August 2015

Update to the Original Study Report delivered in August 2014

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 Inc and The Programs for Assessment of Technology in Health (PATH) Research Institute

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ABBREVIATIONS/GLOSSARY

Cholinesterase inhibitors (ChEIs)Alzheimer's Drug Therapy Initiative (ADTI)

Clinical Evidence Review (CER)

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)

Neuropsychiatric Instrument (NPI)

Quality Adjusted Life Year(s) (QALY(s))

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)

1. Review and Highlights of the Original August 2014 Alzheimer's Drug Therapy Initiative Clinical Evidence Review (ADTI-CER) Study

The objective of the original August 2014 Alzheimer's Drug Therapy Initiative Clinical Evidence Review (ADTI-CER) 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 (AD). Patient outcomes of interest for the review included the following:

Efficacy outcomes:

- Cognitive function as assessed by any valid method (ADAS-cog, MMSE)
- Daily function as assessed by any valid method (ADCS-ADL)
- Clinician's global impression of change as assessed by any valid method (CIBIC-plus, ADCS-CGIC)
- Behavioral disturbance (e.g. agitation, psychosis, depression) as assessed by any valid method (NPI)

Harm outcomes:

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

Other outcomes:

- Quality of Life (QoL) 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.

A systematic literature review was conducted for the original study 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 March 2010, which is the date of the literature search conducted by Bond (2012) for NICE up to the end of December 2013. 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 QoL, health care resource utilization, and cost effectiveness analysis from January 2006 to present date and where RCTs are not identified, observational evidence was included in the descriptive portion of the report. 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. GRADE was developed by Guyatt

and colleagues (2011) to help determine the risk of bias in clinical trials. It captures parameters such as randomization, blinding, allocation concealment, accounting of outcomes, accounting of patients, use of valid outcome measures and source of funding. Fourth, a separate exploration was conducted for the relative efficacy, safety, QoL, resource utilization and caregiver impact for rivastigmine patches versus oral capsules.

2. Results of the Original August 2014 ADTI-CER Study

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.

Behavioral Disturbance:

Change in behavioral 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. (2007) randomized patients to low dose patches, high dose patches and capsules. There were no differences in efficacy between the three treatments, while low dose patches had fewer adverse events. This effect may be dose related since high dose patches had similar safety risks 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 QoL of 0.001 Quality Adjusted Life Years (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. (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 QoL. Based on the evidence, there is an absence of differences in costs and QoL 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 cutoff date for data capture for the NICE review) to December 2013. If there were few high quality publications the search was extended back to January 2006 to uncover any studies that may not have been included in the NICE review. The literature search 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 QoL 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 QoL 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 reviews.

There were not any new high quality studies addressing QoL published after the NICE review. One study by Ward (2008) assessed the impact of cholinesterase therapy on unmet needs in both patients and caregivers. The needs and QoL 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 Mini-mental 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 QoL 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' QoL 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 QoL similar to newly referred patients.

3. 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 such as the NICE and the Cochrane Collaboration reviews.

4. Limitations of Review

The main limitation of the overall findings of this study 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.

5. 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 of these agents by NICE and Cochrane. 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 also 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 was 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 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 is no new information on cost utilization outside of the follow up Hyde (2013) study. This reinforced that there are some savings in resource utilization that offset the cost of the medications. There was a small improvement in the QoL 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 QoL with net resource savings. There has been no new information in the recent literature that captures costs for the Canadian situation.

There are no new high quality studies of QoL published since 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 QoL 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 QoL similar to newly referred patients.

6. Objectives of the Updated August 2015 ADTI-CER Study

The objective of the updated August 2015 ADTI-CER study, carried out by ReVue Drug Evaluation group Inc., was to conduct a literature review using a similar search criteria as was used for the original August 2014 ADTI-CER, also carried out by ReVue. The updated ADTI-CER study, however, expands the original search period from March 1, 2010 to December 31, 2013, to also cover the period up until June 1, 2015.[1]

a. Search Criteria

The original August 2014 ADTI-CER used the following search criteria:

(((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])) AND (("2010 /01/01"[PDat] : "2013/12/31"[PDat]) AND Humans[Mesh])

b. Table 1: Overview of Search Strategy of the Updated August 2015 ADTI-CER Study

OVERVIEW of Search Strategy	
Interface	PubMed
Date of Search	June 1, 2015
Date Range	2010/03/01 through 2015/06/01 *("2010:2015 [PDat])*
Disease terms	Alzheimer's disease [MeSH Major Topic] *Found to be contaminated by non-Alzheimer's and non-clinical studies*

[1] The original search period (March 1, 2010 to December 31, 2013) was run again when the search was expanded up to June 1, 2015 to ensure consistency of results.

	which were eliminated by hand.
Drug terms	Cholinesterase inhibitors[MeSH Major Topic] Galantamine [MeSH Terms] Donepezil [Text Word] Galantamine [Text Word] Rivastigmine [Text Word] *(Cholinesterase inhibitors[MeSH Major Topic] OR 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 [mesh] *("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
Elimination of duplicates	Duplicates were removed in MS Excel (using the remove duplicates function) and other citations from the April 1, 2014 search were removed manually.

* Does not alter search results

c. Preliminary Search Results

- The search on June 1, 2015 yielded 235 results for the March 1, 2010 through June 1, 2015 period
- The updated results were combined with the results from the original search conducted on April 1, 2014, for the March 1, 2010 through December 31, 2013 period
- After duplicate studies from the original and updated searches were removed from the combined output, there were 236 total results remaining
- Study results from the original April 1, 2014 search were then removed and 90 results remained for the January 1, 2014 to June 1, 2015 updated search period

d. Study Selection

All of the studies that were included in the literature search for the original ADTI-CER report that was delivered in August 2014 were subtracted from the updated search period. This left a a list of 90 new studies published between January 1, 2014 and June 1, 2015. These studies are included in Appendix 1 Excel Worksheet *90 Trials June 2015*.

Level 1 screening was conducted and included a review of each study abstract to determine qualification based on the inclusion criteria. The 90 studies were examined for relevance and quality. A short list of nine studies were identified as being worthy of further investigation. These studies are numbered 1, 4, 8, 37, 44, 46, 52, 71 and 78 and are highlighted in the Appendix 2 Excel Worksheet entitled *Final 9 Trials June 2015*.

Copies of the full publications of these nine studies were purchased and reviewed. As well, since the original ADTI-CER August 2014 report was delivered, a systematic review was published that attempted to assess the cholinesterase inhibitors. This systematic review was assessed according to the inclusion criteria used for other studies included in the original and updated ADTI-CER analyses.

e. Results of GRADE Analysis

Level 2 screening was conducted on the nine studies through GRADE analysis of each publication. GRADE is a systematic and explicit approach to making judgments about quality of evidence and strength of recommendations.

After the Level 2 assessment of the potential studies to be included in the updated ADTI-CER report, it was determined that none of the studies satisfied the inclusion criteria. The studies and the reasons for exclusion included are summarized in Table 1 and in Appendix 2.

f. Table 2: Studies Reviewed and Assessment of Inclusion in the Updated August 2015 ADTI-CER Study

Study	Study Number	Study Design/GRADE Assessment	Inclusion
The ADAS-cog and clinically meaningful change in the VISTA clinical trial of galantamine for Alzheimer's disease. Rockwood K, Fay S, Gorman M. Int J Geriatr Psychiatry. 2010 Feb;25(2):191-201.	1	6 month follow up results from the VISTA trial, patients were tested at 24 weeks, 8 weeks into the open label phase of the trial where all patients received galantamine, not an RCT, a subgroup analysis of a study that was included in the original August 2014 analysis	NO
A 25-week, open-label trial investigating rivastigmine transdermal patches with concomitant memantine in mild-to-moderate Alzheimer's disease: a post hoc analysis. Farlow MR, Alva G, Meng X, Olin JT. Curr Med Res Opin. 2010 Feb;26(2):263-9.	4	Stratified by concomitant use of memantine, an add-on study that compared the addition of memantine (rivastigmine plus memantine versus rivastigmine alone), not an RCT	NO
Safety and tolerability of rivastigmine transdermal patch compared with rivastigmine capsules in patients switched from donepezil: data from three clinical trials. Sadowsky CH, Farlow MR, Meng X, Olin JT. Int J Clin Pract. 2010 Jan;64(2):188-93.	8	3 trial results of tolerability in switch to patch. Ad Hoc pooled analysis of three trials, with all 3 studies not being eligible for inclusion (2 studies were single arm, and 1 study was a delayed intervention study where rivastigmine was delayed for only 7 days)	NO

Safety and tolerability of rivastigmine transdermal patch formulation in newly diagnosed patients with Alzheimer's dementia in naturalistic conditions. Pregelj P. Psychogeriatrics. 2012 Sep;12(3):165-71.	37	safety of patch, observational, non-interventional, post marketing surveillance trial, conducted by Novartis, absence of a comparator group in an observational study	NO
Real-life effectiveness and tolerability of the rivastigmine transdermal patch in patients with mild-to-moderate Alzheimer's disease: the EMBRACE study. Gauthier S, Robillard A, Cohen S, Black S, Sampalis J, Colizza D, de Takacsy F, Schecter R; EMBRACE investigators. Curr Med Res Opin. 2013 Aug;29(8):989-1000	44	Open label assessment of the patch, absence of a comparator group in an observational study	NO
From high doses of oral rivastigmine to transdermal rivastigmine patches: user experience and satisfaction among caregivers of patients with mild to moderate Alzheimer disease. Reñé R Ricart J, Hernandez B; researchers in the Experience study. Neurologia. 2014 Mar;29(2):86-93.	46	satisfaction with patch use, not randomized, observational, cross sectional study focused only on caregiver response	NO
A 24-week, randomized, controlled trial of rivastigmine patch 13.3 mg/24 h versus 4.6 mg/24 h in severe Alzheimer's dementia.	52	RCT of patch vs. patch, compared high versus low dose patch in patients with severe Alzheimer’s disease	NO

Farlow MR, Grossberg GT, Sadowsky CH, Meng X, Somogyi M. CNS Neurosci Ther. 2013 Oct;19(10):745-52.			
Efficacy of higher-dose 13.3mg/24 h (15 cm2) rivastigmine patch on the Alzheimer's Disease Assessment Scale-cognitive subscale: domain and individual item analysis. Alva G, Isaacson R, Sadowsky C, Grossberg G, Meng X, Somogyi M. Int J Geriatr Psychiatry. 2014 Sep;29(9):920-7.	71	A methodological paper that investigated the internal reliability of the ADAS-Cog scale, based on data from a trial that was previously included in the original August 2014 analysis	NO
Efficacy and safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. Tan CC, Yu JT, Wang HF, Tan MS, Meng XF, Wang C, Jiang T, Zhu XC, Tan L. J Alzheimer's Dis. 2014;41(2):615-31.	78	A systematic review and meta-analysis, only used 2 of the studies we included, went way back to 2000 for references, does not look to be a very well conducted meta-analysis,	NO

Tan et al. (2014) performed a systematic review and meta-analysis using a similar search strategy (i.e. double-blind, placebo-controlled, with random assignment to a cholinesterase inhibitor) to the original August 2014 report but it included memantine. The Tan et al. review and analysis verified that there were no additional studies that these authors included that were not part of the original August 2014 ADTI-CER meta-analysis. However, the original August 2014 study by ReVue included many studies that Tan et al. overlooked. The Tan et al. analysis also included studies that were beyond the scope of the August 2015 ADTI-CER update to the original August 2014 study, such as patients with severe Alzheimer's disease. The Tan et al. study included the use of memantine and the analysis demonstrated that cognitive effects were significant for all drugs, ranging from a -1.29 points mean difference (95% CI -2.30 to -0.28) in the 20 mg daily memantine trials to -3.20 points (95% CI -3.28 to -3.12) in the 32 mg daily galantamine group. Only memantine had no effect on the Clinicians' Global Impression of

Change scale. No behavioral benefits were observed, except for -2.72 (95% CI -4.92 to -0.52) in the 10 mg daily donepezil group and -1.72 (95% CI -3.12 to -0.33) for 24 mg daily galantamine trial. Only 5 mg daily donepezil had no effect on the function outcome. In comparison, this analysis also did show significant improvement on cognitive function for donepezil and galantamine and improvement in clinical global impression. The methodology of the Tan et al. report was not of the caliber of this analysis and did not address the issue of whether the changes made a clinically meaningful difference. The Tan et al. study is not comparable to the assessment herein.

7. Rivastigmine Patch Trial by Farlow et al. (2013)

The original report covered the clinical efficacy/safety differences between the patch and capsule versions of rivastigmine. The search criteria used in this update revealed a study that compared the two strengths of the rivastigmine patch. Farlow et al. (2013)[2] [study #52 in Table 2] carried out a 24-week, randomized, controlled trial of rivastigmine patch 13.3 mg/24 h versus 4.6 mg/24 h in severe Alzheimer's dementia. The study was published in the CNS Neuroscience and Therapeutics Journal in October 19, 2013. Primary outcome measures in this study were scores using the Severe Impairment Battery (SIB) and AD Cooperative Study–Activities of Daily Living scale–Severe Impairment Version (ADCS-ADL-SIV). Secondary outcomes were measurement of ADCS-Clinical Global Impression of Change (ADCS-CGIC), 12-item Neuropsychiatric Inventory (NPI-12), and safety/tolerability. In total, 1014 patients were screened, 716 were randomized to 13.3 mg/24 h (N = 356) or 4.6 mg/24 h (N = 360) patch. Baseline characteristics/ demographics were comparable. Completion rates were as follows: 64.3% (N = 229) with 13.3 mg/24 h and 65.0% (N = 234) with 4.6 mg/24 h patch. The 13.3 mg/ 24 h patch was significantly superior to 4.6 mg/24 h patch on cognition (SIB) and function (ADCS-ADL-SIV) at Week 16 ($P < 0.0001$ and $P = 0.049$, respectively) and 24 (primary endpoint; $P < 0.0001$ and $P = 0.025$). Significant between-group differences (Week 24) were observed on the ADCS-CGIC ($P = 0.0023$), not NPI-12 ($P = 0.1437$). A similar proportion of the 13.3 mg/24 h and 4.6 mg/24 h patch groups reported adverse events (AEs; 74.6% and 73.3%, respectively) and serious AEs (14.9% and 13.6%). The authors concluded that the 13.3 mg/24 h patch demonstrated superior efficacy to 4.6 mg/24 h patch on SIB and ADCS-ADL-SIV, without marked increase in AEs, suggesting higher-dose patch has a favorable benefit-to-risk profile in severe AD. This study did not satisfy the criteria for inclusion in this analysis because it was conducted in severe Alzheimer disease patients but does add to the stable of data regarding the efficacy and safety of two doses of the rivastigmine patch.

8. Conclusions

In the original ADTI-CER study, the meta-analyses of the safety and efficacy of the three agents did not show meaningful differences from 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 three drugs versus placebo. However, the clinical benefit is small and may not be clinically meaningful. Indirect evidence suggests very little difference between the drugs in terms of efficacy or safety. In addition, cost effectiveness analyses indicate small differences in costs and QoL between the three drugs.

[2] Farlow MR, Grossberg GT, Sadowsky CH, Meng X, Somogyi M., CNS Neurosci Ther. 2013 Oct;19(10):745-52. doi: 10.1111/cns.12158. Epub 2013 Aug 7.

In this August 2015 update of the original report delivered in August 2014, the published data on the efficacy and safety of cholinesterase inhibitors in mild to moderate Alzheimer's disease, a literature search was conducted from March 1, 2010 through June 1, 2015. The original study included studies from March 1, 2010 to December 31, 2013. The current literature search revealed 90 new studies that met the original trial criteria. These studies were further screened to identify nine studies that warranted additional careful review and these were subjected to the GRADE review. None of the nine studies qualified for inclusion in the meta-analysis. A meta-analysis (Tan 2014) was published which used similar inclusion criteria to this analysis but the Tan report was not as rigorous in the study inclusion criteria and the meta-analysis was not as comprehensive as was conducted in this project. Overall, the meta-analysis for the updated ADTI-CER report delivered in August 2015 is consistent with the findings of the meta-analysis and results in the original August 2014. The combined reports are considered complete and clinically relevant and the analysis is now applicable to June 1, 2015.

Appendix 1 - Update to "A Meta-Analysis of Efficacy and Safety of Cholinesterase Inhibitors..."
90 Trials published between January 1, 2014 and June 1, 2015
August 2015

Number, Assigned by ReVue	Title	URL	Authors	Citation	PMID	Trial Excluded	Comments
1	The ADAS-cog and clinically meaningful change in the VISTA clinical trial of galantamine for Alzheimer's disease.	/pubmed/19548273	Rockwood K, Fay S, Gorman M.	Int J Geriatr Psychiatry. 2010 Feb;25(2):191-201. doi: 10.1002/gps.2319.	PMID:19548273	No	6 moth follow up results from the VISTA tiral
2	Increased glutamate in the hippocampus after galantamine treatment for Alzheimer disease.	/pubmed/19833161	Penner J, Rupsingh R, Smith M, Wells JL, Borrie MJ, Bartha R.	Prog Neuropsychopharmacol Biol Psychiatry. 2010 Feb 1;34(1):104-10. doi: 10.1016/j.pnpbp.2009.10.007. Epub 2009 Oct 13.	PMID:19833161	yes	glutmate levels in hippocampus
3	A 22-week, multicenter, randomized, double-blind controlled trial of Crocus sativus in the treatment of mild-to-moderate Alzheimer's disease.	/pubmed/19838862	Akhondzadeh S, Shafiee Sabet M, Harirchian MH, Togha M, Cheraghmakani H, Razeghi S, Hejazi SS, Yousefi MH, Alimardani R, Jamshidi A, Rezazadeh SA, Yousefi A, Zare F, Moradi A, Vossoughi A.	Psychopharmacology (Berl). 2010 Jan;207(4):637-43. doi: 10.1007/s00213-009-1706-1. Epub 2009 Oct 20.	PMID:19838862	yes	treatment with saffron

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4	A 25-week, open-label trial investigating rivastigmine transdermal patches with concomitant memantine in mild-to-moderate Alzheimer's disease: a post hoc analysis.	/pubmed/19929593	Farlow MR, Alva G, Meng X, Olin JT.	Curr Med Res Opin. 2010 Feb;26(2):263-9. doi: 10.1185/03007990903434914.	PMID:19929593	No	rivastigmine patch
5	Rivastigmine transdermal patch skin tolerability: results of a 1-year clinical trial in patients with mild-to-moderate Alzheimer's disease.	/pubmed/19995097	Cummings JL, Farlow MR, Meng X, Tekin S, Olin JT.	Clin Drug Investig. 2010;30(1):41-9. doi: 10.2165/11531270-000000000-00000.	PMID:19995097	Yes	skin irritation of patch

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6	Safety and tolerability of transdermal and oral rivastigmine in Alzheimer's disease and Parkinson's disease dementia.	/pubmed/20021294	Darreh-Shori T, Jelic V.	Expert Opin Drug Saf. 2010 Jan;9(1):167-76. doi: 10.1517/14740330903439717. Review.	PMID:20021294	Yes	review article
7	Donepezil treatment and changes in hippocampal structure in very mild Alzheimer disease.	/pubmed/20065136	Wang L, Harms MP, Staggs JM, Xiong C, Morris JC, Csernansky JG, Galvin JE.	Arch Neurol. 2010 Jan;67(1):99-106. doi: 10.1001/archneurol.2009.292.	PMID:20065136 | PMCID:PMC2855123	Yes	hippocampal deformation with therapy
8	Safety and tolerability of rivastigmine transdermal patch compared with rivastigmine capsules in patients switched from donepezil: data from three clinical trials.	/pubmed/20089009	Sadowsky CH, Farlow MR, Meng X, Olin JT.	Int J Clin Pract. 2010 Jan;64(2):188-93. doi: 10.1111/j.1742-1241.2009.02253.x.	PMID:20089009	No	3 trial results of tolerability in switch to pach

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9	Effects of donepezil, galantamine and rivastigmine in 938 Italian patients with Alzheimer's disease: a prospective, observational study.	/pubmed/20088621	Santoro A, Siviero P, Minicuci N, Bellavista E, Mishto M, Olivieri F, Marchegiani F, Chiamenti AM, Benussi L, Ghidoni R, Nacmias B, Bagnoli S, Ginestroni A, Scarpino O, Feraco E, Gianni W, Cruciani G, Paganelli R, Di Iorio A, Scognamiglio M, Grimaldi LM, Gabelli C, et al.	CNS Drugs. 2010 Feb;24(2):163-76. doi: 10.2165/11310960-000000000-00000.	PMID:20088621	Yes	open-label observational study

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10	Changes in cognitive functions of patients with dementia of the Alzheimer type following long-term administration of donepezil hydrochloride: relating to changes attributable to differences in apolipoprotein E phenotype.	/pubmed/20102379	Kanaya K, Abe S, Sakai M, Fujii H, Iwamoto T.	Geriatr Gerontol Int. 2010 Jan;10(1):25-31. doi: 10.1111/j.1447-0594.2009.00551.x.	PMID:20102379	Yes	long term follow up not RCT
11	Pharmacological treatment of Alzheimer's disease: effect of race and demographic variables.	/pubmed/20110610	Hernandez S, McClendon MJ, Zhou XH, Sachs M, Lerner AJ.	J Alzheimers Dis. 2010;19(2):665-72. doi: 10.3233/JAD-2010-1269.	PMID:20110610 | PMCID:PMC2827609	yes	impct of race and demographics, not RCT
12	Effects of rivastigmine in Alzheimer's disease patients with and without hallucinations.	/pubmed/20164585	Cummings J, Emre M, Aarsland D, Tekin S, Dronamraju N, Lane R.	J Alzheimers Dis. 2010;20(1):301-11. doi: 10.3233/JAD-2010-1362.	PMID:20164585	Yes	retrospective

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13	Treatment effects of therapeutic cholinesterase inhibitors on visuospatial processing in Alzheimer's disease: a longitudinal functional MRI study.	/pubmed/20215749	Thiyagesh SN, Farrow TF, Parks RW, Accosta-Mesa H, Hunter MD, Young C, Wilkinson ID, Woodruff PW.	Dement Geriatr Cogn Disord. 2010;29(2):176-88. doi: 10.1159/000275674. Epub 2010 Mar 6.	PMID:20215749	Yes	not RCT
14	Galantamine does not cause aggravated orthostatic hypotension in people with Alzheimer's disease.	/pubmed/20370881	van Beek AH, Sijbesma JC, Olde Rikkert MG, Claassen JA.	J Am Geriatr Soc. 2010 Feb;58(2):409-10. doi: 10.1111/j.1532-5415.2009.02712.x. No abstract available.	PMID:20370881	Yes	hypotension study
15	Cortical oxygen supply during postural hypotension is further decreased in Alzheimer's disease, but unrelated to cholinesterase-inhibitor use.	/pubmed/20555135	van Beek AH, Sijbesma JC, Jansen RW, Rikkert MG, Claassen JA.	J Alzheimers Dis. 2010;21(2):519-26. doi: 10.3233/JAD-2010-100288.	PMID:20555135	Yes	hypotension study

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16	The dramatic effects of Galantamine in a patient with early-onset Alzheimer's disease.	/pubmed/20562785	Dev H, Agius M, Zaman R.	Psychiatr Danub. 2010 Jun;22(2):367-9.	PMID:20562785	Yes	case study
17	How do we treat people with dementia in Croatia.	/pubmed/20562784	Mimica N, Presecki P.	Psychiatr Danub. 2010 Jun;22(2):363-6.	PMID:20562784	Yes	commentary
18	Longitudinal medication usage in Alzheimer disease patients.	/pubmed/20625271	Zhu CW, Livote EE, Kahle-Wrobleski K, Scarmeas N, Albert M, Brandt J, Blacker D, Sano M, Stern Y.	Alzheimer Dis Assoc Disord. 2010 Oct-Dec;24(4):354-9. doi: 10.1097/WAD.0b013e3181e6a17a.	PMID:20625271 | PMCID:PMC3087865	Yes	observational study
19	Effect of donepezil on cognition in severe Alzheimer's disease: a pooled data analysis.	/pubmed/20634594	Cummings J, Jones R, Wilkinson D, Lopez O, Gauthier S, Waldemar G, Zhang R, Xu Y, Sun Y, Richardson S, Mackell J.	J Alzheimers Dis. 2010;21(3):843-51. doi: 10.3233/JAD-2010-100078.	PMID:20634594	Yes	pooled analysis

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20	Role of cytochrome P4502D6 functional polymorphisms in the efficacy of donepezil in patients with Alzheimer's disease.	/pubmed/20859244	Seripa D, Bizzarro A, Pilotto A, D'onofrio G, Vecchione G, Gallo AP, Cascavilla L, Paris F, Grandone E, Mecocci P, Santini SA, Masullo C, Pilotto A.	Pharmacogenet Genomics. 2011 Apr;21(4):225-30. doi: 10.1097/FPC.0b013e32833f984c.	PMID:20859244	Yes	assessment of CYP2D6
21	Cholinesterase inhibitor use is associated with increased plasma levels of anti-AÎ² 1-42 antibodies in Alzheimer's disease patients.	/pubmed/20869427	Conti E, Galimberti G, Tremolizzo L, Masetto A, Cereda D, Zanchi C, Piazza F, Casati M, Isella V, Appollonio I, Ferrarese C.	Neurosci Lett. 2010 Dec 17;486(3):193-6. doi: 10.1016/j.neulet.2010.09.050. Epub 2010 Oct 1.	PMID:20869427	Yes	assessment of anti-A beta 1-42 antibodies
22	Phenserine efficacy in Alzheimer's disease.	/pubmed/20930279	Winblad B, Giacobini E, FrÃ¶lich L, Friedhoff LT, Bruinsma G, Becker RE, Greig NH.	J Alzheimers Dis. 2010;22(4):1201-8. doi: 10.3233/JAD-2010-101311.	PMID:20930279	yes	study of phenserine

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23	Predicting cognitive decline in Alzheimer's disease: an integrated analysis.	/pubmed/21044773	Lopez OL, Schwam E, Cummings J, Gauthier S, Jones R, Wilkinson D, Waldemar G, Zhang R, Schindler R.	Alzheimers Dement. 2010 Nov;6(6):431-9. doi: 10.1016/j.jalz.2010.04.003. Review.	PMID:21044773	Yes	pooled data from 14 trials on predictors of decline
24	Motor cortex excitability in Alzheimer's disease: a transcranial magnetic stimulation follow-up study.	/pubmed/21281700	Ferreri F, Pasqualetti P, MÃ¤Ã¤ttÃ¤ S, Ponzo D, Guerra A, Bressi F, Chiovenda P, Del Duca M, Giambattistelli F, Ursini F, Tombini M, Vernieri F, Rossini PM.	Neurosci Lett. 2011 Apr 1;492(2):94-8. doi: 10.1016/j.neulet.2011.01.064. Epub 2011 Jan 31.	PMID:21281700	Yes	motor cortex reorganization
25	A double-blind placebo-controlled randomized trial of Melissa officinalis oil and donepezil for the treatment of agitation in Alzheimer's disease.	/pubmed/21335973	Burns A, Perry E, Holmes C, Francis P, Morris J, Howes MJ, Chazot P, Lees G, Ballard C.	Dement Geriatr Cogn Disord. 2011;31(2):158-64. doi: 10.1159/000324438. Epub 2011 Feb 19.	PMID:21335973	Yes	melissa aromatherapy

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26	An economic evaluation of early assessment for Alzheimer's disease in the United Kingdom.	/pubmed/21420366	Getsios D, Blume S, Ishak KJ, Maclaine G, HernÃ¡ndez L.	Alzheimers Dement. 2012 Jan;8(1):22-30. doi: 10.1016/j.jalz.2010.07.001. Epub 2011 Mar 21.	PMID:21420366	Yes	modelled cost of early assessment
27	1-H MRS changes in dorsolateral prefrontal cortex after donepezil treatment in patients with mild to moderate Alzheimer's disease.	/pubmed/21648328	Henigsberg N, Kalember P, HrabaÄ‡ P, Rados M, Bajs M, Rados M, KovaviÄ‡ Z, Loncar M, Madzar T.	Coll Antropol. 2011 Jan;35 Suppl 1:159-62.	PMID:21648328	Yes	dorsolateral prefrontal cortex
28	Reversible" Alzheimer's disease?"	/pubmed/21668917	Peter F, Susanne J, Margareta H, Silvia W, Wolfgang K, Thomas L, Heinz TK.	J Am Geriatr Soc. 2011 Jun;59(6):1137-8. doi: 10.1111/j.1532-5415.2011.03437.x. No abstract available.	PMID:21668917	Yes	commentary

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29	Disease progression and costs of care in Alzheimer's disease patients treated with donepezil: a longitudinal naturalistic cohort.	/pubmed/21822729	Gustavsson A, JÃ¶nsson L, Parmler J, Andreasen N, Wattmo C, Wallin Ã…K, Minthon L.	Eur J Health Econ. 2012 Oct;13(5):561-8. doi: 10.1007/s10198-011-0334-y. Epub 2011 Aug 6.	PMID:21822729	Yes	modelled outcomes and cost
30	aChE and BuChE inhibition by rivastigmin have no effect on peripheral insulin resistance in elderly patients with Alzheimer disease.	/pubmed/22323348	Isik AT, Bozoglu E, Eker D.	J Nutr Health Aging. 2012 Feb;16(2):139-41.	PMID:22323348	Yes	effect on insulin
31	Acetylcholinesterase inhibitors and the risk of hip fracture in Alzheimer's disease patients: a case-control study.	/pubmed/22467182	Tamimi I, Ojea T, Sanchez-Siles JM, Rojas F, Martin I, Gormaz I, Perez A, Dawid-Milner MS, Mendez L, Tamimi F.	J Bone Miner Res. 2012 Jul;27(7):1518-27. doi: 10.1002/jbmr.1616.	PMID:22467182	Yes	impact on hip fracture

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32	Is there a rationale for including only patients already being treated with acetylcholinesterase inhibitors in a prodromal AD trial?	/pubmed/22499453	Grundman M, Yang E, Dibernardo A.	J Nutr Health Aging. 2012 Apr;16(4):336-8.	PMID:22499453	Yes	prodromal AD
33	Use of antidementia drugs in frontotemporal lobar degeneration.	/pubmed/22605780	LÃ³pez-Pousa S, CalvÃ³-Perxas L, Lejarreta S, Cullell M, MelÃ©ndez R, HernÃ¡ndez E, Bisbe J, Perkal H, Manzano A, Roig AM, TurrÃ³-Garriga O, Vilalta-Franch J, Garre-Olmo J; Registry of Dementias of Girona Study Group (ReDeGi Study Group).	Am J Alzheimers Dis Other Demen. 2012 Jun;27(4):260-6. doi: 10.1177/1533317512447887. Epub 2012 May 17.	PMID:22605780	Yes	frontotemporal degeneration

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34	Acetylcholinesterase inhibitors reduce spreading activation in dementia.	/pubmed/22609576	Foster PS, Branch KK, Witt JC, Giovannetti T, Libon D, Heilman KM, Drago V.	Neuropsychologia. 2012 Jul;50(8):2093-9. doi: 10.1016/j.neuropsychologia.2012.05.010. Epub 2012 May 17.	PMID:22609576	Yes	not RCT
35	Concentrations of rivastigmine and NAP 226-90 and the cognitive response in Taiwanese Alzheimer's disease patients.	/pubmed/22751168	Chou MC, Chen CH, Liu CK, Chen SH, Wu SJ, Yang YH.	J Alzheimers Dis. 2012;31(4):857-64. doi: 10.3233/JAD-2012-120109.	PMID:22751168	Yes	pilot study
36	Rivastigmine patch ameliorates depression in mild AD: preliminary evidence from a 6-month open-label observational study.	/pubmed/22760171	Spalletta G, Gianni W, Giubilei F, Casini AR, Sancesario G, Caltagirone C, Cravello L.	Alzheimer Dis Assoc Disord. 2013 Jul-Sep;27(3):289-91. doi: 10.1097/WAD.0b013e318260ab0a.	PMID:22760171	Yes	not RCT, impact on depression

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37	Safety and tolerability of rivastigmine transdermal patch formulation in newly diagnosed patients with Alzheimer's dementia in naturalistic conditions.	/pubmed/22994614	Pregelj P.	Psychogeriatrics. 2012 Sep;12(3):165-71. doi: 10.1111/j.1479-8301.2011.00400.x.	PMID:22994614	No	safety of patch
38	Use of rivastigmine or galantamine and risk of adverse cardiac events: a database study from the Netherlands.	/pubmed/23217530	KrÃ¶ger E, Berkers M, Carmichael PH, Souverein P, van Marum R, Egberts T.	Am J Geriatr Pharmacother. 2012 Dec;10(6):373-80. doi: 10.1016/j.amjopharm.2012.11.002.	PMID:23217530	Yes	assessment of cardiac risk
39	Hemodynamic effects of cholinesterase inhibition in mild Alzheimer's disease.	/pubmed/23239554	Chaudhary S, Scouten A, Schwindt G, Janik R, Lee W, Sled JG, Black SE, Stefanovic B.	J Magn Reson Imaging. 2013 Jul;38(1):26-35. doi: 10.1002/jmri.23967. Epub 2012 Dec 13.	PMID:23239554	Yes	hemodynamic effects

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40	Long-term associations between cholinesterase inhibitors and memantine use and health outcomes among patients with Alzheimer's disease.	/pubmed/23332671	Zhu CW, Livote EE, Scarmeas N, Albert M, Brandt J, Blacker D, Sano M, Stern Y.	Alzheimers Dement. 2013 Nov;9(6):733-40. doi: 10.1016/j.jalz.2012.09.015. Epub 2013 Jan 17.	PMID:23332671 | PMCID:PMC3633652	Yes	natural history study
41	[Rivastigmine as treatment for patients with mild to moderately severe Alzheimer disease under normal clinical practice conditions. The ENTERPRISE study].	/pubmed/23582372	Cruz Jentoft AJ, HernÃ¡ndez B.	Neurologia. 2014 Jan-Feb;29(1):1-10. doi: 10.1016/j.nrl.2013.01.008. Epub 2013 Apr 10. Spanish.	PMID:23582372	Yes	article in Spanish
42	Blood pro-inflammatory cytokines in Alzheimer's disease in relation to the use of acetylcholinesterase inhibitors.	/pubmed/23585364	Richardson C, Gard PR, Klugman A, Isaac M, Tabet N.	Int J Geriatr Psychiatry. 2013 Dec;28(12):1312-7. doi: 10.1002/gps.3966. Epub 2013 Apr 14.	PMID:23585364	Yes	cytokine study

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43	Phase I study on the pharmacokinetics and tolerance of ZT-1, a prodrug of huperzine A, for the treatment of Alzheimer's disease.	/pubmed/23624756	Jia JY, Zhao QH, Liu Y, Gui YZ, Liu GY, Zhu DY, Yu C, Hong Z.	Acta Pharmacol Sin. 2013 Jul;34(7):976-82. doi: 10.1038/aps.2013.7. Epub 2013 Apr 29.	PMID:23624756 | PMCID:PMC4002618	Yes	not target drugs
44	Real-life effectiveness and tolerability of the rivastigmine transdermal patch in patients with mild-to-moderate Alzheimer's disease: the EMBRACE study.	/pubmed/23647369	Gauthier S, Robillard A, Cohen S, Black S, Sampalis J, Colizza D, de Takacsy F, Schecter R; EMBRACE investigators.	Curr Med Res Opin. 2013 Aug;29(8):989-1000. doi: 10.1185/03007995.2013.802230. Epub 2013 May 23.	PMID:23647369	No	patch
45	A longitudinal study of risk factors for community-based home help services in Alzheimer's disease: the influence of cholinesterase inhibitor therapy.	/pubmed/23682212	Wattmo C, Paulsson E, Minthon L, Londos E.	Clin Interv Aging. 2013;8:329-39. doi: 10.2147/CIA.S40087. Epub 2013 Mar 20.	PMID:23682212 | PMCID:PMC3610439	Yes	community based, not RCT

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46	From high doses of oral rivastigmine to transdermal rivastigmine patches: user experience and satisfaction among caregivers of patients with mild to moderate Alzheimer disease.	/pubmed/23684446	ReÃ±Ã© R, Ricart J, HernÃ¡ndez B; researchers in the Experience study.	Neurologia. 2014 Mar;29(2):86-93. doi: 10.1016/j.nrl.2013.02.012. Epub 2013 May 17. English, Spanish.	PMID:23684446	No	satisfaction with patch use
47	Memantine is associated with longer survival than donepezil in a Veterans Affairs prescription database, 1997 to 2008.	/pubmed/23703151	Lazzeroni LC, Halbauer JD, Ashford JW, Noda A, Hernandez B, Azor V, Hozack N, Hasson N, Henderson VW, Yesavage JA, Tinklenberg JR.	J Alzheimers Dis. 2013;36(4):791-8. doi: 10.3233/JAD-130662.	PMID:23703151	Yes	memantine and survival

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48	The use of cholinesterase inhibitors and the risk of myocardial infarction and death: a nationwide cohort study in subjects with Alzheimer's disease.	/pubmed/23735859	NordstrÃ¶m P, Religa D, Wimo A, Winblad B, Eriksdotter M.	Eur Heart J. 2013 Sep;34(33):2585-91. doi: 10.1093/eurheartj/eht182. Epub 2013 Jun 4.	PMID:23735859	Yes	MI risk
49	Evaluating the cognitive effects of donepezil 23 mg/d in moderate and severe Alzheimer's disease: analysis of effects of baseline features on treatment response.	/pubmed/23742728	Sabbagh M, Cummings J, Christensen D, Doody R, Farlow M, Liu L, Mackell J, Fain R.	BMC Geriatr. 2013 Jun 6;13:56. doi: 10.1186/1471-2318-13-56.	PMID:23742728 | PMCID:PMC3681558	Yes	post hoc analysis
50	Australian population trends and disparities in cholinesterase inhibitor use, 2003 to 2010.	/pubmed/23849590	Zilkens RR, Duke J, Horner B, Semmens JB, Bruce DG.	Alzheimers Dement. 2014 May;10(3):310-8. doi: 10.1016/j.jalz.2013.04.001. Epub 2013 Jul 10.	PMID:23849590	Yes	descriptive report

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51	Alzheimer's disease treated patients showed different patterns for oxidative stress and inflammation markers.	/pubmed/23871825	Gubandru M, Margina D, Tsitsimpikou C, Goutzourelas N, Tsarouhas K, Ilie M, Tsatsakis AM, Kouretas D.	Food Chem Toxicol. 2013 Nov;61:209-14. doi: 10.1016/j.fct.2013.07.013. Epub 2013 Jul 16.	PMID:23871825	Yes	not desired outcomes of review
52	A 24-week, randomized, controlled trial of rivastigmine patch 13.3 mg/24 h versus 4.6 mg/24 h in severe Alzheimer's dementia.	/pubmed/23924050	Farlow MR, Grossberg GT, Sadowsky CH, Meng X, Somogyi M.	CNS Neurosci Ther. 2013 Oct;19(10):745-52. doi: 10.1111/cns.12158. Epub 2013 Aug 7.	PMID:23924050 | PMCID:PMC4233957	No	RCT of patch
53	Effect of the timing of acetylcholinesterase inhibitor ingestion on sleep.	/pubmed/23948729	Song HR, Woo YS, Wang HR, Jun TY, Bahk WM.	Int Clin Psychopharmacol. 2013 Nov;28(6):346-8. doi: 10.1097/YIC.0b013e328364f58d.	PMID:23948729	Yes	impact on sleep

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54	Serum adipokine levels modified by donepezil treatment in Alzheimer's disease.	/pubmed/23979024	PÃ¡kÃ¡ski M, FehÃ©r A, JuhÃ¡sz A, DrÃ³tos G, Fazekas OC, KovÃ¡cs J, Janka Z, KÃ¡lmÃ¡n J.	J Alzheimers Dis. 2014;38(2):371-7. doi: 10.3233/JAD-131139.	PMID:23979024	Yes	not required outcome
55	Efficacy of higher dose 13.3 mg/24 h rivastigmine patch on instrumental activities of daily living in patients with mild-to-moderate Alzheimer's disease.	/pubmed/23982674	Grossberg G, Cummings J, FrÃ¶lich L, Bellelli G, Molinuevo JL, Krahnke T, Strohmaier C.	Am J Alzheimers Dis Other Demen. 2013 Sep;28(6):583-91. doi: 10.1177/1533317513495104.	PMID:23982674	Yes	post hoc analysis
56	Evaluation of an 8-item Severe Impairment Battery (SIB-8) vs. the full SIB in moderate to severe Alzheimer's disease patients participating in a donepezil study.	/pubmed/24073978	Schmitt FA, Saxton J, Ferris SH, Mackell J, Sun Y.	Int J Clin Pract. 2013 Oct;67(10):1050-6. doi: 10.1111/ijcp.12188.	PMID:24073978 | PMCID:PMC3930878	Yes	comparison of tools

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57	The prediction of response to galantamine treatment in patients with mild to moderate Alzheimer's disease.	/pubmed/24156269	Ohnishi T, Sakiyama Y, Okuri Y, Kimura Y, Sugiyama N, Saito T, Takahashi M, Kobayashi T.	Curr Alzheimer Res. 2014 Feb;11(2):110-8.	PMID:24156269 | PMCID:PMC3979115	Yes	not RCT
58	Effect of donepezil in Alzheimer disease can be measured by a computerized human analog of the Morris water maze.	/pubmed/24192578	Hort J, Andel R, Mokrisova I, Gazova I, Amlerova J, Valis M, Coulson EJ, Harrison J, Windisch M, LaczÃ³ J.	Neurodegener Dis. 2014;13(2-3):192-6. doi: 10.1159/000355517. Epub 2013 Oct 30.	PMID:24192578	Yes	not RCT
59	Pharmacodynamics of cholinesterase inhibitors suggests add-on therapy with a low-dose carbamylating inhibitor in patients on long-term treatment with rapidly reversible inhibitors.	/pubmed/24217282	Darreh-Shori T, Hosseini SM, Nordberg A.	J Alzheimers Dis. 2014;39(2):423-40. doi: 10.3233/JAD-130845.	PMID:24217282	Yes	not outcomes of review

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60	Berberis aetnensis and B.â€‰libanotica: a comparative study on the chemical composition, inhibitory effect on key enzymes linked to Alzheimer's disease and antioxidant activity.	/pubmed/24236982	Bonesi M, Loizzo MR, Conforti F, Passalacqua NG, Saab A, Menichini F, Tundis R.	J Pharm Pharmacol. 2013 Dec;65(12):1726-35. doi: 10.1111/jphp.12172. Epub 2013 Nov 6.	PMID:24236982	Yes	not target drugs
61	Efficacy of memantine, donepezil, or their association in moderate-severe Alzheimer's disease: a review of clinical trials.	/pubmed/24288512	Molino I, Colucci L, Fasanaro AM, Traini E, Amenta F.	ScientificWorldJournal. 2013;2013:925702. doi: 10.1155/2013/925702. Review.	PMID:24288512 | PMCID:PMC3830825	Yes	review article
62	Acetylcholinesterase inhibitors and healing of hip fracture in Alzheimer's disease patients: a retrospective cohort study.	/pubmed/24292615	Eimar H, Perez Lara A, Tamimi I, MÃ¡rquez SÃ¡nchez P, Gormaz Talavera I, Rojas Tomba F, GarcÃ-a de la Oliva T, Tamimi F.	J Musculoskelet Neuronal Interact. 2013 Dec;13(4):454-63.	PMID:24292615	Yes	retrospective

Number, Assigned by ReVue	Title	URL	Authors	Citation	PMID	Trial Excluded	Comments
63	Increased levels of plasma p3-alcÎ±35, a major fragment of AlcadeinÎ± by Î³-secretase cleavage, in Alzheimer's disease.	/pubmed/24305499	Omori C, Kaneko M, Nakajima E, Akatsu H, Waragai M, Maeda M, Morishima-Kawashima M, Saito Y, Nakaya T, Taru H, Yamamoto T, Asada T, Hata S, Suzuki T; Japanese Alzheimerâ€™s Disease Neuroimaging Initiative.	J Alzheimers Dis. 2014;39(4):861-70. doi: 10.3233/JAD-131610.	PMID:24305499	Yes	not desired outcomes of review
64	Novel tacrine analogs as potential cholinesterase inhibitors in Alzheimer's disease.	/pubmed/24343873	El-Malah A, Gedawy EM, Kassab AE, Salam RM.	Arch Pharm (Weinheim). 2014 Feb;347(2):96-103. doi: 10.1002/ardp.201300121. Epub 2013 Dec 16.	PMID:24343873	Yes	not target drugs
65	CHRNA7 polymorphisms and response to cholinesterase inhibitors in Alzheimer's disease.	/pubmed/24391883	Weng PH, Chen JH, Chen TF, Sun Y, Wen LL, Yip PK, Chu YM, Chen YC.	PLoS One. 2013;8(12):e84059. doi: 10.1371/journal.pone.0084059.	PMID:24391883 | PMCID:PMC3877150	Yes	not required outcome

Number, Assigned by ReVue	Title	URL	Authors	Citation	PMID	Trial Excluded	Comments
66	A 2-year prospective cohort study of antidementia drug non-persistency in mild-to-moderate Alzheimer's disease in Europe : predictors of discontinuation and switch in the ICTUS study.	/pubmed/24408842	Gardette V, Lapeyre-Mestre M, Piau A, Gallini A, Cantet C, Montastruc JL, Vellas B, Andrieu S; ICTUS Group.	CNS Drugs. 2014 Feb;28(2):157-70. doi: 10.1007/s40263-013-0133-3.	PMID:24408842	Yes	not RCT
67	The effects of combine treatment of memantine and donepezil on Alzheimer's disease patients and its relationship with cerebral blood flow in the prefrontal area.	/pubmed/24436135	Araki T, Wake R, Miyaoka T, Kawakami K, Nagahama M, Furuya M, Limoa E, Liaury K, Hashioka S, Murotani K, Horiguchi J.	Int J Geriatr Psychiatry. 2014 Sep;29(9):881-9. doi: 10.1002/gps.4074. Epub 2014 Jan 17.	PMID:24436135	Yes	not desired outcomes of review

Number, Assigned by ReVue	Title	URL	Authors	Citation	PMID	Trial Excluded	Comments
68	Galantamine treatment in outpatients with mild Alzheimer's disease.	/pubmed/24461047	Richarz U, Gaudig M, Rettig K, Schauble B.	Acta Neurol Scand. 2014 Jun;129(6):382-92. doi: 10.1111/ane.12195. Epub 2014 Jan 25.	PMID:24461047	Yes	not RCT
69	Parallel improvement of cognitive functions and P300 latency following donepezil treatment in patients with Alzheimer's disease: a case-control study.	/pubmed/24492450	Chang YS, Chen HL, Hsu CY, Tang SH, Liu CK.	J Clin Neurophysiol. 2014 Feb;31(1):81-5. doi: 10.1097/01.wnp.0000436899.48243.5e.	PMID:24492450	Yes	not RCT
70	Hallucinators find meaning in noises: pareidolic illusions in dementia with Lewy bodies.	/pubmed/24491313	Yokoi K, Nishio Y, Uchiyama M, Shimomura T, Iizuka O, Mori E.	Neuropsychologia. 2014 Apr;56:245-54. doi: 10.1016/j.neuropsychologia.2014.01.017. Epub 2014 Jan 31.	PMID:24491313	Yes	not targeted outcome

Number, Assigned by ReVue	Title	URL	Authors	Citation	PMID	Trial Excluded	Comments
71	Efficacy of higher-dose 13.3â€‰mg/24 h (15â€‰cm2) rivastigmine patch on the Alzheimer's Disease Assessment Scale-cognitive subscale: domain and individual item analysis.	/pubmed/24549933	Alva G, Isaacson R, Sadowsky C, Grossberg G, Meng X, Somogyi M.	Int J Geriatr Psychiatry. 2014 Sep;29(9):920-7. doi: 10.1002/gps.4080. Epub 2014 Feb 18.	PMID:24549933	No	efficacy of patch
72	Effects of Gingko biloba supplementation in Alzheimer's disease patients receiving cholinesterase inhibitors: data from the ICTUS study.	/pubmed/24548724	Canevelli M, Adali N, Kelaiditi E, Cantet C, Ousset PJ, Cesari M; ICTUS/DSA Group.	Phytomedicine. 2014 May 15;21(6):888-92. doi: 10.1016/j.phymed.2014.01.003. Epub 2014 Feb 16.	PMID:24548724	Yes	not target drug
73	Cognitive subdomain responses to galantamine in Alzheimer's disease.	/pubmed/24566512	Song J, Ahn IS, Kang HS, Myung W, Lee Y, Woo SY, Ku HM, Hwang TY, Carroll BJ, Kim DK.	J Nerv Ment Dis. 2014 Mar;202(3):253-9. doi: 10.1097/NMD.0000000000000107.	PMID:24566512	Yes	not RCT

Number, Assigned by ReVue	Title	URL	Authors	Citation	PMID	Trial Excluded	Comments
74	Do cholinesterase inhibitors act primarily on attention deficit? A naturalistic study in Alzheimer's disease patients.	/pubmed/24577458	Bracco L, Bessi V, Padiglioni S, Marini S, Pepeu G.	J Alzheimers Dis. 2014;40(3):737-42. doi: 10.3233/JAD-131154.	PMID:24577458	Yes	longitudinal study
75	Cognitive and affective changes in mild to moderate Alzheimer's disease patients undergoing switch of cholinesterase inhibitors: a 6-month observational study.	/pubmed/24586603	Spalletta G, Caltagirone C, Padovani A, Sorbi S, Attar M, Colombo D, Cravello L; E V O L U T I O N study Working Group.	PLoS One. 2014;9(2):e89216. doi: 10.1371/journal.pone.0089216.	PMID:24586603 | PMCID:PMC3929703	Yes	not RCT

Number, Assigned by ReVue	Title	URL	Authors	Citation	PMID	Trial Excluded	Comments
76	Antidementia drug use among community-dwelling individuals with Alzheimer's disease in Finland: a nationwide register-based study.	/pubmed/24608822	Taipale H, Tanskanen A, Koponen M, Tolppanen AM, Tiihonen J, Hartikainen S.	Int Clin Psychopharmacol. 2014 Jul;29(4):216-23. doi: 10.1097/YIC.0000000000000032.	PMID:24608822 | PMCID:PMC4047310	Yes	not RCT
77	Retrospective study on the benefits of combined Memantine and cholinEsterase inhibitor treatMent in AGEd Patients affected with Alzheimer's Disease: the MEMAGE study.	/pubmed/24643135	Gareri P, Putignano D, Castagna A, Cotroneo AM, De Palo G, Fabbo A, Forgione L, Giacummo A, Lacava R, Marino S, Simone M, Zurlo A, Putignano S.	J Alzheimers Dis. 2014;41(2):633-40. doi: 10.3233/JAD-132735.	PMID:24643135	Yes	retrospective

Number, Assigned by ReVue	Title	URL	Authors	Citation	PMID	Trial Excluded	Comments
78	Efficacy and safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease: a systematic review and meta-analysis.	/pubmed/24662102	Tan CC, Yu JT, Wang HF, Tan MS, Meng XF, Wang C, Jiang T, Zhu XC, Tan L.	J Alzheimers Dis. 2014;41(2):615-31. doi: 10.3233/JAD-132690. Review.	PMID:24662102	No	would like to look at this to compare their results to ours
79	Apathy in Alzheimer's disease: any effective treatment?	/pubmed/24672318	Rea R, Carotenuto A, Fasanaro AM, Traini E, Amenta F.	ScientificWorldJournal. 2014;2014:421385. doi: 10.1155/2014/421385. Review.	PMID:24672318 | PMCID:PMC3929376	Yes	not RCT
80	Gait changes with anti-dementia drugs: a prospective, open-label study combining single and dual task assessments in patients with Alzheimer's disease.	/pubmed/24683126	Beauchet O, Launay CP, Allali G, Herrmann FR, Annweiler C.	Drugs Aging. 2014 May;31(5):363-72. doi: 10.1007/s40266-014-0175-3.	PMID:24683126	Yes	not RCT

Number, Assigned by ReVue	Title	URL	Authors	Citation	PMID	Trial Excluded	Comments
81	Insights and ideas garnered from marine metabolites for development of dual-function acetylcholinesterase and amyloid-Î² aggregation inhibitors.	/pubmed/24714126	Stoddard SV, Hamann MT, Wadkins RM.	Mar Drugs. 2014 Apr 4;12(4):2114-31. doi: 10.3390/md12042114.	PMID:24714126 | PMCID:PMC4012451	Yes	not target drugs
82	High-dose cholinergic therapy with rivastigmine patch does not prolong QTc time in patients with Alzheimer's disease.	/pubmed/24717382	Riepe MW.	J Clin Psychiatry. 2014 Mar;75(3):288. doi: 10.4088/JCP.13l08730. No abstract available.	PMID:24717382	Yes	not targeted outcome
83	Donepezil and life expectancy in Alzheimer's disease: a retrospective analysis in the Tajiri Project.	/pubmed/24720852	Meguro K, Kasai M, Akanuma K, Meguro M, Ishii H, Yamaguchi S.	BMC Neurol. 2014 Apr 11;14:83. doi: 10.1186/1471-2377-14-83.	PMID:24720852 | PMCID:PMC3997195	Yes	retrospective

Appendix 1 - Update to "A Meta-Analysis of Efficacy and Safety of Cholinesterase Inhibitors..."
90 Trials published between January 1, 2014 and June 1, 2015
August 2015

Number, Assigned by ReVue	Title	URL	Authors	Citation	PMID	Trial Excluded	Comments
84	The potentially protective effect of donepezil in Alzheimer's disease.	/pubmed/24732387	Ishiwata A, Mizumura S, Mishina M, Yamazaki M, Katayama Y.	Dement Geriatr Cogn Disord. 2014;38(3-4):170-7. doi: 10.1159/000358510. Epub 2014 Apr 9.	PMID:24732387	Yes	not RCT
85	Early-onset Alzheimer's disease: a global cross-sectional analysis.	/pubmed/24780092	Panegyres PK, Chen HY; Coalition against Major Diseases (CAMD).	Eur J Neurol. 2014 Sep;21(9):1149-54, e64-5. doi: 10.1111/ene.12453. Epub 2014 Apr 30.	PMID:24780092	Yes	not RCT
86	Changes in gait variability with anti-dementia drugs: a systematic review and meta-analysis.	/pubmed/24806974	Beauchet O, Launay CP, Allali G, Annweiler C.	CNS Drugs. 2014 Jun;28(6):513-8. doi: 10.1007/s40263-014-0170-6.	PMID:24806974	Yes	review article
87	Rivastigmine transdermal patch and physical exercises for Alzheimer's disease: a randomized clinical trial.	/pubmed/24938502	Aguiar P, Monteiro L, Feres A, Gomes I, Melo A.	Curr Alzheimer Res. 2014;11(6):532-7.	PMID:24938502	Yes	not RCT

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90 Trials published between January 1, 2014 and June 1, 2015
August 2015

Number, Assigned by ReVue	Title	URL	Authors	Citation	PMID	Trial Excluded	Comments
88	Safety and efficacy of idalopirdine, a 5-HT6 receptor antagonist, in patients with moderate Alzheimer's disease (LADDER): a randomised, double-blind, placebo-controlled phase 2 trial.	/pubmed/25297016	Wilkinson D, Windfeld K, Colding-JÃ¸rgensen E.	Lancet Neurol. 2014 Nov;13(11):1092-9. doi: 10.1016/S1474-4422(14)70198-X. Epub 2014 Oct 5.	PMID:25297016	Yes	not target drug
89	FOXO1 locus and acetylcholinesterase inhibitors in elderly patients with Alzheimer's disease.	/pubmed/25364236	Paroni G, Seripa D, Fontana A, D'Onofrio G, Gravina C, Urbano M, Cascavilla L, Pellegrini F, Greco A, Pilotto A.	Clin Interv Aging. 2014;9:1783-91. doi: 10.2147/CIA.S64758.	PMID:25364236 | PMCID:PMC4211854	Yes	not RCT
90	[Clinical observation of Alzheimer's disease treated with acupuncture].	/pubmed/25876339	Gu W, Jin XX, Zhang YJ, Li ZJ, Kong Y.	Zhongguo Zhen Jiu. 2014 Dec;34(12):1156-60. Chinese.	PMID:25876339	Yes	Language - Chinese

Appendix 2 - Update to "A Meta-Analysis of Efficacy and Safety of Cholinesterase Inhibitors..."
Final 9 Trials June 2015
August 2015

Number, Assigned by ReVue	Title	URL	Authors	Citation	PMID	Trial Excluded	Comments	RCT Randomization
1	The ADAS-cog and clinically meaningful change in the VISTA clinical trial of galantamine for Alzheimer's disease.	/pubmed/19548273	Rockwood K, Fay S, Gorman M.	Int J Geriatr Psychiatry. 2010 Feb;25(2):191-201.	PMID:19548273	Yes, patients were tested at 24 weeks, 8 weeks into the open labe lphase of the trial where all patients received galantamine	6 moth follow up results from the VISTA trial not an RCT, a subgroup analysis of a study that was included in the previous report (August 2014)	No
4	A 25-week, open-label trial investigating rivastigmine transdermal patches with concomitant memantine in mild-to-moderate Alzheimer's disease: a post hoc analysis.	/pubmed/19929593	Farlow MR, Alva G, Meng X, Olin JT.	Curr Med Res Opin. 2010 Feb;26(2):263-9.	PMID:19929593	Yes, Stratified by concomitant use of memantine, an add-on study that compared the addition of memantine (rivastigmine plus memantine versus rivastigmine alone), not an RCT	RCT, on switch to patch after donepezil; either immediate switch or delayed switch. Stratified by concommitant use of memantine. Post hoc analysis	No

Appendix 2 - Update to "A Meta-Analysis of Efficacy and Safety of Cholinesterase Inhibitors..."
Final 9 Trials June 2015
August 2015

Number, Assigned by ReVue	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 Unvalidated Outcome Measures	Carryover Effects of Crossover Trial	Recruitment Bias in Cluster-randomized Trials	Funding
1	Yes	Yes	No	No	No	No	No	N/A	N/A	industry; Canadian Institute of Health
4	No	No	No	No	No	No	No	N/A	N/A	Novartis

Appendix 2 - Update to "A Meta-Analysis of Efficacy and Safety of Cholinesterase Inhibitors..."
Final 9 Trials June 2015
August 2015

Number, Assigned by ReVue	Title	URL	Authors	Citation	PMID	Trial Excluded	Comments	RCT Randomization
8	Safety and tolerability of rivastigmine transdermal patch compared with rivastigmine capsules in patients switched from donepezil: data from three clinical trials.	/pubmed/20089009	Sadowsky CH, Farlow MR, Meng X, Olin JT.	Int J Clin Pract. 2010 Jan;64(2):188-93.	PMID:20089009	Yes, ad hoc pooled analysis of three trials, with all 3 studies not being eligible for inclusion (2 studies were single arm, and 1 study was a delayed intervention study where rivastigmine was delayed for only 7 days)	3 trial results of tolerability in switch to patch. Ad Hoc analysis of three trials, not an RCT	No
37	Safety and tolerability of rivastigmine transdermal patch formulation in newly diagnosed patients with Alzheimer's dementia in naturalistic conditions.	/pubmed/22994614	Pregelj P.	Psychogeriatrics. 2012 Sep;12(3):165-71.	PMID:22994614	Yes	safety of patch, observational, non-interventional, post marleting surveillance trial, conducted by Novartis	No
44	Real-life effectiveness and tolerability of the rivastigmine transdermal patch in patients with mild-to-moderate Alzheimer's disease: the EMBRACE study.	/pubmed/23647369	Gauthier S, Robillard A, Cohen S, Black S, Sampalis J, Colizza D, de Takacsy F, Schecter R; EMBRACE investigators.	Curr Med Res Opin. 2013 Aug;29(8):989-1000.	PMID:23647369	Yes	Open label assessment of the patch	No

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Final 9 Trials June 2015
August 2015

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8	Yes	Yes	No	Yes	No	N/A	No	N/A	N/A	Industry
37	Yes	Yes	No	No	No	No	No	N/A	N/A	Novartis
44	Yes	Yes	No	No	No	N/A	No	N/A	N/A	Novartis

Number, Assigned by ReVue	Title	URL	Authors	Citation	PMID	Trial Excluded	Comments	RCT Randomization
46	From high doses of oral rivastigmine to transdermal rivastigmine patches: user experience and satisfaction among caregivers of patients with mild to moderate Alzheimer disease.	/pubmed/23684446	Renee R, Ricart J, Hernaįndez B; researchers in the Experience study.	Neurologia. 2014 Mar;29(2):86-93.	PMID:23684446	Yes	satisfaction with patch use, not randomized	No
52	A 24-week, randomized, controlled trial of rivastigmine patch 13.3 mg/24 h versus 4.6 mg/24 h in severe Alzheimer's dementia.	/pubmed/23924050	Farlow MR, Grossberg GT, Sadowsky CH, Meng X, Somogyi M.	CNS Neurosci Ther. 2013 Oct;19(10):745-52.	PMID:23924050 | PMCID:PMC4233957	Yes	RCT of patch in severee Alzheimer's	Yes
71	Efficacy of higher-dose 13.3mg/24 h (15 cm2) rivastigmine patch on the Alzheimer's Disease Assessment Scale-cognitive subscale: domain and individual item analysis.	/pubmed/24549933	Alva G, Isaacson R, Sadowsky C, Grossberg G, Meng X, Somogyi M.	Int J Geriatr Psychiatry. 2014 Sep;29(9):920-7.	PMID:24549933	Yes	Ad hoc factor analysis using data from the double blind study	No

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Final 9 Trials June 2015
August 2015

Number, Assigned by ReVue	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 Unvalidated Outcome Measures	Carryover Effects of Crossover Trial	Recruitment Bias in Cluster-randomized Trials	Funding
46	Yes	Yes	No	No	No	N/A	No	N/A	N/A	industry
52	No	No	No	No	No	No	NA	NA	NA	Novartis
71	Yes	Yes	No	?	?	N/A	no	N/A	N/A	industry

Appendix 2 - Update to "A Meta-Analysis of Efficacy and Safety of Cholinesterase Inhibitors..."
Final 9 Trials June 2015
August 2015

Number, Assigned by ReVue	Title	URL	Authors	Citation	PMID	Trial Excluded	Comments	RCT Randomization
78	Efficacy and safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease: a systematic review and meta-analysis.	/pubmed/24662102	Tan CC, Yu JT, Wang HF, Tan MS, Meng XF, Wang C, Jiang T, Zhu XC, Tan L.	J Alzheimers Dis. 2014;41(2):615-31.	PMID:24662102	Yes, meta-anlysis used severe AD patients and included memantine	Only used 2 of the studies we included, went way back to 2000 for references, does not look to be a very well conducted meta-analysis	No

Appendix 2 - Update to "A Meta-Analysis of Efficacy and Safety of Cholinesterase Inhibitors..."
Final 9 Trials June 2015
August 2015

Number, Assigned by ReVue	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 Unvalidated Outcome Measures	Carryover Effects of Crossover Trial	Recruitment Bias in Cluster-randomized Trials	Funding
78	N/A	Yes	N/A	N/A	No	N/A	No	N/A	N/A	Natural Science Foundation China