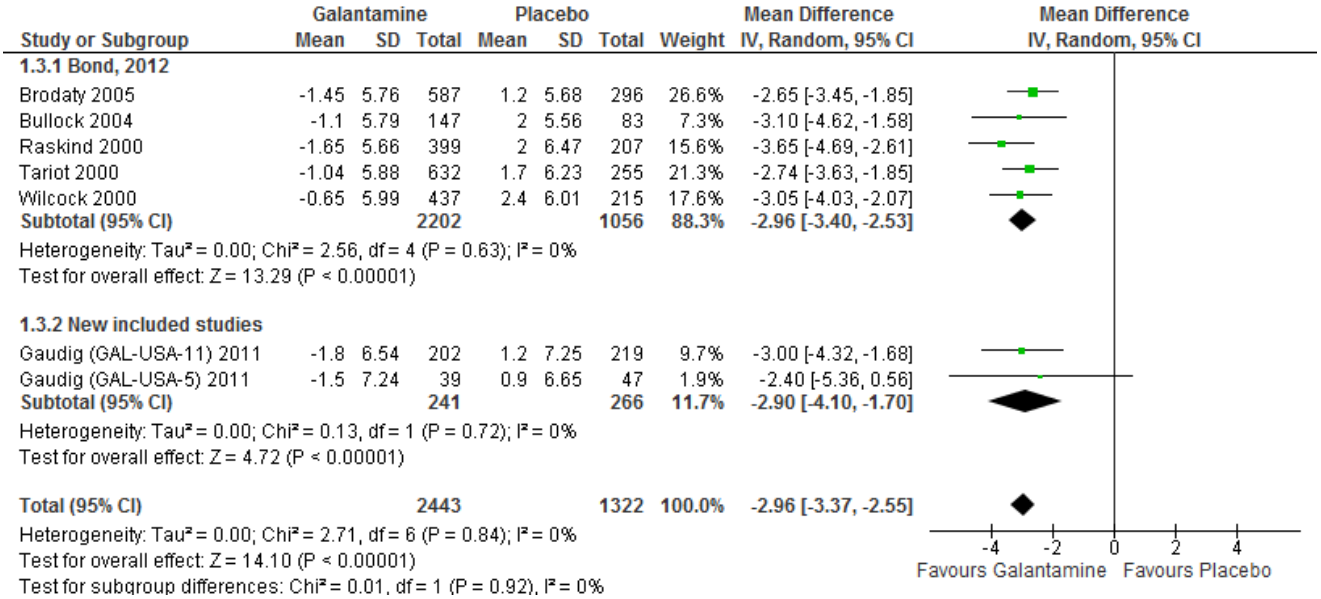


Figure 4: Random-effects meta-analysis – MMSE at 24 weeks (mean change from baseline): donepezil (all dosages) vs placebo

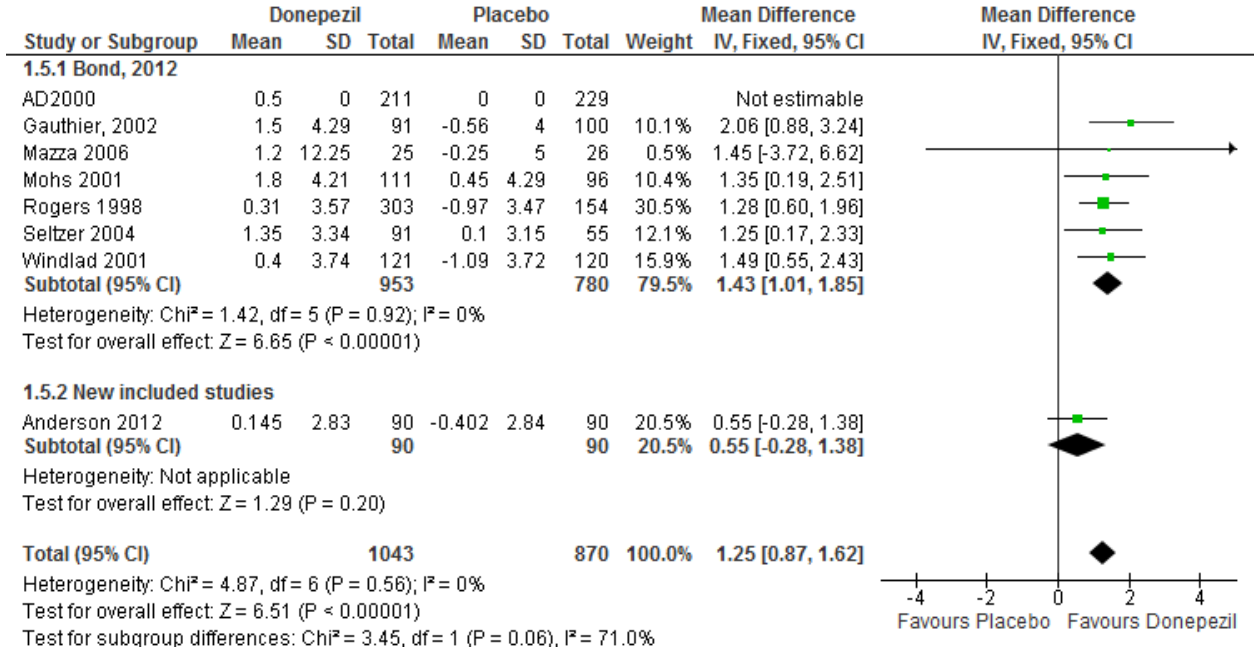


Figure 5: Random-effects meta-analysis – CIBIC-plus at 24 weeks (mean change from baseline): donepezil (all dosages) vs placebo

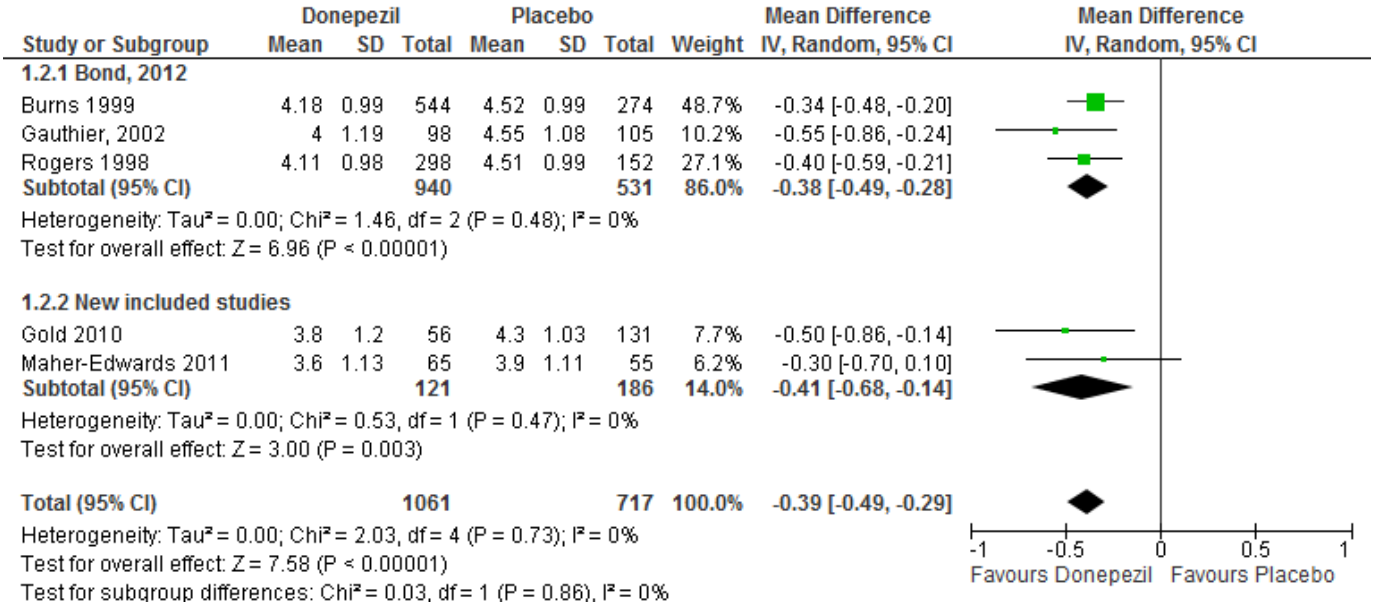
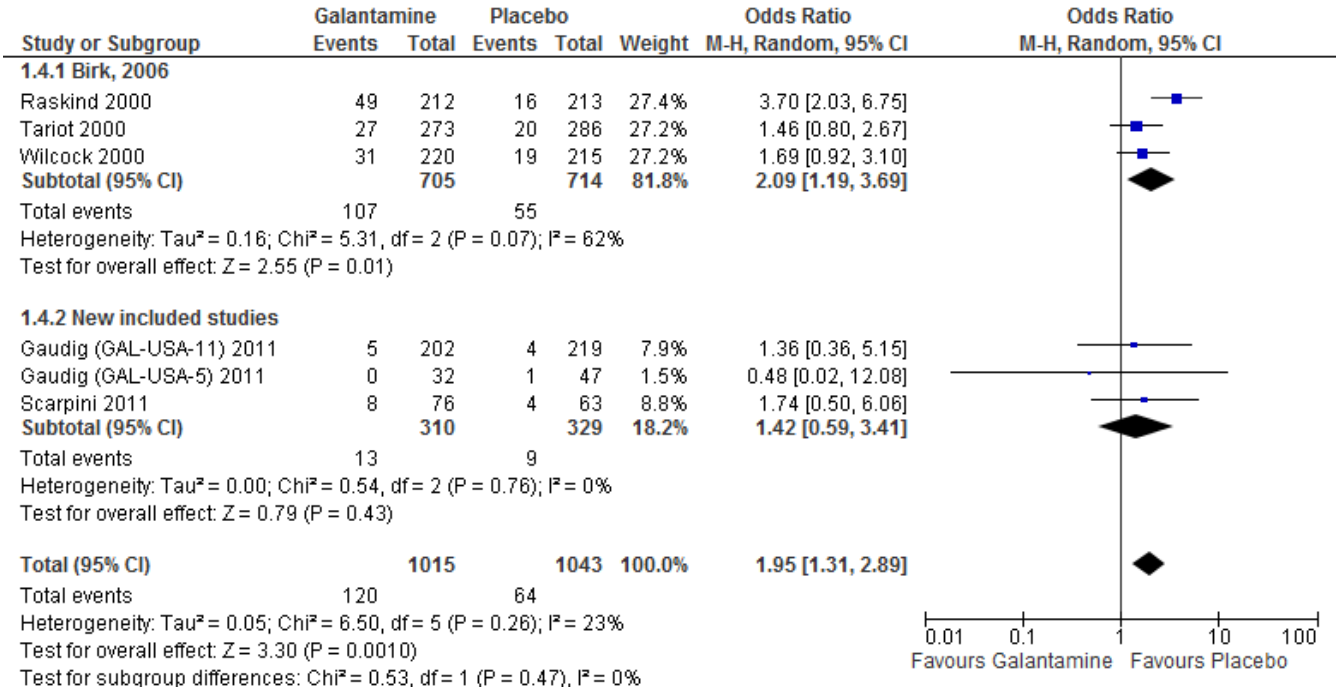


Figure 6: Total number of withdrawals due to an adverse event before end of treatment at 6 months or later: galantamine (all dosages) vs placebo



APPENDICES

Appendix 1: Canadian Provincial Drug Program Guidelines

British Columbia

CRITERIA FOR COVERAGE
DONEPEZIL (ARICEPT®), GALANTAMINE (REMINYL®) AND RIVASTIGMINE (EXELON®)

For coverage, diagnosis must be Alzheimer's disease, Alzheimer's disease with a vascular component, Alzheimer's disease with Lewy bodies or mixed dementia with predominant Alzheimer's disease.

Initiation of coverage in a cholinesterase inhibitor-naïve patient:
Coverage will be provided for an initial 6-month period, when the following criteria are met:
► a Standardized Mini Mental State Examination (SMMSE) score of ≥ 10 to ≤ 26, **AND**
► a Global Deterioration Scale (GDS) stage of 4, 5 or 6.

Note: Check for tolerability in naïve patients within the first 1 - 3 months.

Continuation of coverage for 6-month periods:
Coverage is continued for patients in 6-month increments when:
► the information provided indicates that the patient remains in the mild to moderate stage of Alzheimer's disease (if repeat SMMSE testing at 6-month intervals results in scores of ≥ 10 **AND**
► a GDS stage of 4, 5 or 6) **AND**
► there is demonstrated stabilization or improvement during the previous six months of therapy.

Coverage when switching for lack of efficacy to another cholinesterase inhibitor
Coverage of another cholinesterase inhibitor is provided for an initial 6 months if:
► the clinician documents the reason for discontinuing the previous cholinesterase inhibitor on the Special Authority Renewal/Switching Form.

Note: Coverage of another cholinesterase inhibitor is provided in the same manner as the previous one (check for tolerability within the first 1 - 3 months, coverage to be renewed in 6-month increments if criteria continue to be met).

Alberta

All three cholinesterase inhibitors are available through Special Authorization with the following criteria for use:

- For the treatment of Alzheimer's disease in patients with an MMSE (Mini Mental State Exam) score between 10-26 and/or an InterRAI-Cognitive Performance Scale score between 1-4.
- Coverage cannot be provided for two or more medications used in the treatment of Alzheimer's disease (donepezil, galantamine, rivastigmine) when these medications are intended for use in combination.
- Special authorization coverage may be granted for a maximum of 24 months per request.

- For each request, an updated MMSE score or InterRAI-Cognitive Performance Scale score and the date on which the exam was administered must be provided.
- Renewal requests may be considered for patients where the updated MMSE score is 10 or higher or the InterRAI-Cognitive Performance Scale is 4 or lower while on this drug."

All requests (including renewal requests) for donepezil HCI must be completed using the Donepezil/Galantamine/Rivastigmine Special Authorization Request Form (ABC 30776).

Atlantic Canada

The cholinesterase inhibitors are available through the Exception Status Drugs mechanism:

CHOLINESTERASE INHIBITORS (ChEI) *(Donepezil, Galantamine, Rivastigmine)*

- for the treatment of mild to moderate probable Alzheimer's disease or possible Alzheimer's disease with vascular component, with Lewy bodies who meet the following criteria:
    - a Mini-Mental State Examination (MMSE) score of 10 to 30 AND
    - a Functional Assessment Staging Test (FAST) score of 4 to 5

Initial requests for reimbursement will be considered for a maximum 4 month approval; subsequent requests may be considered for a maximum 12 month approval. Requests to switch from one agent in the class to another will not be considered beyond the initial 4 month approval.

Manitoba

All three cholinesterase inhibitors are listed with Exception Drug Status with the following criteria:

Confirmed diagnosis of Alzheimer's Disease with DSMIV criteria with:

- Memory impairment (impaired ability to learn new information or to recall previously learned information); plus
- at least one of the following:
    - Aphasia; problems with language (receptive and expressive)
    - Apraxia; impaired ability to carry out motor activities despite intact motor function
    - Agnosia; failure of recognition - especially people
    - Disturbance in executive functioning

  The above deficits must have:
    - Caused significant decline in previous levels; and
    - A gradual onset and continued cognitive decline; and
    - The absence of other causative conditions; and
    - The deficits do not occur exclusively during the course of delirium; and
    - Normal test results for all of the following values: CBC, TSH, Electrolytes, Vitamin B12, and Glucose; and
    - The initial MMSE score must be between 10 and 26 and measured within 30 days of the application.

Ontario

All three cholinesterase inhibitors are available through the Limited Use mechanism. The guidelines are the same for all three.

Initial Trial: For patients with mild to moderate Alzheimer's Disease (Mini-Mental State Exam [MMSE] 10-26). Patients will be reimbursed for a period of up to 3 months after which continued treatment must be reassessed.

Network note: Maximum duration 3 months.

LU Authorization Period: 1 year.

Continuation: Further reimbursement will be made available to those patients whose disease has not progressed/deteriorated while on this drug. Patients must continue to have a MMSE score of 10-26.

Quebec

The three cholinesterase inhibitors have the same guidelines for use in Quebec:
As monotherapy for persons suffering from Alzheimer's disease at the mild or moderate stage.
Upon the initial request, the following elements must be present:

- an MMSE score of 10 to 26, or as high as 27 or 28 if there is proper justification;
- medical confirmation of the degree to which the person is affected (intact domain, mildly, moderately or severely affected) in the following five domains:
    - intellectual function, including memory;
    - mood;
    - behaviour;
    - autonomy in activities of daily living (ADL) and in instrumental activities of daily living (IADL);
    - social interaction, including the ability to carry on a conversation.

The duration of the initial authorization for a treatment with the cholinesterase inhibitor is six months from the beginning of treatment. However, where the cholinesterase inhibitor is used following treatment with memantine, the concomitant use of both medications is authorized for one month.
Upon subsequent requests, the physician must provide evidence of a beneficial effect confirmed by each of the following elements:

- an MMSE score of 10 or more, unless there is proper justification;
- a maximum decrease of 3 points in the MMSE score per six-month period compared with the previous evaluation, or a greater decrease accompanied by proper justification;
- stabilization or improvement of symptoms in one or more of the following domains:
    - intellectual function, including memory;
    - mood;
    - behaviour;
    - autonomy in activities of daily living (ADL) and in instrumental activities of daily living (IADL);
    - social interaction, including the ability to carry on a conversation.

The maximum duration of authorization is 12 months.

Saskatchewan

Guidelines for the three cholinesterase inhibitors:

- A diagnosis of probable Alzheimer's disease as per DSM-IV criteria.
- A mild to moderate stage of the disease with a MMSE score of 10-26 established within 60-days prior to application for coverage by a clinician or nurse practitioner.
- A Functional Activities Questionnaire (FAQ) must be completed within 60- days prior to initial application for coverage by a clinician or nurse practitioner.
- Patients must discontinue all drugs with anticholinergic activity at least 14 days before the MMSE and FAQ are administered. Drugs with anticholinergic activity are not to be used concurrently with donepezil/galantamine/rivastigmine therapy. List all current medications patient was taking at the time of assessment.
- Patients intolerant to one drug may be switched to another drug in this class. Intolerance should be observed within the first month of treatment.

Eligible patients currently taking a cholinesterase inhibitor would require assessment at 6 month intervals. To continue receiving a cholinesterase inhibitor, patients must not have a greater than 2 point reduction in MMSE and a 1 point increase in FAQ in a 6 month evaluation period. Scores are compared to the most recent test results.

Eligible new patients will enter a 3 month treatment period with donepezil/galantamine/rivastigmine. During the 3 month trial, patients must exhibit an improvement from the initial MMSE or FAQ to continue treatment with donepezil. The improvement must be at least 2 MMSE points or -1 FAQ. Patients who meet these requirements will be re-evaluated at 6 month intervals. To continue receiving donepezil, patients must not have both a greater than 2 point reduction in MMSE and a 1 point increase in FAQ in a 6 month evaluation period. Scores are compared to the most recent test results.

- The MMSE score must remain at 10 or greater at all times to be eligible for coverage.
- Patients who do not meet criteria to continue donepezil can be re-evaluated within 3 months to confirm deterioration before coverage is discontinued.
- Donepezil does not need to be discontinued prior to MMSE or FAQ testing.
- A patient intolerant of one drug and switching to a second will be considered a "new" patient and will be assessed as such. Coverage will not be considered for patients who have failed on other drugs in this class.

Appendix 2: Selected results credited to Bond 2012 Health Technol Assess

NOTE: The information in this section was taken directly from Bond 2012 Health Technol Assess (NICE Technology Appraisal No. 111).

Summary: Efficacy of donepezil versus placebo

This analysis found no new donepezil studies reporting the ADAS-cog at 12 or 24 weeks compared to their previous report. The meta-analyses presented are of studies included in the previous assessment report. Similarly, no new evidence was found for the outcome measure MMSE at 12 weeks post randomization, but one new study was found with measures at 24 weeks' follow-up.

Pooled cognitive outcomes showed a significant benefit from donepezil measured by the ADAScog and MMSE with greater benefit shown at 24 weeks [ADAS-cog: WMD = –2.90 (95% CI –3.61 to –2.18), $p < 0.001$; MMSE: WMD = 1.21 (95% CI 0.84 to 1.57), $p < 0.001$]. Only one new study looked at functional outcomes for this comparison; at 12 weeks this showed a significant gain for those taking donepezil [mean difference: I = 40.5 (SD 7.6), C = 49.5 (SD 6.3), $p < 0.01$)]. At 24 weeks there were data from only the 2004 assessment trials, and the results from all the studies reporting functional outcomes were pooled; this analysis again showed a significant benefit from taking donepezil.

Just one new study looked at global outcomes; this showed a benefit from taking donepezil on the CDR [I = 1.2 (SD 0.2), C = 2.0 (SD 0.2), $p < 0.01$)]. The pooled results for the CIBIC-plus scale were only from the previous technology assessment report (TAR) and they showed a significant advantage from donepezil at 12 and 24 weeks' follow-up [24 weeks: WMD = –0.43 (95% CI –0.55 to –0.31), $p < 0.001$]. When both the global outcome measures were pooled at 24–26 weeks, the results again showed a significant benefit from donepezil. None of the new studies measured behavioural outcomes; the pooled estimates from the previous assessment, using the NPI, failed to show a significant gain on behavioural outcomes at either 12 or 24 weeks.

None of the new studies provided additional data on QoL or safety under randomized conditions. The new studies found have added to the body of evidence showing a benefit from donepezil compared with placebo for cognitive, functional and global outcomes. However, there is no new or pooled evidence to show a behavioural benefit from donepezil versus placebo in people with mild-to-moderate AD. All but two of the studies included in these meta-analyses calculated their missing data points using LOCF or OC methods, thereby potentially biasing their results in favour of donepezil.

Summary: Efficacy of galantamine versus placebo

The authors reported that an additional three RCTs were added to the five reported in the 2004 review. Overall cognitive results from the new studies using ADAS-cog showed improvements for those taking galantamine. When these studies were pooled with the existing evidence the benefit remained and increased with time, with greater benefit seen at 21–26 weeks [WMD = –2.96 (95% CI –3.41 to –2.51), $p < 0.001$] than 12–16 weeks [WMD = –2.39 (95% CI –2.80 to –1.97), $p < 0.001$].

All of the new studies reported functional outcomes. Those measured by the DAD and ADCSADL scales generally showed significant improvement; those measured by the Goal Attainment Scale (GAS) were rather more ambiguous. Pooled results of the ADCS-ADL and the DAD at 21–26 weeks continued to show benefit from galantamine compared with placebo [WMD = 2.23 (95% CI 1.33 to 3.14), $p < 0.001$; WMD = 3.76 (95% CI 1.66 to 5.86), $p < 0.001$, respectively].

When data from both these outcome measures were pooled, results still favoured galantamine. Behavioural outcomes from one new study, measured by the NPI, failed to show a benefit from galantamine. This lack of benefit was also seen from the pooled results at 13 weeks from follow-up. However, when the new data were pooled with those of the previous assessment a significant difference favouring galantamine was found at 21–26 weeks [WMD = –1.46 (95% CI –2.59 to –0.34), $p = 0.012$].

Two of the new studies measured global outcomes; one found that it produced a significant benefit on the CIBIC-plus. When these data were pooled with the data from the previous review, significant benefit was found on the CIBIC-plus at 26 weeks' follow-up: WMD = –0.20 (95% CI–0.30 to –0.09), $p < 0.001$, with doses of ≤ 24 mg/day.

No QoL data were reported in either the new or the old studies for this comparison. The main AEs found were gastrointestinal.

Summary: Efficacy of rivastigmine versus placebo

The new report identified three new RCTs that were added to the four included in the previous review. All three studies showed benefits from rivastigmine on the ADAS-cog and MMSE, although these benefits were dependent on dose, with greater benefits seen at 12 mg/day than at 6 mg/day. When these data were pooled with the existing evidence, significant differences favouring rivastigmine continued to be seen on the ADAS-cog at 24–26 weeks (≥ 12 mg/day), WMD = –2.46(95% CI –3.37 to –1.56), $p < 0.001$. However, the benefits from rivastigmine were not apparent on MMSE scores until 24–26 weeks' follow-up [WMD = 1.02 (95% CI 0.63 to 1.41), $p < 0.001$]; this may be due to the MMSE's difficulties with detecting change. When the outcomes from both cognitive measures were combined they continued to show an advantage from taking rivastigmine on cognitive outcomes.

Two of the three new studies reporting functional outcomes showed significant gains for these measures. When these new data were synthesized with existing evidence using the PDS, significant gains were shown at 24–26 weeks [WMD = 3.10 (95% CI 1.81 to 4.40), $p = 0.001$]. The data on behavioural outcomes from the new studies were unclear, with the smaller study showing a benefit from rivastigmine that the larger one140 did not. The existing evidence was too heterogeneous for meta-analysis, so the overall effectiveness of rivastigmine for behavioural outcomes is unknown.

When all the results were pooled for the cognitive outcomes from the new and existing studies, it was found that the overall pooled estimate showed a significant benefit from rivastigmine compared with placebo: SMD = 0.28 (95% CI 0.14 to 0.42), $p < 0.001$. Two new studies were found to add to this combined meta-analysis of functional outcomes at 24–26 weeks. Again, the overall pooled estimate showed a benefit from rivastigmine compared with placebo: SMD = 0.21 (95% CI 0.12 to 0.29), $p < 0.001$.

Comparison of Agents

Bullock and colleagues' RCT provided the only new evidence on the relative effectiveness of the technologies under review in the functional domain. In the primary – ITT LOCF – analysis, a significant advantage for rivastigmine over donepezil after 2 years' treatment was detected.

Individuals who had been randomized to receive rivastigmine declined by around two fewer points on the ADCS-ADL instrument. It should be noted, however, that this finding was not replicated in the secondary analyses, which relied on evaluable cases (all participants who were treated for at least 16 weeks, with LOCF imputation for subsequent missing values) and OCs.

Behavioural and mood

New data from Bullock and colleagues found no significant difference between donepezil and rivastigmine on the NPI scale, with participants in both groups declining by an average of between two and three points over 2 years' treatment.

Individuals taking rivastigmine were also reported to have a higher probability of remaining free of behavioural symptoms at 18 months than those taking donepezil, although the methods adopted in the time-to-event (TTE) analysis are unclear.

Bullock and colleagues used the GDS to measure overall effect. They found that, over the 2-year trial, individuals who had been randomized to donepezil deteriorated by around 0.1 points more than those taking rivastigmine. As with the difference found on their chosen functional measure, this discrepancy appeared significant in the ITT LOCF analysis ($p < 0.05$ by Wilcoxon's rank-sum test), but this finding was not repeated in secondary analyses based on evaluable and OCs.

In one trial it was found that none of the individuals taking galantamine experienced a global decline, according to the CIBIC-plus, over the 8 weeks of treatment, whereas 13% of those taking donepezil deteriorated on the same measure, although this difference did not appear to be a significant one.

Summary: head-to-head comparisons

Four new head to head RCTs were found; two compared all included ChEIs, one compared donepezil to rivastigmine and one compared donepezil to galantamine. Pooling of data from head-to-head trials was not possible owing to the heterogeneity of the data. The quality of the evidence they provide is limited because of the poor quality of most of the trials. The exception to this was Bullock and colleagues, whose good-quality study found no significant difference between donepezil and rivastigmine for cognitive or behavioural outcomes.

However, when they looked at functional and global outcomes, patients taking rivastigmine fared significantly better than those taking donepezil in the primary analysis.

Conclusions from efficacy and safety results

- From 1843 titles and abstracts screened, four systematic reviews and 17 RCTs were found that matched our inclusion criteria, which had been published since 2004.
- Overall, the quality of the trials was disappointing, and there was insufficient evidence to suggest that one treatment is better than another. Therefore it was suggested that the ChEIs are taken as a class of drugs.
- When combined with data from the previous review in 2004, donepezil was shown to provide gains on cognitive, functional and global outcomes when compared with placebo.

- Similar pooling of data from galantamine studies was conducted, showing clear benefits from cognitive, functional and global outcomes. Additionally, results favouring treatment were seen for behavioural outcomes at later (6-month) follow-up.
- Pooled estimates of cognitive benefits from rivastigmine were favourable, but were shown to be dose dependent as in the previous review in 2004. The results from functional and global outcomes also showed significant gains. However, results from individual trials of behavioural outcomes were mixed (pooling was not possible owing to heterogeneity). The lower dose transdermal patch (9.5 mg/day) was shown to be as effective as the capsule (12 mg/day), but with fewer side effects.
- Pooling of data from head-to-head trials was not possible owing to the heterogeneity of the data. Results from the one reasonably good-quality trial showed no significant difference between donepezil and rivastigmine for cognitive or behavioural outcomes. However, when looking at functional and global outcomes, patients taking rivastigmine fared significantly better than those taking donepezil in the primary analysis.

Economic Analysis

The focus of the economic analysis was on the evidence and analyses that had been produced since 2004. There was not a review of work that would already have been considered in previous technology assessments.

Key economic considerations

Different incremental cost-effectiveness ratios (ICERs) for moderate and mild AD were recognized. It (the appraisal committee) therefore considered whether it might be possible to define, prospectively, subgroups of people with Alzheimer's disease who might benefit more than average, and for whom ChEIs might be a relatively cost-effective treatment. In accepting the subgroup analyses using severity of cognitive impairment, the Committee reviewed the estimates of cost-effectiveness. It noted that for people with moderate Alzheimer's disease these estimates ranged from £23,000 to £35,000 depending on the choice of AChE inhibitor and by including carer benefits in the augmented base-case. Conversely, the Committee noted that for the subgroup of people with mild Alzheimer's disease estimates of cost-effectiveness ranged from £56,000 to £72,000 depending on the choice of AChE inhibitor and by including carer benefits in the augmented base-case.

The specific ICERs given for moderate AD were:

For moderate disease treated with donepezil, the augmented base-case ICER was £31,550 per QALY gained.

Further detail on the ICERs for mild AD included:

The Committee concluded that the cumulative impact of the changes it considered appropriate reduced the base-case ICER for mild Alzheimer's disease to approximately £55,000 to £58,000 per QALY gained (for galantamine and donepezil, respectively) which is further reduced by approximately £1500 when using the appropriate starting age of the full-time care (FTC) index.

There were nine included studies addressing the cost-effectiveness of donepezil. Three further included papers were interim reports of or correspondence on the main study by Feldman and colleagues.

The review of cost-effectiveness studies reveals some potentially valuable new evidence since the last guidance. The studies fall into four categories:

Primary economic evaluations

There were two studies in this category. Of the two, the study by Feldman and colleagues (2004) is the more robust, representing a bottom-up costing alongside a RCT in Canada, Australia and France (Gauthier 2002) in which 144 patients with moderate to severe AD (MMSE 5–17) were randomized to donepezil for 24 weeks and 146 to placebo. The societal cost per patient was CDN$9904 in the donepezil group and CDN$10,236 in the placebo group, representing a net saving of CDN$332. When caregiver costs were excluded, the cost was CDN$4355 in the donepezil group and CDN$4321 in placebo, representing a net increase of CDN$34 with donepezil.

The study by Lu and colleagues (2005) was an observational study, and, hence, much more open to bias and confounding, but, nonetheless, also suggested that prescription of donepezil was associated with lower costs to a large Medicare-managed health-care plan. The difference in costs was US$2500 (95% CI US$330 to US$4671) and was adjusted for differences in patient characteristics between cases and controls. Both studies were funded by the manufacturer of donepezil.

Application of existing models to different settings

Three studies of donepezil essentially apply existing model structures to new settings, defined in terms of the healthcare systems in different countries. Parameters, where country-specific estimates exist, were substituted for the parameters and assumptions in the parent models. The conclusions are consistent with the parent models that were reported in the last guidance, indicating that donepezil is cost saving, particularly when a societal perspective is considered. The study based in Germany (Teipel 2009)as perhaps more cautious in its conclusions than past models, acknowledging the enormous impact of uncertainty on its cost-effectiveness estimates and also suggesting that implementation might not be justified in the context of the German reimbursement system. The Spanish study (Lopez-Batista 2009) was interesting in that it suggested that cost effectiveness might be better in mild AD, but not in moderate AD. This is the opposite conclusion to that reached by NICE in its last guidance. In terms of industry involvement, only the model by Fuh 2008 and colleagues was supported by the manufacturers. The models by Lopez-Bastida/Teipel and colleagues represent two of the few economic evaluations apparently performed independently of manufacturer influence.

Newly developed or updated models

Three conference abstracts representing two models donepezil appear to represent novel approaches to modelling. The analysis of donepezil from the UK perspective has also been published as a full paper in early 2010. In the model by Getsios and colleagues (2009, 2010), a discrete-event simulation approach has been developed to deal with limitations of the previous

models. There is very limited information in the abstracts about the details of the model, but it seems clear from the full-paper version that the approach adopted is very similar, or even identical, to the manufacturer's submission for donepezil for this NICE guidance. For this reason we did not explore it further at this stage, relying instead on the working model supplied by the manufacturer. The study by Mesterton and colleagues also provided very limited details to support the view that it genuinely provides an updated approach using new data on costs and utilities. Concerning results, both models in this category suggest that donepezil produces health benefits and is cost-saving, and so dominates the no-drug treatment alternative. In the second abstract and the full paper using the Getsios model, the new model is applied to the question of whether or not screening for AD, followed by donepezil treatment is cost-effective relative to donepezil treatment in those presenting with AD. The screening approach is claimed to be cost-effective, although this is not an issue of direct interest in this appraisal. Both models in this group of studies have been developed with the support of the manufacturer.

Other

There was one poorly described model, which claimed to have assessed the cost effectiveness of donepezil, high-dose rivastigmine and low-dose rivastigmine relative to no-drug treatment in a Thai private hospital (Pattanaprateep 2005). The details were so scant, however, that it is debatable whether or not the conclusions can be given any credibility.

Results: rivastigmine

There were only two included studies claiming to provide new evidence on the cost-effectiveness of rivastigmine. The first study (Brennan 2006) was a model that claimed to assess the cost-effectiveness of a rivastigmine patch. Unfortunately, the scant methodological details undermine the credibility of its findings that the Exelon patch was cost-effective with a cost per quality-adjusted life-year (QALY) of about £13,000 from a UK NHS perspective. The study had support from the manufacturer. The second study (Pattanaprateep 2005) attempted to compare rivastigmine at high and low doses with donepezil, and has already been described in the donepezil section. As already indicated, the details of the modelling process are so scant that the credibility of the conclusion that high-dose rivastigmine is more cost-effective than donepezil, which, in turn, is more cost-effective than low-dose rivastigmine must be questioned.

Results: galantamine

There were again only two included studies claiming to provide new evidence on the cost effectiveness of galantamine (Suh 2008, 2009). The first was an industry-sponsored economic evaluation alongside a controlled trial in which the costs of galantamine administered in the context of a RCT comparing different galantamine doses were compared with the costs in a community-derived untreated control group. The duration of the study was 1 year and showed a cost saving of US$5372. The second study by Suh is an economic model, in which an existing framework is applied to the Korean setting. The results suggest that, from the perspective of a third-party payer over 5 years, galantamine is cost-effective relative to usual care (cost per QALY US$4939). The author claims that there are no conflicts to declare, but this is somewhat inconsistent with the manufacturer sponsorship of the previously mentioned economic evaluation alongside the RCT in which the same author is the lead.

Conclusions

The systematic review of cost-effectiveness studies published since the last guidance raises the following key points:

- There have been further publications on cost-effectiveness of pharmacological interventions for AD in the general medical literature. These are generally supportive of the cost effectiveness of the acetylcholinesterase inhibitors (donepezil in particular) in the treatment of AD at all stages of disease. Most work is supported by the manufacturers as it was in the last appraisal. There are, however, a few more examples of independent assessments, which, although more cautious, also support the cost-effectiveness of drug treatments for AD.
- Many studies apply existing models to new settings and, as such, appear to add little further general understanding concerning the cost-effectiveness of AD drug treatments outside the new setting considered.
- There are some new economic evaluations alongside trials and other studies, which appear to offer new evidence. They support the cost-effectiveness of donepezil and memantine, in contrast with the AD2000 study in the last guidance, but are all manufacturer supported.

There also appear to be a small number of novel approaches to modelling, attempting to overcome problems observed with previous models. The most obvious of these is the discrete-event simulation model of the cost-effectiveness of donepezil

Appendix 3: Selected results credited to Birks 2012 Cochrane

NOTE: The information in this section was taken directly from Birks 2012 Cochrane Collaboration

ChEI vs. placebo

In this analysis 13 trials met the criteria for inclusion. Results were assessed for all three ChEI vs. placebo and not each agent separately vs. placebo. All studies examined the cognitive, functional and global effects of a ChEI. Meta-analyses on the ITT population, where LOCF assessments were incorporated when assessments were missing, are reported where data are available. Models were fitted using fixed effects. There is evidence of heterogeneity between the studies for a few meta-analyses, but not a high level of heterogeneity as measured by I-squared. The rating scales and cognitive tests differ in the direction representing improvement. A decrease in score indicates improvement with the ADAS-Cog, CIBIC-Plus, GBS, and ADL, whereas increase shows improvement for the MMSE.

Global assessment

The 7-point CIBIC-Plus scale, measuring global clinical state, was dichotomized, counting those showing no change or decline, against those showing improvement, and analyzed using the odds ratio. There are benefits associated with ChEI compared with placebo after approximately 6 months of treatment as shown by the ITT-LOCF analyses (numbers improved 428/1755 (24%) vs. 277/1647 (17%), OR 1.56, 95% CI 1.32 to 1.85, p<0.00001, 8 studies). The results are fairly homogeneous across the three ChEIs. The 7-point CIBIC-Plus scale, measuring global clinical state, was dichotomized, counting those showing decline, against those showing improvement or no change, and analyzed using the odds ratio. There are benefits associated with a ChEI compared with placebo after approximately 6 months of treatment as shown by the ITT-LOCF analyses (numbers improved or unchanged 425/ 645 vs. 340/661, OR 1.84, 95% CI 1.47 to 2.30, p<0.00001, 2 studies).

The GBS is a global assessment scale. Only one trial used this scale, the DON-Nordic and there is no evidence of benefit or risk associated with a ChEI after one year of treatment.

Cognitive function

The meta-analysis reveals benefits associated with a ChEI compared with placebo on cognitive function as shown by improvement in the ADAS-Cog and MMSE test scores after treatment of approximately 6 months. Ten studies contribute data to the ADAS-Cog meta analysis, three of donepezil, 3 of galantamine and four of rivastigmine, nine studies to the MMSE meta analysis, five of donepezil and four of rivastigmine. ADAS-cog (MD -2.66, 95%CI -3.02 to -2.31, P=<0.00001, 10 studies) MMSE (MD 1.37, 95%CI 1.13 to 1.61, P=<0.00001, 9 studies). For ADAS-Cog, the treatment effect for individual trials is between -1.4 and -3.9 points. The rivastigmine trials show the most variation, with low and high treatment effects within this range.

They also show decline for treatment and placebo groups, whereas the donepezil and galantamine trials show improvement on treatment, and decline on placebo. There is heterogeneity between trials for MMSE which is due to RIV-B352. Whereas the treatment effect

is between 0.65 and 1.80 points for eight trials, that of RIV-B352 is 2.9 points. Activities of daily living with placebo after 6months or more of treatment (MD2.40, 95% CI 1.55 to 3.37, p<0.00001, ITT-LOCF analysis). DON-Feldman and GAL-INT-1 Wilcock used the DAD scale. ChEI showed benefit compared with placebo after 6 months or more of treatment (MD 4.39, 95% CI 1.96 to 6.81, p=0.0004, ITT-LOCF analysis)

Behavioural disturbance

DON-311, DON-Feldman and GAL-USA-10 Tariot assessed behavioural disturbance (NPI-TOTAL), and ChEI showed benefit compared with placebo at 6 months (ITT-LOCF). (MD -2.44, 95%CI -4.12 to -0.76, P=0.004).

Side effects

The ChEIs were judged to be fairly well tolerated. The meta-analyses of withdrawals before the end of treatment, using the odds ratio, showed significant differences in withdrawals between the

ChEI group and the placebo group in favour of placebo after 6 months or more of treatment (778/2672 29% vs. 453/2471 18%, OR 1.76, 95% CI 1.54 to 2.02, p<0.00001, 14 studies). The percentage of withdrawals from the treatment group varies from 16% to 43%, and from the placebo group from 0% to 33%, and variation over this range is seen within the results for each ChEI.

Various adverse events were recorded. The meta-analyses of withdrawals before the end of treatment due to an adverse event, using the odds ratio, show that there were significant differences between withdrawals from the ChEI group compared with the placebo group in favour of placebo (488/2672 18% ChEI, 209/ 2471 8%placebo) (OR 2.32 95%CI 1.95 to 2.76, p<0.00001, 13 studies). The percentage of withdrawals from the treatment group varies from 7% to 29%, and from the placebo group from 7% to 18%, and variation over this range is seen within the results for each ChEI.

The meta-analyses of the total number of patients who suffered at least one adverse event before the end of treatment, using the odds ratio, show that there were significant differences between the ChEI group compared with the placebo group in favour of placebo (1802/2515 72% ChEI, 1326/2309 57% placebo) (OR 2.51 95%CI 2.14 to 2.95, p<0.00001, 12 studies). There were far fewer adverse events in both groups of the galantamine trials, although overall the odds of an adverse event was highest in the galantamine trials and lowest in the donepezil trials.

Forty seven different types of adverse events were reported in the trials. There were significant differences, in favour of placebo, compared with ChEI for several types of adverse events during treatment of 6 months or more.

Abdominal pain (159/1441 compared with 74/1263) (OR 1.95,95% CI 1.46 to 2.61, p<0.00001, 7 studies)

Abnormal dreams (9/96 compared with 0/105) (Peto OR 5.38, 95% CI 1.34 to 21.55, p=0.02, 1 study)

Anorexia (281/2296 compared with 76/2123) (OR 3.75 95%CI 2.89 to 4.87, p<0.00001, 10 studies)

Asthenia (47/485 compared with 22/452) (OR 2.47 95%CI 1.27 to 4.81, p=0.008, 3 studies) Diarrhoea (386/2686 compared with 197/2487) (OR 1.91 95%CI 1.59 to 2.30, p=<0.00001, 13 studies)

Dizziness (355/2399 compared with 171/2184) (OR1.99 95%CI 1.64 to 2.42, p<0.00001, 12 studies)

Fatigue (12/157 compared with 3/162) (OR 4.39 95%CI 1.21 to 15.85, p=0.02, 1 study)

Headache (280/1934 compared with 170/1752) (OR 1.56 95%CI 1.27 to 1.91, p<0.0001, 9 studies)

Insomnia (133/1564 compared with 79/1342) (OR 1.49 95%CI 1.12 to 2.00, p=0.007, 7 studies)

Muscle cramp (12/157 compared with 1/162) (OR 13.32 95%CI 1.71 to 103.74, p=0.01, 1 study)

Nausea (833/2648 compared with 222/2441) (OR 4.87 95%CI 4.13 to 5.74, p<0.00001, 13 studies)

Peripheral oedema (25/103 compared with 14/105) (OR 2.08 95%CI 1.01 to 4.28, p=0.05, 1 study)

Syncope (41/1194 compared with 19/1012) (OR 1.90 95%CI 1.09 to 3.33, p=0.02, 5 studies)

Tremor (19/315 compared with 3/318) (OR 6.82 95%CI 1.99 to 23.37, p=0.002, 2 studies)

Vertigo (11/142 compared with 3/144) (OR 3.95 95%CI 1.08 to 14.46, p=0.04, 1 study)

Vomiting (521/2434 compared with 122/2269) (OR4.82 95%CI 3.91 to 5.94, p<0.00001, 11 studies)

Weight loss (73/679 compared with 27/679) (OR 2.99 95%CI 1.89 to 4.75, p<0.00001, 4 studies)

Several donepezil trials reported only adverse events suffered by more than 5% of patients.

Direct comparisons between the cholinesterase inhibitors

There was one included trial, DON vs. RIV/Bullock, which compared donepezil with rivastigmine.

Donepezil vs. rivastigmine

There was no significant difference between donepezil and rivastigmine for cognitive function, activities of daily living and behavioural disturbance and global assessment as measured by the Global Deterioration Scale (GDS). The analysis of withdrawals before the end of treatment, using the odds ratio, showed significant differences in withdrawals between donepezil and

rivastigmine in favour of donepezil after 2 years of treatment (182/499 vs. 234/495, OR 0.64 95% CI 0.50 to 0.83, p=0.0006).

Various adverse events were recorded. The meta-analyses of withdrawals before the end of treatment due to an adverse event, using the odds ratio, show that there were significant differences between withdrawals from the donepezil group compared with the rivastigmine group in favour of donepezil (47/499 donepezil, 90/ 495 rivastigmine) (OR 0.47 95%CI 0.32 to 0.68, p<0.0001).

There were significant differences, in favour of donepezil, compared with rivastigmine for several types of adverse events during treatment of 12 -16 weeks

Nausea (76/499 donepezil 163/495 rivastigmine) (OR 0.37, 95% CI 0.27 to 0.5, p<0.00001)

Vomiting (29/499 donepezil 138/495 rivastigmine) (OR 0.16, 95% CI 0.10 to 0.24, p<0.00001)

Falls (10/499 donepezil 25/495 rivastigmine) (OR 0.38, 95% CI 0.18 to 0.81, p=0.01)

Hypertension(7/499 donepezil 20/495 rivastigmine) (OR 0.34, 95% CI 0.14 to 0.81, p=0.01)

Anorexia (20/499 donepezil 45/495 rivastigmine) (OR 0.42, 95% CI 0.23 to 0.66, p=0.0005)

Weight loss (9/499 donepezil 30/495 rivastigmine) (OR 0.28, 95% CI 0.13 to 0.61, p=0.001) and between 16 weeks and 2 years of treatment

Nausea (24/453 donepezil 52/404 rivastigmine) (OR 0.38, 95% CI 0.23 to 0.63, p=0.0002)

Vomiting (20/453 donepezil 62/404 rivastigmine) (OR0.25, 95% CI 0.15 to 0.43, p<0.00001)

Anorexia (14/453 donepezil 26/404 rivastigmine) (OR 0.46, 95% CI 0.24 to 0.90, p=0.02)

The analysis of serious adverse events, using the odds ratio, show that there was no significant difference between the donepezil group compared with the rivastigmine group. There is no evidence of a difference between donepezil and rivastigmine for cognitive function, activities of daily living and behavioural disturbance. Fewer patients suffer adverse events on donepezil than rivastigmine.

Economic Analysis

Only two studies assessed outcomes relating to health care resource use and the associated costs, but they were not reviewed in detail. These trials were discussed in detail in the NICE review.

Summary

The author concluded that from the evidence from 13 trials the three drugs show similar benefit for cognitive function and global assessment. The results of randomized, double blind, placebo controlled trials demonstrate that treatment for 6 months, with donepezil, galantamine or rivastigmine at the recommended dose for people with mild, moderate or severe dementia due to Alzheimer's disease produced improvements in cognitive function, on average -2.7 points

(95%CI -3.0 to -2.3, p<0.00001), in the midrange of the 70 point ADAS-Cog Scale. Study clinicians rated global clinical state more positively in treated patients. Benefits of treatment were also seen on measures of activities of daily living and behaviour. None of these treatment effects are large. The effects are similar for patients with severe dementia, although there is very little evidence, from only two trials.

More patients leave ChEI treatment groups, 29%, on account of adverse events than leave the placebo groups (18%). There is evidence of more adverse events in total in the patients treated with a ChEI than with placebo. Although many types of adverse event were reported, nausea, vomiting, diarrhoea, were significantly more frequent in the ChEI groups than in placebo.

There is only one randomized, double blind study in which two ChEIs are compared, donepezil compared with rivastigmine. There is no evidence of a difference between donepezil and rivastigmine for cognitive function, activities of daily living and behavioural disturbance at two years. Fewer patients suffer adverse events on donepezil than rivastigmine.

Appendix 4: Selected results credited to CADTH

CADTH Implications for Decision Making: (Technology report no 58, Perras et. al.) For patients, the long-term benefit of using ChEIs remains to be determined. Studies show that ChEIs can lead to modest short-term decreases in functional disability and global impressions of disability. The clinical significance of these changes is difficult to predict.

- There is no clear advantage to choosing one ChEI in place of another. Studies that compared a ChEI to another ChEI showed that the drugs have comparable benefits. However, the studies were of poor quality, which prevents the formation of definitive conclusions.
- Between 8% and 25% of patients will not continue taking therapy. Compared with placebo, patients on galantamine and rivastigmine experienced AE that led to a greater chance of stopping treatment. ChEIs did not cause an increase in the number of deaths; or of patients requiring hospitalization or emergency room visits (serious AE).
- QoL and rates of institutionalization, measured in studies comparing donepezil with placebo, did not show a difference. There is insufficient information to comment on time to institutionalization. It is unknown if this effect will occur with the other ChEIs.
- The economic implications of using ChEIs require consideration. Decision makers will need to determine if the funds dedicated to ChEIs are warranted despite small to modest benefits in the short term and largely unknown clinical benefits after one year.

Appendix 5: Literature search strategy

OVERVIEW of Search Strategy	
Interface	PubMed
Date of Search	April 1, 2014
Date Range	2010/01/01 through 2013/12/31 *("2010 /01/01"[PDat] : "2013/12/31"[PDat])*
Disease terms	Alzheimer's disease [MeSH Major Topic] *Found to be contaminated by non-Alzheimer's and non-clinical studies which were eliminated by hand.*
Drug terms	• Cholinesterase inhibitors[MeSH Major Topic] • Galantamine [MeSH Terms] • Donepezil [Text Word] • Galantamine [Text Word] • Rivastigmine [Text Word] *(galantamine OR rivastigmine OR donepezil[Text Word]) OR galantamine[MeSH Terms]*
Study types	• Clinical trial [publication type] • Controlled clinical trial [publication type] • Retrospective study [publication type] • Meta analysis [publication type] • Multicentre [publication type] • Randomized controlled trial [publication type] • Epidemiologic studies [publication type] *("clinical trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR retrospective study[MeSH terms] or "meta analysis"[Publication Type] OR "multicenter study"[Publication Type] OR "comparative study"[Publication Type] OR "randomized controlled trial"[Publication Type] OR "epidemiologic studies"[mesh])*
Restrictions	Humans *Humans[Mesh]*
Sort*	Author
Hand search	References of relevant articles were searched by hand to identify other relevant publications

Contact with authors for additional details of their studies	Not required; data sets adequate

* Does not alter search results

Appendix 6: Trials included in other meta-analyses but not included in Cochrane and NICE reviews

Meta Analysis -Reference	Studies included that were not included in Bond analysis	Comments
Impact of cholinesterase inhibitors on behavioral and psychological symptoms of Alzheimer's disease: A meta-analysis Campbell N, Ayub A, Boustani MA, Fox C, Farlow M, Maidment I, Howard R	1.Feldman H, Gauthier S, Hecker J, et al. 2001. A 24-week, randomized, double-blind study of Donepezil in moderate to severe Alzheimer's disease. *Neurology*, 57:613–20. 2.Tariot PN, Cummings JL, Katz IR, et al. 2001. A randomized, double-blind, placebo-controlled study of the efficacy and safety of donepezil in patients with Alzheimer's disease in the nursing home setting. *J Am Geriatr Soc*, 49:1590–9	Older publication Older publication
Efficacy and safety of donepezil, galantamine, and rivastigmine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. Hansen RA[1], Gartlehner G, Webb AP, Morgan LC, Moore CG, Jonas DE. Clin Interv Aging. 2008;3(2):211-25	1.Courtney C, Farrell D, Gray R, et al. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomized double-blind trial. Lancet. 2004;363:2105–15. 2.Feldman H, Gauthier S, Hecker J, et al. A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease. Neurology. 2001;57:613–20 3.Tariot PN, Cummings JL, Katz IR, et al. A randomized, double-blind, placebo-controlled study of the efficacy and safety of donepezil in patients with Alzheimer's disease in the nursing home setting. J Am Geriatr Soc. 2001;49:1590–9	Older publication Older publication Older publication
Are cholinesterase inhibitors effective in the management of the behavioral and psychological symptoms of dementia in Alzheimer's disease? A systematic review of randomized, placebo-controlled trials of donepezil, rivastigmine and galantamine. Rodda J, Morgan S, Walker Z. Int Psychogeriatr. 2009 Oct;21(5):813-24.	1.Courtney C, Farrell D, Gray R, et al. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomized double-blind trial. Lancet. 2004;363:2105–15. 2.Feldman H, Gauthier S, Hecker J, et al. A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease. Neurology. 2001;57:613–20 3.Tariot PN, Cummings JL, Katz IR, et al. A randomized, double-blind, placebo-controlled	Older publication Older publication Older publication

	study of the efficacy and safety of donepezil in patients with Alzheimer's disease in the nursing home setting. J Am Geriatr Soc. 2001;49:1590–9 4. Winblad, B. *et al.* (2007). IDEAL: a 6-month, double-blind, placebo-controlled study of the first skin patch for Alzheimer disease. *Neurology*, 69, S14–S22.	 Included
To treat or not to treat? A meta-analysis of the use of cholinesterase inhibitors in mild cognitive impairment for delaying progression to Alzheimer's disease. Diniz BS[1], Pinto JA Jr, Gonzaga ML, Guimarães FM, Gattaz WF, Forlenza OV. Eur Arch Psychiatry Clin Neurosci. 2009 Jun;259(4):248-56.	1.Koontz J, Baskys A (2005) Effects of galantamine on working memory and global functioning in patients with mild cognitive impairment: a double-blind placebo-controlled study. Am J Alzheimers Dis Other Demen 20:295–302 2.Petersen RC, Thomas RG, Grundman M, Bennett D, Doody R, Ferris S, Galasko D, Jin S, Kaye J, Levey A, Pfeiffer E, Sano M, van Dyck CH, Thal LI, Alzheimer's Disease Cooperative Study Group (2005) Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med 352:2379–2388 3.Pirttila T, Wilcock G, Truyen L, Damaraju CV (2004) Long term efficacy and safety of galantamine in patients with mild to- moderate Alzheimer's disease: multicenter trial. Eur J Neurol 11:734–741 4.Salloway S, Ferris S, Kluger A, Goldman R, Griesing T, Kumar D, Richardson S (2004) Efficacy of donepezil in mild cognitive impairment: a randomized placebo-controlled trial. Neurology 63:651–657 5.Winblad B, Gauthier S, Scinto L, Feldman H, Wilcock GK, Truyen L, Mayorga AJ, Wang D, Brashear HR, Nye JS (2008) Safety and efficacy of galantamine in subjects with mild cognitiveimpairment. Neurology 70:2024–2035	Older publication Older publication Older publication Older publication Older publication
Effects of donepezil on activities of daily living: integrated analysis of patient data from studies in mild, moderate and severe Alzheimer's disease. Gauthier S, Lopez OL, Waldemar G, Jones RW, Cummings J, Zhang R, Schindler R, Schwam E. Int Psychogeriatr. 2010 Sep;22(6):973-83.	1.Feldman H, Gauthier S, Hecker J, et al. A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease. Neurology. 2001;57:613–20 2.Feldman, H. H., Van Baelen, B., Kavanagh, S. M. and Torfs, K. E. (2005). Cognition, function, and care giving time patterns in patients with mild-to-moderate Alzheimer disease: a 12-month analysis. *Alzheimer Disease and Associated Disorders*, 19, 29–36. 3.Tariot PN, Cummings JL, Katz IR, et al. A randomized, double-blind, placebo-controlled study of the efficacy and safety of donepezil in patients with Alzheimer's disease in the nursing home setting. J Am Geriatr Soc. 2001;49:1590–9	Older publication Older publication Older publication

Galantamine and behavior in Alzheimer disease: analysis of four trials. Kavanagh S, Gaudig M, Van Baelen B, Adami M, Delgado A, Guzman C, Jedenius E, Schäuble B. Acta Neurol Scand. 2011 Nov; 124(5): 302-8.	1.Auchus AP, Brashear HR, Salloway S, Korczyn AD, De Deyn PP, Gassmann-Mayer C. Galantamine treatment of vascular dementia: a randomized trial. Neurology 2007;69: 448–58. 2.Gauthier S, Feldman H, Hecker J et al. Efficacy of donepezil on behavioral symptoms in patients with moderate to severe Alzheimer's disease. Int Psychogeriatr 2002;14:389–404.	Vascular dementia severe
Efficacy and safety of cognitive enhancers for patients with mild cognitive impairment: a systematic review and meta-analysis. Tricco AC, Soobiah C, Berliner S, Ho JM, Ng CH, Ashoor HM, Chen MH, Hemmelgarn B, Straus SE. CMAJ. 2013 Nov 5;185(16):1393-401.	1.Winblad B, Gauthier S, Scinto L, et al. Safety and efficacy of galantamine in subjects with mild cognitive impairment. *Neurology* 2008;70:2024-35. 2.Özenli Y, Yagci d, Karaca S. Efficacy of donepezil on cognitive functions in mild cognitive impairment. *Klinik Psikofarmakoloji Bulteni* 2007;17:62-7. 3.Salloway S, Ferris S, Kluger A, et al. Efficacy of donepezil in mild cognitive impairment: a randomized placebo-controlled trial. *Neurology* 2004;63:651-7. 4.Petersen RC, Thomas RG, Grundman M, et al. Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med* 2005; 352:2379-88. 5.Doody RS, Ferris SH, Salloway S, et al. donepezil treatment of patients with MCI: a 48-week randomized, placebo-controlled trial. *Neurology* 2009;72:1555-61. 6.Koontz J, Baskys A. Effects of galantamine on working memory and global functioning in patients with mild cognitive impairment: a double-blind placebo controlled study. *Am J Alzheimers Dis Other Demen* 2005; 20:295-302.	Older publication Not English Older publication Older publication Older publication Older publication
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	double-blind trial. Lancet. 2004;363:2105–15. 4.R.S. Doody, D.S. Geldmacher, B. Gordon, C.A. Perdomo, R.D. Pratt Open-label, multicenter, phase 3 extension study of the safety and efficacy of donepezil in patients with Alzheimer disease Arch Neurol, 58 (2001), pp. 427–433 5.M. Farlow, R. Anand, J. Messina Jr., R. Hartman, J. Veach A 52-week study of the efficacy of rivastigmine in patients with mild to moderately severe Alzheimer's disease Eur Neurol, 44 (2000), pp. 236–241	Older publication Older publication
A meta-analysis of the efficacy of donepezil, rivastigmine, galantamine, and memantine in relation to severity of Alzheimer's disease. Di Santo SG[1], Prinelli F, Adorni F, Caltagirone C, Musicco M. J Alzheimers Dis. 2013;35(2):349-61.	1.Farlow MR, Grossberg GT, Meng X, Olin J, Somogyi M (2011) Rivastigmine transdermal patch and capsule in Alzheimer's disease: Influence of disease stage on responseto therapy. *Int J Geriatr Psychiatry* 26, 1236- 1243. 2.Wilkinson DG, Hock C, Farlow M, Van BB,Schwalen S (2002) Galantamine provides broad benefits in patients with 'advanced moderate' Alzheimer's disease (MMSE < or = 12) for up to six months. *Int J Clin Pract* 56, 509-514. 3.Burns A, Spiegel R, Quarg P (2004) Efficacy of rivastigmine in subjects with moderately severe Alzheimer's disease. *Int J Geriatr Psychiatry* 19, 243-249. 4.Maher-Edwards G, Dixon R, Hunter J, Gold M, Hopton G, Jacobs G, Hunter J, Williams P (2011) SB-742457 and donepezil in Alzheimer disease: A randomized, placebo controlled study. *Int J Geriatr Psychiatry* 26, 536-544. 5.Tune L, Tiseo PJ, Ieni J, Perdomo C, Pratt RD, Votaw JR, Jewart RD, Hoffman JM (2003) Donepezil HCl (E2020) maintains functional brain activity in patients with Alzheimer disease: Results of a 24-week, doubleblind, placebo-controlled study.*AmJ Geriatr Psychiatry* 11,169-177. 6.Tariot PN, Cummings JL, Katz IR, Mintzer J, Perdomo CA, Schwam EM,Whalen E (2001) A randomized, doubleblind, placebo-controlled study of the efficacy and safety of donepezil in patients with Alzheimer's disease in the nursing home setting. *J Am Geriatr Soc* 49, 1590-1599.	Included in current review Older publication Older publication Included Older publication Older publication
Evolution of the evidence on the effectiveness and cost-effectiveness of acetylcholinesterase inhibitors and memantine for Alzheimer's disease: systematic review and economic model. Hyde C[1], Peters J, Bond M, Rogers G, Hoyle M, Anderson R, Jeffreys M, Davis S, Thokala P, Moxham T. Age Ageing.	1.Getsios D, Blume S, Ishak KJ, MacLaine G. Cost-effectiveness of donepezil in the treatment of mild to moderate Alzheimer's disease: a UK evaluation using discrete-event simulation. Pharmacoeconomics 2010; 28: 411-27.	Modeled cost effectiveness

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Effectiveness of cholinesterase inhibitors and memantine for treating dementia: evidence review for a clinical practice guideline. Raina P[1], Santaguida P, Ismaila A, Patterson C, Cowan D, Levine M, Booker L, Oremus M. Ann Intern Med. 2008 Mar 4;148(5):379-97.	1.Feldman H, Gauthier S, Hecker J, Vellas B, Subbiah P, Whalen E, et al. Donepezil MSAD Study Investigators Group. A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease. Neurology. 2001; 57:613.-20 2.Tariot PN, Cummings JL, Katz IR, Mintzer J, Perdomo CA, Schwam EM. et al. A randomized, double-blind, placebo-controlled study of the efficacy and safety of donepezil in patients with Alzheimer's disease in the nursing home setting. J Am Geriatr Soc. 2001; 49:1590 3.Salloway S, Ferris S, Kluger A, Goldman R, Griesing T, Kumar D, et al. Donepezil 401 Study Group. Efficacy of donepezil in mild cognitive impairment: a randomized placebo-controlled trial. Neurology. 2004; 63:651.-7 4.Courtney C, Farrell D, Gray R, Hills R, Lynch L, Sellwood E, et al. AD2000 Collaborative Group. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. Lancet. 2004; 363:2105.-15 5. Petersen RC, Thomas RG, Grundman M, Bennett D, Doody R, Ferris S, et al. Alzheimer's Disease Cooperative Study Group. Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med. 2005; 352:2379.-88 6.Wilcock G, Howe I, Coles H, Lilienfeld S, Truyen L, Zhu Y, et al. GALGBR-2 Study Group. A long-term comparison of galantamine and donepezil in the treatment of Alzheimer's disease. Drugs Aging. 2003; 20:777.-89 7.Karaman Y, Erdoğan F, Köseoğlu E, Turan T, Ersoy AO. A 12-month study of the efficacy of rivastigmine in patients with advanced moderate Alzheimer's disease. Dement Geriatr Cogn Disord. 2005; 19:51.-6 8.Ballard C, Margallo-Lana M, Juszczak E, Douglas S, Swann A, Thomas A. et al. Quetiapine and rivastigmine and cognitive decline in Alzheimer's disease: randomised double blind placebo controlled trial. BMJ. 2005; 330:874	Older publication Older publication Older publication Older publication Older publication Older publication Older publication Older publication

Appendix 7: Excluded studies with reasons

Authors	Title	Citation, abbreviated	Reason for Exclusion
Alvarez XA	Combination treatment in Alzheimer's disease: results of a randomized, controlled trial with cerebrolysin and donepezil.	Curr Alzheimer Res. 2011	Other comparators
Articus K	A 24-week, multicentre, open evaluation of the clinical effectiveness of the rivastigmine patch in patients with probable Alzheimer's disease.	Int J Clin Pract 2011	Single-arm (no comparator)
Blesa Gonzalez R	Evaluation of the convenience of changing the rivastigmine administration route in patients with Alzheimer disease.	Neurologia 2011	Single-arm (no comparator)
Choi SH	Tolerability and efficacy of memantine add-on therapy to rivastigmine transdermal patches in mild to moderate Alzheimer's disease: a multicenter, randomized, open-label, parallel-group study.	Curr Med Res Opin. 2011	Other comparators
Cummings J	Randomized, double-blind, parallel-group, 48-week study for efficacy and safety of a higher-dose rivastigmine patch (15 vs. 10 cmÂ²) in Alzheimer's disease.	Dement Geriatr Cogn Disord. 2012	Other comparators
Engedal K	Two galantamine titration regimens in patients switched from donepezil.	Acta Neurol Scand. 2012	Other comparators
Farlow MR	Effects of Oral Rivastigmine on Cognitive Domains in Mild-to-Moderate Alzheimer's Disease	Am J Alzheim Dis Oth Demen 2010	Pooled analysis
Farlow MR	Effectiveness and tolerability of high-dose (23 mg/d) versus standard-dose (10 mg/d) donepezil in moderate to severe Alzheimer's disease: A 24-week, randomized, double-blind study.	Clin Ther 2010	Other comparators
Gadzhanova S	Anticholinesterase duration in the Australian veteran population.	Aust N Z J Psychiatry 2010	Retrospective database analysis
Gauthier S	Effects of rivastigmine on common symptomatology of Alzheimer's disease (EXPLORE).	Curr Med Res Opin 2010	Single-arm (no comparator)
Han HJ	Response to rivastigmine transdermal patch or memantine plus rivastigmine patch is affected by apolipoprotein E genotype in Alzheimer patients.	Dement Geriatr Cogn Disord 2012	Other comparators
Howard R	Donepezil and memantine for moderate-to-severe Alzheimer's disease.	N Engl J Med 2012	Population (moderate-to-severe AD)
Kroger E	Discontinuation of cholinesterase inhibitor treatment and determinants thereof in the Netherlands: A retrospective cohort study.	Drugs Aging 2010	Not a comparative study
Modrego PJ	Memantine versus donepezil in mild to moderate Alzheimer's disease: a randomized trial with magnetic resonance spectroscopy.	Eur J Neurol 2010	Other comparators
Molinuevo JL	Impact of transdermal drug delivery on treatment adherence in patients with Alzheimer's disease.	Expert Rev Neurother 2012	Observational study (treatment adherence)
Van Puyvelde K	Galantamine (Reminyl) once daily outcome and satisfaction survey (RODOS) in mild to moderate Alzheimer's disease: a study in a real life population.	Geriatr Gerontol Int 2011	Observational study
Wattmo C	Risk factors for nursing home placement in Alzheimer's disease: a longitudinal study of cognition, ADL, service utilization, and cholinesterase inhibitor treatment.	Gerontologist 2011	Not a comparative study
Wimo A	The economic impact of galantamine vs placebo: an analysis based on functional capacity in a Swedish cohort study.	J Med Econ 2012	Economic evaluation, no primary data

Appendix 8: Search strategy for older resource utilization and quality of life publications

Search details

(((((((((alzheimer's disease[MeSH Major Topic]) AND (cholinesterase inhibitors[MeSH Major Topic]) OR ((galantamine OR rivastigmine OR donepezil[Text Word]))) OR galantamine[MeSH Terms])) AND ((("clinical trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR retrospective study[MeSH terms] or "meta analysis"[Publication Type] OR "multicenter study"[Publication Type] OR "comparative study"[Publication Type] OR "randomized controlled trial"[Publication Type] OR "epidemiologic studies"[mesh]))) AND (("2006/01/01"[PDat] : "20013/12/31"[PDat]) AND Humans[Mesh])))))) AND (("Costs and Cost Analysis"[Mesh]) OR "Caregivers"[Mesh])

Appendix 9: Resource utilization and quality of life studies: design and results

Articus K, et al. A 24-week, multicentre, open evaluation of the clinical effectiveness of the rivastigmine patch in patients with probable Alzheimer's disease. *Int J Clin Pract.* 2011 Jul;65(7):790-6.

In 2007, a 6-month, double- blind, randomized, placebo-controlled study (IDEAL) demonstrated the 9.5 mg⁄24 h rivastigmine patch to provide similar efficacy to the highest dose of rivastigmine capsule (12 mg⁄day) but with a superior tolerability profile. In addition, the caregiver preference sub-study of the IDEAL trial showed that 72% of caregivers preferred patches to capsules for drug delivery.

This trial was a multicentre, 24-week, open-label, single arm study. For the first 4 weeks, patients were treated with 4.6 mg⁄24 h (5 cm2) rivastigmine patch. After the week 4 assessment, dosage was increased to 9.5 mg⁄ 24 h (10 cm2) with adjustments as necessary for safety and tolerability. Patients were then maintained at their highest well-tolerated patch-dose (according to physicians' judgment of tolerability) at or below the target dose of 9.5 mg⁄ 24 h for an additional 20 weeks.

Results

Compliance

Within the ITT population, 135⁄182 patients (adherence rate 74.2%; 95% CI 67.8–80.5%) were treated for at least 8 weeks with the 9.5 mg⁄24 h rivastigmine patch and completed the study ($p < 0.0001$). There were 147⁄182 patients (adherence rate 80.8%; 95% CI 75.0–86.5%) treated for at least 8 weeks with the 9.5 mg⁄24 h rivastigmine patch regardless of whether they completed the study ($p < 0.0001$).

Safety and tolerability

The most common AEs with a suspected relation to the study drug were erythema (8.2% of patients), nausea (7.7% of patients), pruritus (7.2% of patients) and vomiting (4.8% of patients). Within the psychiatric disorders, agitation occurred in 4.3%, anxiety in 1%, depression in 1.4% and hallucination in 0.5% of patients. There were 39 patients (18.8%) with AEs that led to

permanent discontinuation of the study (serious in 6 patients). Consistent with the known safety profile of the rivastigmine patch, the most common AEs leading to discontinuation were skin and subcutaneous tissue disorders (7.2% of patients), psychiatric disorders (4.8% of patients), nervous system disorders (4.3% of patients) and gastrointestinal disorders (4.3% of patients).

Cognitive and global outcomes

Mean MMSE scores improved from screening (19.6 points) through to week 8 (21.4 points) and remained improved compared with baseline at week 24 (20.9 points). Mean ADCS-ADL scores improved from baseline (50.3 points) through to week 8 (51.5 points) and remained improved compared with baseline at week 24 (51.4 points). The TMT-A scores improved from baseline at each visit through to week 24. Improvements on the ADCS-CGIC (minimal, moderate or marked) at week 24 were seen in 34.6% of patients when assessed by the patient, and 29.7% of patients when assessed by the caregiver. With respect to tolerability, mean ADCPQ scores improved from baseline (12.2 points) at week 4 (30.5 points) and showed further improvements at week 24 (30.7 points). The Zarit Burden Interview Score improved slightly at each visit from baseline to week 24.

The 74.5% completion rate may limit interpretation of the results, but while this discontinuation rate is slightly higher than that reported in the IDEAL study with rivastigmine patch and capsules, it is consistent with or lower than those reported in other clinical trials with cholinesterase inhibitors. The authors note that the proportion of patients able to reach and maintain the highest available dose of rivastigmine in this open label setting may be attributed to factors additional to the mode of delivery, such as the presence of comorbidities, the level of care of therapeutic teams and the degree of engagement of relatives or caregivers. Longer-term follow-up is required to elucidate the full impact of the rivastigmine patch on treatment adherence, compliance and ability to permit access to optimal therapeutic doses of rivastigmine.

Relevance to BC ADTI – Low. Demonstrates adherence to the patch with good efficacy but due to non-randomized format may be due to other confounding factors that were not assessed. Importantly the question still remains whether this adherence to treatment improves clinical outcomes and this was not addressed. Duplicates results of Winblad 2007 which has been assessed in this review.

Molinuevo JL et al. Impact of transdermal drug delivery on treatment adherence in patients with Alzheimer's disease. *Expert Rev Neurother* 2012 Jan;12(1):31-7

This study assessed the impact of the galenic form (oral medications or patches) on treatment adherence in patients with dementia of Alzheimer's type (DAT). It was a 6-month prospective, multicenter, observational study with three study visits (baseline, 3 months and 6 months). Patients with mild-to-moderately severe DAT receiving medication for ≥3 months who were nonadherent to treatment were recruited.

The main outcome measure was adherence rate recorded at each visit. Patients were adherent if they missed <20% of the doses of their medication and they took it at the dose, manner and timing prescribed by the physician >80% of times. Secondary variables included strategies

followed by physicians to improve adherence and reasons for non-adherence reported by patients.

Results

A total of 649 patients (35.2% men) were included. The percentage of adherent patients reached 73.6% at 3 months and rose to 85.9% at 6 months. The most common reasons for non-adherence were forgetfulness, avoidance of adverse events and refusal of treatment. Modification of treatment was the most frequent strategy followed by physicians for improving treatment adherence at baseline, and the only intervention that substantially improved adherence at the 3-month visit (the percentage of patients treated with patches increased from 6.1% at baseline to 64.8% at 3-month visit). Patients using patches were more likely to comply than patients using capsules/tablets, as demonstrated by logistic regression analysis.

The authors suggested that the transdermal patch may improve adherence, which may lead to an increase of treatment benefits in patients with DAT.

Relevance to BC ADTI – Low. Demonstrates good adherence to therapy but once again the question still remains whether this adherence to treatment improves clinical outcomes and this was not addressed.

Gadzhanova S et al. Anticholinesterase duration in the Australian veteran population. *Aust N Z J Psychiatry* 2010 May;44(5):469-74.

The objective of the study was to determine the duration of initial anti-cholinesterase treatment in veteran patients in Australia. Three anti-dementia medications were investigated (donepezil, rivastigmine and galantamine) and two different setting were compared (community and residential aged care facilities). A retrospective cohort study was performed using the Department of Veterans' Affairs pharmacy claims data. Patients were included in the cohort if they had been dispensed at least one anti-cholinesterase prescription (index) between 2003 and 2006, were aged 65 years or over at the time of that index dispensing, and had not been dispensed any anti-cholinesterase medicine in the previous 12 months. Patients were followed until discontinuation (ceased or switched), death or 1 year of follow up. Time to treatment discontinuation was analyzed utilizing the Kaplan-Meier method. Cox proportional hazards models were used to compare the risk of treatment discontinuation among the three treatment groups adjusting for the effect of patients' characteristics.

Results

Of the new users of anti-cholinesterases (n=10088), 47% of those on donepezil, 46% of those on galantamine, and 47% of rivastigmine patients discontinued their initial therapy within 6 months. A total of 32% of patients who ceased therapy reinitiated it during the study period; 28% returned to the same index medication and 4% restarted therapy with a different anti-cholinesterase. The median treatment duration was: 199 days (95% CI, 182–208) for donepezil patients (n=6705), 233 days (95% CI, 212–259) for galantamine patients (n=2898), and 219 days (95% CI, 176–260) for rivastigmine patients (n =394). Patients in community settings were more likely to discontinue their initial anti-cholinesterases earlier compared to those living at

residential aged care facilities (relative risk, RR=1.21; 95% CI, 1.12, 1.31). The reasons for discontinuation were not determined.

The authors concluded that almost half of the Australian veteran patients who initiated anti-cholinesterases treatment discontinued (ceased or switched) therapy within 6 months. However, one-third of those who ceased therapy reinitiated it during the study period.

Relevance to BC ADTI – Low. Demonstrated discontinuation rates in Australian veterans but reasons for discontinuation were not given. Patients in community settings were more likely to discontinue therapy than those in care facilities.

Gauthier S, et al. Effects of rivastigmine on common symptomatology of Alzheimer's disease (EXPLORE). ***Curr Med Res Opin*** **2010 May;26(5):1149-60.**

This study was designed to evaluate, in a real-world clinical setting, the efficacy of rivastigmine in the management of six symptoms commonly associated with Alzheimer's disease (AD). This was a naturalistic, prospective, open-label, multi-centre, post-marketing, observational study. Data were collected by the participating study physicians at their practices across Canada. Subjects had a clinical diagnosis of mild-to-moderate AD and were prescribed rivastigmine by their treating physician. Efficacy was primarily evaluated by a physician-assessed, abbreviated Clinical Global Impression of Change (CGI-C) scale, focusing on six symptoms: attention, apathy, anxiety, agitation, irritability and sleep disturbance. Changes were assessed at months 3, 6 and 12.

Results

A total of 4460 patients were recruited by 353 study physicians; 3800 were deemed evaluable, having taken at least one dose of rivastigmine and with at least one post-baseline assessment. At baseline, attention problems were present in 86.0% of evaluable patients, anxiety in 77.3%, apathy in 68.3%, irritability in 64.0%, agitation in 54.6% and sleep disturbance in 54.5%. At both month 6 and month 12, for each symptom, the percentage of patients experiencing an improvement was considerably larger than the percentage of patients who experienced symptom worsening. Among evaluable patients, the proportions improving vs. deteriorating at month 6 were 46.4 vs. 8.8% for attention; 42.8 vs. 7.2% for apathy; 41.1 vs. 9.4% for anxiety; 33.8 vs. 7.7% for agitation; 35.1 vs. 10.1% for irritability; and 30.8 vs. 5.4% for sleep disturbance.

As with all open-label studies there is an inherent potential for bias by both the caregiver and the physician. This study demonstrates that rivastigmine-treated patients experience improvements on each of the six symptoms studied. These findings add further support to previous randomized, clinical studies showing benefit of rivastigmine in AD.

Relevance to BC ADTI – Low. Physician assessment of CGI-C and was non-randomized. Does not add to the body of evidence derived from RCTs.

Kroger E, et al. Discontinuation of cholinesterase inhibitor treatment and determinants thereof in the Netherlands: A retrospective cohort study. ***Drugs Aging*** **2010 Aug 1;27(8):663-75.**

Differences between ChEIs regarding persistence or the use of effective doses in daily clinical practice have been observed. However, most studies assessing ChEI discontinuation and associated determinants have been conducted in North America and there is a lack of knowledge about ChEI discontinuation and its determinants in daily clinical practice in Europe. The objective of this study was to assess ChEI discontinuation in daily practice in the Netherlands and to seek its determinants, including suboptimal utilization. A retrospective cohort study was performed using data from the Dutch PHARMO Record Linkage System. Included patients were aged ≥50 years at first dispensing of a ChEI, had a first dispensing of a ChEI between 1998 and 2008, had a prior medication history of 12 months and had at least one subsequent dispensing of any kind of medication. The proportion of patients who discontinued ChEIs over 3 years was determined. Cox regression was used to assess determinants for early (≤6 months) discontinuation and, separately, for late discontinuation during a subsequent 30-month follow-up among those persisting with treatment for >6 months.

Results

At 6 months, 30.8% of 3369 study patients had discontinued ChEIs, compared with 59.0% after 3 years. Thirty-five percent of patients taking rivastigmine reached the WHO-defined daily dose compared with 80% taking galantamine. At 6 months, compared with regular-dose rivastigmine, low dose rivastigmine or low-dose galantamine was associated with an increased risk of early discontinuation, whereas regular-dose galantamine was associated with a decreased risk, as was concurrent use of cardiac medications, drugs for Parkinson's disease, propulsives, selective serotonin reuptake inhibitors and benzodiazepines. Associations of ChEI type/dose or co medications with discontinuation among patients persisting for >6 months differed somewhat from associations with discontinuation before 6 months.

Fewer patients taking rivastigmine than those taking galantamine reached recommended doses. Furthermore, patients taking rivastigmine had an increased risk of early discontinuation compared with patients taking galantamine. The authors suggest that adverse effects leading to treatment intolerance and suboptimal utilization may have been contributing factors to these observed differences but there was no data to support this claim. Therefore the reason for discontinuation in these patients remains unclear.

Relevance to BC ADTI – Low. Quantified discontinuation rates but reasons for discontinuation were not assessed. It appeared that fewer patients taking rivastigmine than those taking galantamine reached recommended doses. Once again, importance of adherence to therapy remains questionable when the level of clinical improvement may be minimal.

Wattmo et al. Risk factors for nursing home placement in Alzheimer's disease: a longitudinal study of cognition, ADL, service utilization, and cholinesterase inhibitor treatment. *Gerontologist.* 2011 Feb;51(1):17-27.

The objective of this study was to identify risk factors for early nursing home placement (NHP) in Alzheimer's disease (AD), focusing on the impact of longitudinal change in cognition, activities of daily living (ADL), service utilization, and cholinesterase inhibitor treatment (ChEI). The trial was an open, 3-year, prospective, multicenter study in a routine clinical setting where 880 AD patients were treated with either donepezil, rivastigmine, or galantamine. At baseline

and every 6 months, they were assessed with several rating scales including Mini-Mental State Examination, Instrumental Activities of Daily Living scale (IADL), and Physical Self-Maintenance scale. Also, the dose of ChEI, the amount of weekly assistance (home help service and adult day care), and the date of NHP were recorded. Cox regression models were constructed to predict the risk of NHP.

Results

During the study, 206 patients (23%) were admitted to nursing homes. Factors that precipitated institutionalization were lower cognitive and functional abilities at baseline, faster rate of decline in IADLs, female gender, solitary living, and a lower mean dose of ChEI. The men living alone and patients with a substantial increase in adult day care also demonstrated shorter time to NHP. It was found that the rate of change in IADL decline, but not in cognitive deterioration, was an important predictor of the time to NHP, after controlling for multiple factors previously shown to be of importance. It was suggested that higher doses of ChEI, regardless of the specific drug agent, might postpone institutionalization in AD but this was not assessed. Other factors that precipitated admission to nursing homes in the multivariate Cox regression model were lower cognitive and functional abilities at baseline; female gender; solitary living; and the interaction effect, men living alone. A substantial increase in adult day care predicted shorter time to NHP as well.

This study shows that a more rapid deterioration in IADL increases the risk for early NHP. The authors concluded that the rate of functional but not cognitive decline was a strong risk factor for NHP. The results could be used to identify the care recipients that might risk early NHP to ensure that these individuals receive a sufficient level of assistance.

Relevance to BC ADTI – Low. Is not within the scope of the outlined project. This study may however give hints to reasons for increased risk for NHP. This could have cost implications to the BC government but there were no data to substantiate this.

Van Puyvelde K, RODOS Study Group Galantamine (Reminyl) once daily outcome and satisfaction survey (RODOS) in mild to moderate Alzheimer's disease: a study in a real life population. *Geriatr Gerontol Int* 2011 Jul;11(3):256-61.

This study was designed to record in real life the appreciation of elderly patients, their caregivers and physicians of a once daily formulation of prolonged release of galantamine in the treatment of mild to moderate Alzheimer’s disease. A prospective, multicenter, observational study was conducted in 128 elderly patients, treated for 6 months with a prolonged release form of galantamine, donepezil or rivastigmine.

Results

Of the patients treated with galantamine, 82 of the 97 (84.5%) were continuing their treatment after 6 months. These patients reported their condition as improved in 49%, unchanged in 47% and worsened in 4%. Caregivers rated global evaluation as 37% better, 41% unchanged and 22% worse. Physicians rated global clinical impression of change as 46% better, 34% unchanged and 20% worse. Measurements of cognition and behavior remained stable. The appreciation of physicians and caregivers corresponded well ($P < 0.001$). The incidence of serious side-effects

possibly related to galantamine was 9.3%, which was not different from that in patients treated with other cholinesterase inhibitors.

The authors concluded that in a real life setting, galantamine once daily is safe and is favorably appreciated by patients, their caregivers and physicians.

Relevance to BC ADTI – Low. Does not fall into the scope of the project. Once a day galantamine is preferred but that is the preparation that is routinely used now.

Wimo et al. The economic impact of galantamine vs. placebo: An analysis based on functional capacity in a Swedish cohort study. *J Med Econ* 2012;15(5):1019-24.

This study was designed to analyze the economic impact of galantamine, based on basic activities of daily living (ADL). Data were derived from Swedish patients enrolled in a 6-month placebo-controlled trial of galantamine (GAL-INT-1; *n*=80), and from the Kungsholmen–Nordanstig Project, a longitudinal study of 919 elderly persons in Sweden. Basic ADL were assessed using the Katz' Index of Independence in Activities of Daily Living (ADL) (number of ADL lost [dependency in 0, 1–2, 3–4, or 5–6 ADL]). Costs were appraised based on regression analysis and on costs directly linked to ADL. Six-month costs for galantamine and placebo were calculated.

In the regression analyses, each increase in a Katz stage was associated with an annual cost increase of SEK 81,415–83,683 (€8000). Results were similar using stage-specific costs. Overall, there was a small, non-significant numerical cost benefit for galantamine indicating cost neutrality. Actual resource utilization was not reported.

This study was based on the GAL-INT-1 study which unfortunately had a small number of patients and was not powered for economic outcomes. This limited the statistical power of the analysis. The authors noted that in addition, long-term outcomes are difficult to assess in persons with dementia because of practical and logistical problems.

Relevance to BC ADTI – Low. Modelled results for the Swedish healthcare system. No actual resource utilization breakdown or assessment was provided.

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

Assess long-term cost-effectiveness of rivastigmine patch in Alzheimer's disease (AD) management in the UK, using cognitive and functional models based on clinical trial efficacy data. In this study incremental costs and Quality Adjusted Life Years (QALYs) associated with rivastigmine patch and capsule treatment versus best supportive care (BSC) were calculated using two economic models, one based solely on Mini-Mental State Examination (MMSE) scores, and one also incorporating activities of daily living (ADL) scores. The clinical pathway was populated with data from a clinical trial of rivastigmine patch (9.5 mg/24 h) and capsules (12 mg/day) versus placebo. Costs were based on the UK health and social care costs and basic UK National Health Service (NHS) prices. Disease progression was modelled beyond the trial

period over 5 years using published equations to predict natural decline in AD patients. Base case costing variables included drugs, clinical monitoring, and institutionalization.

Results

The MMSE model estimated incremental costs per QALY of £10 579 for rivastigmine patch and £15 154 for capsule versus BSC. The MMSE-ADL model estimated incremental costs per QALY of £9114 for rivastigmine patch and £13 758 for capsules. The main difference between the models was a greater number of institutionalized days avoided for rivastigmine versus BSC estimated by the MMSE-ADL model.

The authors conclude that both the MMSE and MMSE-ADL models suggest that rivastigmine patch and capsules are cost-effective treatments versus BSC. Incorporating ADL evidence makes a marginal but important difference to estimates in this case. Future economic evaluations of AD treatment should include measures of both cognition and functioning.

Cost-effectiveness analysis base case:

Model used	Rivastigmine patch		Rivastigmine capsule		Best supportive care	
	MMSE	MMSE-ADL	MMSE	MMSE-ADL	MMSE	MMSE-ADL
Benefits						
QALYs gained	1.6318	1.6091	1.5209			
MMSE scores gained	86.2	84.7	78.7			
Mean survival in years	3.77	3.77	3.77			
Costs (£)						
Drug costs	1678	1678	1639	1639	—	—
Monitoring costs	533	533	521	521	—	—
Institutionalization costs	37216	47082	37619	47559	39179	49353
Community care costs	37698	33046	37508	32821	36773	31975
Informal care costs	—	—	—	—	—	—
Total costs	**77126**	**82339**	**77288**	**82541**	**75952**	**81328**

	MMSE model	MMSE-ADL model
Rivastigmine patch versus BSC		
Incremental cost per QALY gained (£)	10579	9114
Incremental cost per MMSE scores gained (£)	158	136
Number of institutional days avoided over 5 years	22.8	26.5
Rivastigmine capsules versus BSC		
Incremental cost per QALY gained (£)	15154	13758
Incremental cost per MMSE scores gained (£)	226	205
Number of institutional days avoided over 5 years	18.0	20.8
Rivastigmine patch versus capsules		
Incremental cost per QALY gained (£)	Patch dominates (−7124)	Patch dominates (−8856)
Incremental cost per MMSE scores gained (£)	−106	−132
Number of institutional days avoided over 5 years	4.8	5.7

[a]Where results do not differ between the two models, only one value is reported, for clarity. QALY, Quality Adjusted Life Year; MMSE, Mini-Mental State Examination; ADL, Activities of Daily Living; BSC, Best Supportive Care.

There are several possible limitations to this analysis. Firstly, only one explanatory variable (MMSE score) was included in the regression analyses relating ADL scores to MMSE. Other patient characteristics (e.g. age, sex) were not included as they could not be incorporated in the cost-effectiveness model, which primarily characterizes patients according to MMSE. However, as the randomization process of the clinical trial produced groups of patients with very similar baseline characteristics between the study arms, this may not have biased our findings. Second, these regression analyses were based on relatively short-term cross-sectional data. It was, therefore, not possible to test the validity of the MMSE–ADL relationship over a longer time scale. Long-term (5-year) ADL and MMSE evidence to validate the ADL-based predictions would be useful. A third limitation is that our mapping of the ADCS-ADL scale to the Townsend-ADL scale was based on a qualitative approach which we are not able to validate empirically. A survey of a patient population using both scales would be helpful for this purpose. Fourth, the analyses incorporating ADL data focused mostly on estimation of institutionalization, the most influential predictor of AD costs. Further evidence on the relationships between ADL

and other inputs, especially utilities, community care costs, and informal care costs, would enable refinement of the cost-effectiveness estimates.

Relevance to BD ADTI – Moderate. Demonstrates that both oral and transdermal patch therapy with rivastigmine is cost effective compared to BSC in the UK. This analysis suggests that the patch may be more cost effective than oral therapy.

Hyde C 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: 14–20

Included in the PATH assessment.

Winblad B et al Caregiver preference for rivastigmine patch relative to capsules for treatment of probable Alzheimer's disease. *Int J Geriatr Psychiatry* 2007; 22: 485–491.

Family caregivers comprise a critical component in the care of Alzheimer's disease (AD) patients. Among their many tasks, caregivers are responsible for administering and managing medications. Effective interventions incorporate the needs of both the AD patient and the caregiver, and understanding treatment preferences may maximize intervention effectiveness. Transdermal patches may offer advantages over conventional oral formulations. This was a 24-week randomized controlled trial compared the rivastigmine patch to the rivastigmine capsule and placebo in patients with probable AD. At baseline and Weeks 8 and 24, the AD Caregiver Preference Questionnaire (ADCPQ) was used to evaluate caregiver expectations, preferences and satisfaction with treatment. Double-dummy treatment blinding ensured that caregiver preference for the patch or capsule was not confounded by perceptions of efficacy or tolerability.

Reasons for preference were also elicited. The analytic sample included caregivers who completed the ADCPQ at Weeks 8 and/or 24.

Results

One thousand and fifty-nine caregivers completed the ADCPQ. More than 70% of caregivers preferred the rivastigmine patch to the capsule. The patch was significantly preferred to the capsule with respect to ease of following the schedule and ease of use. Caregivers indicated greater satisfaction overall, greater satisfaction with administration, and less interference with daily life with the patch versus the capsule (all $p \leq 0.01$).

Preference outcomes at Weeks 8 and 24:

Caregiver preference	Population	*n*	Proportion	95% Confidence Interval	*p*-value
Patch preferred to capsule at Week 24	C-ITT	985	0.72	0.69–0.75	<0.0001
	C-ITT + RDO	1067	0.71	0.68–0.73	<0.0001
Patch preferred to capsule on ease of use at Week 24	C-ITT	983	0.64	0.61–0.67	<0.0001
	C-ITT + RDO	1065	0.63	0.60–0.66	<0.0001
Patch preferred to capsule on ease of following schedule at Week 24	C-ITT	982	0.74	0.71–0.77	<0.0001
	C-ITT + RDO	1064	0.73	0.70–0.76	<0.0001
Patch preferred to capsule overall at Week 8	C-ITT	1027	0.68	0.66–0.71	<0.0001
	C-ITT + RDO	1087	0.68	0.65–0.71	<0.0001
Patch preferred to capsule on ease of use at Week 8	C-ITT	1028	0.55	0.52–0.58	0.0008
	C-ITT + RDO	1088	0.55	0.52–0.58	0.0013
Patch preferred to capsule on ease of following schedule at Week 8	C-ITT	1029	0.70	0.67–0.72	<0.0001
	C-ITT + RDO	1089	0.70	0.67–0.72	<0.0001

C-ITT = Caregiver–Intent to Treat population; C-ITT + RDO = Caregiver–Intent to Treat with Retrieved Dropouts population; Data shown for non-missing values only; no imputation used. *p*-values based on normal approximation (Hahn and Meeker, 1991).

Satisfaction outcomes at Week 8:

	n	Patch		Capsule		Mean difference	*p*-value
		Mean	SD	Mean	SD		
Easy to use	1034	3.38	0.55	3.39	0.57	−0.01	0.6112
Easy to follow schedule	1034	3.39	0.54	3.31	0.56	0.08	<0.0001
Easy to administer	1033	3.38	0.46	3.30	0.49	0.08	<0.0001
Interferes with daily life	1032	4.28	0.87	4.22	0.90	0.06	0.0083
Satisfaction with administration	1033	3.35	0.45	3.25	0.46	0.10	<0.0001
Satisfaction overall	1033	3.37	0.59	3.28	0.58	0.09	<0.0001

C-ITT = Caregiver–Intent to Treat population; C-ITT + RDO Caregiver–Intent to Treat with Retrieved Dropouts population; Data shown for non-missing values only; no imputation used.
Mean scores calculated on a Likert scale ranging from 1 to 4, where 1 represented the worst result (e.g. very difficult or very dissatisfied) and 4 the best (e.g. very easy or very satisfied); this assessed satisfaction at Week 8 only; Week 24 satisfaction data were not collected.
p-values calculated using Wilcoxon matched pairs and paired *t*-tests (identical results were obtained from both tests).

Family caregivers are frequently responsible for administering and managing medications for AD patients. In the current study, more than 70% of caregivers preferred the rivastigmine patch to the capsule. Caregivers of AD patients indicated greater satisfaction overall, greater satisfaction with administration, and less interference with daily life with the patch vs. the capsule. Simpler and more effective modes of administration, such as patches, may ease caregiver challenges, which in turn may help to maximize effectiveness of therapy in patients with AD.

Blesa R et al. Caregiver preference for rivastigmine patches versus capsules for the treatment of Alzheimer disease. *Neurology* 2007;69;S23-S28.

Duplicate report of the Winblad 2007 report above.

Ward W and Kunle A. An Observational Study of the Needs and Quality of Life Amongst Patients in the Treatment of Alzheimer's Dementia with Cholinesterase Inhibitors. *Current Aging Science* 2008, 1, 140-143.

This study assessed the impact of outpatients' care and cholinesterase inhibitors in patients being treated for Alzheimer's dementia. The needs and quality of life of patients attending an outpatient dementia care service were assessed using the Camberwell Assessment of Need for the Elderly (CANE) and Quality of Life in Alzheimer's Disease: Patient and Caregiver report. Other tools used were the Problems Checklist and Carer Strain, the Minimental State Examination (MMSE) and a proforma to obtain sociodemographic details. All patients who had informal care were assessed using the questionnaires. 104 patients were seen of whom 34 were new and 70 were follow-up patients. 43 patients lived alone while the rest lived with their spouses or other relatives such as children.

Results

There was reduction in the number of CANE unmet needs and increased combined Quality of Life in Alzheimer's Dementia scores in the first three months amongst the newly referred patients.

Initial and 3-Month Follow-Up Assessments - Mean Total Scores (Standard Deviations) of the Newly Referred Patients to the Outpatients Dementia Care Service (Paired t Test):

	Initial Assessments	Follow-up Assessment at Three Months	P
Number of new patients on cholinesterase inhibitors	34	27	
Mini mental state examination	20 (4)	21.1 (4)	0.12 (N.S)
No. of CANE unmet needs (patient)	1.6 (1.7)	0.2 (0.4)	< 0.01*
No. of CANE unmet needs (carer)	2.1 (2.1)	0.6 (0.9)	< 0.01*
Problem checklist	12.4 (8.3)	14.5 (9.9)	0.26 (N.S)
Carer Strain	45.3 (4.4)	46 (5.4)	0.44 (N.S)
Quality of Life in Alzheimer's dementia (combined patient & carer report)	37.1 (4.8)	39 (3.4)	< 0.01*

Key: N.S – not significant * - Significant at $p < 0.05$*.

Comparing the Initial Assessments of the 34 New Patients at Onset with Those of the 70 Follow-Up Patients Attending the Outpatients Dementia Care Service Using the Analysis of Variance (ANOVA):

	New (S.D)	Follow-up (SD)	p
Age of patients	79.2 (8.2)	80.5 (6)	0.342 (NS)
Age of carers	61.4 (14.5)	66 (12.7)	0.101 (NS)
Length of treatment (days)	10.9 (18.9)	635.1 (382.7)	< 0.001*
Mini-mental State examination	19.6 (4.1)	20.1 (5.5)	>0.05 (N.S)
Number of unmet needs using patients' CANE	1.8 (1.9)	0.5 (0.8)	< 0.001 *
Number of unmet needs using carers' CANE	2.8 (2.6)	1.1 (1,7)	< 0.001 *
Total score of problem checklist	13.9 (9.3)	13.9 (11.03)	0.98 (NS)
Total score of carer strain	46.6 (5.2)	45.6 (4.9)	0.35 (N.S)
Quality of life in Alzheimer's disease (combined patient & carer score)	36.5 (5)	36.4 (5.8)	0.94 (NS)

Key: NS – Not significant with $p > 0.05$ * $p < 0.05$.

The authors state that these findings suggest that outpatient dementia care and prescribing of cholinesterase inhibitors helped to meet the needs of patients and improve patient's quality of life in first three months.

This study was an observational cross-sectional and longitudinal study, which did not have a control group. As a result the impact of a placebo effect, effect of the role of frequent form assessment and naturalistic trends could not be compared with the interventions offered by the outpatient dementia care service.

This study showed that the outpatient prescribing of cholinesterase inhibitors helped to meet the needs of patients and improve patients' quality of life in the first three months. Those patients who were still on cholinesterase inhibitors and being seen in the outpatient dementia care service for nearly two years had low number of unmet needs along with severity of carer strain (distress) and quality of life similar to newly referred patients. However, in longer term, it is expected as in aging in general, patients with Alzheimer's dementia will have increasing physical, social and mental health needs.

Relevance to BCADTI – Moderate - Describes impact of therapy on unmet needs in patients and caregivers. Did not identify drugs or therapies and no comparisons or conclusions on choice of drug therapy were made.