[Updated 2015]

Cholinesterase inhibitors and memantine for treatment of dementia. [Updated 2015]

SCOPING QUESTION: For people with dementia, are cholinesterase inhibitors and memantine effective and safe for treatment of dementia in non-specialist health settings in low- and middle-income countries?

BACKGROUND

It is estimated that 44 million individuals worldwide currently have dementia, with 135 million people estimated to be living with dementia by 2050 (Prince, 2013). Dementia is a clinical syndrome caused by neurodegeneration and characterized by inexorably progressive deterioration in cognitive ability and capacity for independent living (Wimo and Prince, 2010). The most common underlying pathologies are Alzheimer's disease, vascular dementia, dementia with Lewy bodies and frontotemporal dementia (Wimo and Prince, 2010). Dementia is a health- and social-care priority for many high-income countries and governments. The United Kingdom (UK), France, Norway, the United States of America (USA) and South Korea have recently developed specific plans or strategies in response to growing epidemics (Sousa et al., 2009; Sousa et al., 2010).

Although young-onset cases are increasingly recognized, dementia is typically a condition that affects older people, making dementia is a leading contributor to disability and dependence among older adults. Population aging is having a profound impact on the emergence of the dementia epidemic and is driving government responses (Sousa et al., 2009; Sousa et al., 2010). Particularly rapid increases in the numbers and proportion of older people are forecast for China, India and the Latin American region. By 2050, the number of people aged $\geq$ 60 years will have increased by 1.25 billion, accounting for 22% of the world's population, with 79% living in low-income regions, where public awareness of dementia and health system preparedness is much more limited (UN DESA, 2013).

One of the most important issues is that currently patients with dementia cannot be cured; however, the process of cognitive deterioration associated with dementia can be delayed with treatment. In many countries, cholinesterase inhibitors and memantine are registered for the treatment of cognitive impairment in dementia, particularly for Alzheimer's disease. Furthermore, a wide range of medication is used to address the behavioural and psychological symptoms of dementia.

Cholinesterase inhibitors are designed to improve cognitive functioning, global effect and neuropsychiatric symptoms in patients with dementia through enhancement of cholinergic neurotransmission (Birks et al., 2013). Internationally established cholinesterase inhibitors include donepezil, rivastigmine and galantamine. Memantine belongs to a different class of medications that is also used to treat dementia symptoms and functions as

an N-methyl-D-aspartate (NMDA) receptor antagonist, which targets cognitive processes, such as learning, memory and neuroplasticity (Blanke and VanDongen, 2009).

There has been a large amount of research published over the last few years that examines different aspects of the disease, ranging from diagnostic tests and treatment options to the organization of care. This scoping question aims to clarify the efficacy of cholinesterase inhibitors and memantine across different outcomes in order to inform guidelines for treatment of people with dementia in non-specialist health settings in low and middle-income countries (LAMICs).

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome (PICO)

- **Population:** Adults with dementia, including Alzheimer´s Disease, vascular dementia and dementia with Lewy bodies
- **Interventions:**
  - Donepezil
  - Galantamine
  - Rivastigmine
  - Memantine
- **Comparison:** Placebo or one AChEI vs. another AChEI
- **Outcomes:**
  - **Critical** – Cognitive functioning, functional status
  - **Important** – Behavioural disturbances, global effect, mortality, adverse effects

Search strategy

To identify relevant systematic reviews, the following databases were searched: MEDLINE, Embase, the Cochrane Library, BMJ Clinical Evidence and PsychINFO, up to and including September 2014. A search strategy that was developed by McMaster University[i] was used, and is as follows:

- (meta analysis [Publication Type] OR meta analysis[Title/Abstract] OR meta analysis[MeSH Terms] OR review[Publication Type] OR search*[Title/Abstract]).

Additional search terms were also used and are as follows:

- (dementia OR Alzheimer's disease OR vascular dementia OR dementia with Lewy bodies) AND (donepezil OR galantamine OR rivastigmine OR memantine).

In order to identify additional primary studies, the following search strategy was used:

- Cochrane Central Database of Controlled Trials (CENTRAL); (2) MEDLINE; (3) EMBASE.

The search terms used included the words:

- (dementia), (acetylcholinesterase inhibitors therapy) and names of the medications (donepezil OR galantamine OR rivastigmine OR memantine) in combination with any of the above words.

This search was supplemented by the McMaster University search strategy and is as follows:

- (randomized controlled trial[Publication Type] OR randomized[Title/Abstract] OR placebo[Title/Abstract]).

Additional terms used include:

- (dementia OR Alzheimer's OR vascular dementia OR dementia with Lewy bodies) AND (donepezil OR galantamine OR rivastigmine OR memantine).

Included in GRADE tables or footnotes

- Bond M, Rogers G, Peteres J, Anderson R, Hoyle M, Miners A, Moxham T, Davis S, Thokala P, Wailoo A, Jeffreys M, Hyde C (2012). The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer´s disease (review of Technology Appraisal no. 111): a systematic review and economic model. Health Technology Assessment.16(1):1-470. doi:10.3310/hta16210.

- Birks J, McGuiness B, Craig D (2013).. Rivastigmine for vascular cognitive impairment. Cochrane Database of Systematic Reviews.31;5:CD004744. doi:10.1002/14651858.CD004744.pub3.

- Di Santo SG, Prinelli F, Adorni F, Caltagirone C, Musicco M (2013). A meta-analysis of the efficacy of donepezil, rivastigmine, galantamine and memantine in relation to severity of Alzheimer´s Disease. Journal of Alzheimer's Disease.35(2):349-361. doi: 10.3233/JAD-122140.

- Kavirajan H and Schneider LS (2007). Efficacy and adverse effects of cholinesterase inhibitors and memantine in vascular dementia: a meta-analysis of randomised controlled trials. Lancet Neurology.6(9):782-792.

- Kim DH, Brown RT, Ding EL, Kiel DP, Berry SD (2011). Dementia medications and risk of falls, syncope, and related adverse events meta-analysis of randomized controlled trials. Journal of the American Geriatric Society.59(6):1019-1031. doi:10.1111/j.1532-5415.2011.03450.x.

- McShane R, Areosa Sastre A, Minakaran N (2006). Memantine for dementia. Cochrane Database of Systematic Reviews.2:CD003154.

- National Institute for Health and Care Excellence (NICE). 2006. *Appendix 20: Forest plots from the quantitative* reviews. In: Dementia: supporting people with dementia and their carers in health and social care [CG24]. [online]. London: NICE. Available from: https://www.nice.org.uk/guidance/cg42/evidence/cg42-dementia-guidance-appendix-202 (accessed Autumn 2014).

- Wang HF, Yu JT, Tang SW, Jiang T, Tan CC, Meng XF, Wang C, Tan MS, Tan L (2015). Efficacy and safety of cholinesterase inhibitors and memantine in cognitive impairment in Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies: systematic review with meta-analysis and trial sequential analysis. Journal of Neurology Neurosurgery and Psychiatry.86(2):135-143. doi:10.1136/jnnp2014-307659. (E-pub 2014 May 14, ahead of print).

Excluded from GRADE tables and footnotes

Aarsland D, Ballard C, Rongove A, Broadstock M, Svenningsson P (2012). Clinical Trials of Dementia with Lewy Bodies and Parkinson´s Disease Dementia. Current Neurology and Neuroscience Reports.12(5):492-501. doi:10.1007/s11910-012-0290-7.
REASON FOR EXCLUSION: The review provided only narrative description of studies and did not include meta-analysis (see p. 23 for an overview of findings).

Farrimond LE, Roberts E, McShane R (2012). Memantine and cholinesterase inhibitor combination therapy for Alzheimer´s disease: a systematic review. British Medical Journal Open.2(3). pii:e000917. doi:10.1136/bmjopen-2012-000917.
REASON FOR EXCLUSION: Combination therapy was not the intervention of interest.

Loveman E, Green C, Kirby J, Takeda A, Picot J, Payne E, Clegg A. The clinical and cost effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease, TA111. Southampton: University of Southampton; 2004.
REASON FOR EXCLUSION: The study is over 10 years old and does not add to the evidence already included in the evidence profile.

Molino I, Colucci L, Fasanaro AM, Traini E, Amenta F. Efficacy of Memantine, donepezil, or their association in moderate-severe Alzheimer´s Disease: A review of clinical trials. The Scientific World Journal. 2013:eCollection Article ID 925702. doi:10.1155/2013/925702.

REASON FOR EXCLUSION: The review provided only narrative description of studies and did not include meta-analysis (see p. 23 for an overview of findings).

Muayqil T, Camicioli R. Systematic Review and Meta-Analysis of combination therapy with cholinesterase inhibitors and memantine in Alzheimer´s Disease and other Dementias. Dementia and Geriatric Cognitive Disorders Extra. 2012;2(1):546-572. doi: 10.1159/000343479.
REASON FOR EXCLUSION: Combination therapy was not the intervention of interest.

National Institute of Clinical Excellence (NICE). *Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer´s disease*. In: NICE technology appraisal guidance [TA217]. [online]. London: NICE; 2011. Available from: http://www.nice.org.uk/guidance/ta217 (accessed Autumn 2014).
REASON FOR EXCLUSION: The review providied only narrative description of studies and did not include meta-analysis (see p. 23 for an overview of findings).

O´Brien JT and Burns A (2011). Clinical practice with anti-dementia drugs: a revised (second) consensus statement from the British Association for Psychopharmacology. Journal of Psychopharmacology.25(8):997-1019. doi:10.1177/0269881110387547.
REASON FOR EXCLUSION: The review providied only narrative description of studies and did not include meta-analysis (see p. 24 for an overview of findings).

Rolinski M, Fox C, Maidment I, McShane R (2012). Cholinesterase inhibitors for dementia with Lewy bodies, Parkinson's disease dementia and cognitive impairment in Parkinson's disease (Review). The Cochrane Database of Systematic Reviews.3:CD006504. doi:10.1002/14651858.CD006504.pub2.
REASON FOR EXCLUSION: Wang et al. (2015) provides a more comprehensive evidence base with its review of 10 trials vs. Rolinski et al.'s (2012) use of seven trials.

van de Glind EM, van Enst WA, van Munster BC, Olde Rikkert MG, Scheltens P, Scholten RJ, Hooft L (2013). Pharmacological treatment of Dementia: A scoping review of Systematic reviews. Dementia and Geriatric Cognitive Disorders.36(3-4):211-228. doi:10.1159/000353892.
REASON FOR EXCLUSION: The review providied only narrative description of studies and did not include meta-analysis (see p. 24 for an overview of findings).

Tricco AC, Soobiah C, Berliner S, Ho JM, Ng CH, Ashoor HM, Chen MH, Hemmelgarn B, Straus SE (2013). Efficacy and safety of cognitive enhancers for patients with mild cognitive impairment: a systematic review and meta-analysis. Canadian Medical Association Journal.185(16):1393-1401. doi:10.1503/cmaj.130451.
REASON FOR EXCLUSION: The population of interest for the scoping question is not patients with mild cognitive impairmen

[Updated 2015]

PICO Table*

Population 1: Adults with Alzheimer's Disease					
Intervention	**Comparison**	**Outcome**	**Systematic reviews used for GRADE**	**Justification for systematic review used**	**Relevant GRADE Table**
Donepezil Galantamine Rivastigmine Memantine	Placebo	Cognitive functioning Functional status Behavioural disturbances Global effect Mortality Adverse effects	Bond et al. (2012)	Recent systematic review examining the effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer´s disease.	Tables 1 -4
Population 2: Adults with vascular dementia					
Rivastigmine	Placebo	Cognitive functioning Functional status Behavioural disturbances Global effect Mortality Adverse effects	Birks et al. (2013)	Recent systematic review assessing the efficacy of rivastigmine compared with placebo in the treatment of people with cognitive impairment (VCI), vascular dementia or mixed dementia.	Tables 5
Rivastigmine Donepezil	Placebo	Cognitive functioning Global effect Adverse effects	Kavirajan and Schneider (2007)/ NICE (2006)	Recent systematic review examining the effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of vascular dementia.	Tables 6-8

Galantamine Memantine					
Population 3: Adults with dementia with Lewy bodies					
Cholinesterase inhibitors; or Memantine	Placebo	Global effect Cognitive functioning All-cause dropouts	Wang et al. (2014)	Recent systematic review providing updated evidence for treatments of cognitive impairment in Parkinnson's disease, Parkinson's disease dementia and dementia with Lewy bodies.	Table 9-11
Population 4: Adults with all types of dementia (e.g., Alzheimer's Disease, vascular dementia, dementia with Lewy bodies)					
Cholinesterase inhibitors	Placebo	Adverse effects: 1. Fall 2. Syncope 3. Fracture 4. Accidental injury	Kim et al. (2011)	Recent systematic review evaluating the effects of cholinesterase inhibitors and memantine in people with dementia on specified adverse effects.	Table 12
Memantine	Placebo	Adverse effects: 1. Fall 2. Syncope 3. Fracture 4. Accidental injury	Kim et al. (2011)	Recent systematic review evaluating specific adverse events associated with the use of AChEIs[ii] and memantine in the treatment of dementia.	Table 13

Narrative description of the studies that went into analysis

Bond et al.'s (2012) systematic review aimed to review and update the National Institute for Health and Clinical Excellence (NICE) guidelines to the National Health Service (NHS) in England and Wales (issued November 2006, amended September 2007 and August 2009) on the clinical effectiveness and cost-effectiveness of donepezil, galantamine and rivastigmine for mild-to-moderate Alzheimer's disease (AD), and of memantine for moderate-to-severe AD. The authors provide an overview of the previous guidelines and report on new evidence from 2004 to 2012. The clinical effectiveness systematic review was undertaken following the principles published by the NHS Centre for Reviews and Dissemination. Four systematic reviews and 17 RCTs[iii] were identified, which included 12 pair-wise comparisons with placebo (donepezil 5, *n* = 234; galantamine 3, *n* = 1386; rivastigmine 3, *n* = 1995; and memantine 1, *n* = 350), four head-to-head studies and one combination therapy study (memantine added to AChEIs). The quality of the trials was low.

Placebo comparisons: – In addition to the 2009 guidelines, new evidence included in this systematic review include five small poor-quality donepezil studies; three variable-quality RCTs of galantamine versus placebo; three new rivastigmine studies (one of these was of reasonable size and quality); and a new memantine (poorer-quality) study. Only one of these new studies was large and of reasonable quality, comparing donepezil to rivastigmine.

Head to head comparisons: One new study and one earlier study compared donepezil with galantamine, but neither was of good quality. There was also one very poor-quality study included that looked at behavioural outcomes compared all three AChEIs.

Combination therapies: This meta-analysis also found one new, reasonably good study comparing combined memantine with an AChEI vs. AChEI and placebo. The effectiveness evidence suggests that there is a clinical benefit from the AChEIs in alleviating AD symptoms, although there is debate about the magnitude of the effect. While there is also new evidence on the effectiveness of memantine, it remains less supportive of the utility of this medication than the evidence for AChEIs.

Dementia severity of the participants: "Participants in included trials were required to meet the definitions of disease severity specified in the technologies' UK marketing authorisations (**MMSE 26–10 for donepezil, galantamine and rivastigmine; MMSE 20–0 for memantine**)."

Birks et al. (2013) carried out a meta-analysis to assess the efficacy of rivastigmine compared with placebo in the treatment of people with vascular cognitive impairment (VCI), vascular dementia or mixed dementia. Three trials with a total of 800 participants were identified for inclusion. The participants in one trial did not have dementia, while the other two studies included participants with dementia of different severities. The dose of rivastigmine was different in each study. No pooling of study results was possible because of the heterogeneity between the studies.

Participants' dementia severity: "Patients diagnosed as **having VCI, dementia or mixed dementia on a basis of standardized diagnostic criteria,** such as the ADDTC (California State Alzheimer's disease Diagnostic and Treatment Center) (Chui 1992), NINDS/AIREN (National Institute of

Neurological Disorders and Stroke and the Association International pour la Recherche et l'Enseignement en Neurosciences) (Roman 1993) and ICD-10 (International Classification of Diseases of the World Health Organization) (WHO 1992), were eligible for inclusion. Diagnosis of VCI with no dementia was based on scores on cognitive impairment scales."

Di Santo et al. (2013) does not add new evidence to the findings of Bond et al. (2012). As well, Bond et al. (2012) is more complete and discusses this topic in more detail. It is for these reasons that the Di Santo et al. (2013) was not GRADEd; however, it is referred to in GRADE Table 1 in a comment regarding consistency. The objective of the Di Santo et al. (2013) study was to verify whether the efficacy of pharmacological treatment had any dependence on the severity of dementia in AD patients. A systematic review was carried out including randomized placebo-controlled trials evaluating the efficacy of cholinesterase inhibitors or memantine at any dose, over any length of time, in patients with any severity of dementia due to AD. Outcomes were extracted from each study and pooled to obtain a unique indicator of efficacy for cognition, functional impairment and behavioural and psychological disturbances. Relationships between size of the treatment effect and severity of dementia, as measured with the Mini-Mental State Examination, were determined using parametric and non-parametric correlation analyses. Both cholinesterase inhibitors and memantine had significant effects on cognition. Functional and psycho-behavioural outcomes were reported less frequently, but also showed significant efficacy of treatment. High heterogeneity among studies was found within and between the different medications. The efficacy of all medications except memantine was independent from dementia severity in all domains. Memantine effect on functional impairment was better in more severe patients. In conclusion, the modest beneficial effects of anti-dementia medications on cognition are independent from dementia severity. Memantine is more effective in improving functional impairment only in severe patients.

Dementia **severity of participants**: "Most studies recruited subjects with MMSE scores around 18, fewer studies investigated patients with MMSE scores of 10 or below."

Kayirajan and Schneider (2007) conducted a systematic review and meta-analysis to assess the evidence for efficacy and safety of cholinesterase inhibitors and memantine in vascular dementia. The authors searched PubMed, BIOSIS, International Pharmaceutical Abstracts and Cochrane registries for randomised placebo-controlled trials on cholinesterase inhibitors and memantine in patients with vascular dementia. Trial methods, clinical characteristics, outcomes and adverse events were extracted and checked. Meta-analytic methods using fixed-effects models were used to give summaries of each medicationseffects.Three donepezil, two galantamine, one rivastigmine and two memantine trials (comprising 3093 patients on the study medications and 2090 patients on placebo) met the selection criteria. Trials were of 6-month duration with similar vascular dementia criteria and outcome measures.

Cognitive effects on the Alzheimer's Disease Assessment scale were significant for all medications, ranging from a −1·10 point mean difference (95% CI −2.15 to −0.05) for rivastigmine to −2.17 for 10mg daily donepezil (95% CI −2.98 to −1.35). Only 5mg daily donepezil had an effect on the Clinical Global Impression of Change (CGIC) scale (OR 1.51 [95% CI 1.11–2.07]). No behavioural or functional benefits were observed, except for a −0.95 point difference (95% CI −1.74 to −0.16) with 10 mg daily donepezil on the Alzheimer's Disease Functional Assessment and Change Scale. Compared with

placebo, more dropouts and adverse events (e.g., anorexia, nausea, vomiting, diarrhoea and insomnia) occurred with the cholinesterase inhibitors, but not with memantine. The authors found that cholinesterase inhibitors and memantine produce small benefits in cognition of uncertain clinical significance in patients with mild to moderate vascular dementia. However, the data are insufficient to support widespread use of these medications in vascular dementia and the identification of subgroups of patients with vascular dementia who might benefit will require individual patient analyses.

McShane et al. (2006) is a Cochrane review aimed at determining the efficacy and safety of memantine for people with AD, vascular dementia and mixed dementia. The Specialized Register of the Cochrane Dementia and Cognitive Improvement Group was searched on 8 February 2006. This register contains references from all major healthcare databases and many ongoing trial databases and is updated regularly. Additionally, the search engines Copernic and Google were used to identify unpublished trials through inspection of the websites of licensing bodies, such as the FDA[iv], EMA[v] and NICE, and pharmaceutical company websites (e.g., Lundbeck, Merz, Forest, Suntori, etc.) and clinical trials registries. The selection criteria included double-blind, parallel group and placebo-controlled randomized trials of memantine in people with dementia. Data were pooled where possible. Intention-to-treat (ITT) and observed case (OC) analyses are reported.

The main results of McShane et al.'s (2006) review showed that two out of three 6-month studies show a small beneficial effect of memantine for moderate to severe AD. Pooled data indicate a beneficial effect at 6 months on cognition, activities of daily living and behaviour, which are supported by CGIC. For mild to moderate AD, pooled data from three unpublished studies indicate a marginal beneficial effect at 6 months on ITT cognition, which was barely detectable clinically, but no effect on behaviour, activities of daily living or OC analysis of cognition. In patients with mild to moderate vascular dementia, pooled data from two 6-month studies indicated a small beneficial effect of memantine on cognition and behaviour; however, this was not supported by CGIC. Patients taking memantine were slightly less likely to develop agitation. This effect was slightly larger, yet still small, in moderate to severe AD. There is no evidence either way about whether it has an effect on agitation that is already present. Finally, memantine is well tolerated.

Wang et al. (2014) carried out a meta-analysis of randomized controlled trials investigating the efficacy of treatments for cognitive impairment in people with dementia due to Parkinson's disease and dementia with Lewy bodies. A systematic search gave rise to the inclusion of 10 trials eligible for analysis. Cholinesterase inhibitors and memantine produced small global efficacy on CGIC; however, cholinesterase inhibitors, but not memantine, significantly improved cognition on Mini-Mental State Examination. Additionally, both cholinesterase inhibitors and memantine had good safety profiles, although rivastigmine showed an increased risk on mild or moderate adverse events than placebo. All of the medications included have good safety profiles, but the limitations of trials precluded the generalisation of these outcomes.

Dementia severity of participants: "Mean Mini-Mental State Examination (**MMSE**) scores at baseline were **17.9–21.7** in trials, indicating that all included patients were similar on dementia severity (**mild to moderate**)."

Kim et al. (2011) conducted a meta-analysis of 54 randomized placebo-controlled trials and extension studies investigating the use of cholinesterase inhibitors and memantine and increased risk of reported falls, syncope and related events in cognitively-impaired older adults (including those with AD, vascular dementia, dementia with Lewy bodies, Parkinson's disease dementia and mild cognitive impairment). The authors found that cholinesterase inhibitor use was associated with an increased risk of syncope, but not with other events, when compared to placebo. Memantine use was associated with fewer fractures, but not with other events. There was no differential effect by type and severity of cognitive impairment, residential status, nor in terms of length of follow-up. However, due to underreporting and a small number of events, potential benefits or risk cannot be excluded.

Dementia severity of participants: "The study participants averaged 69 to 86 years of age, were 15% to 67% male and had mean MMSE scores of **6 to 27**."

[Updated 2015]

GRADE Tables

Table 1. Donepezil vs. placebo for treatment of Alzheimer's disease

Authors: E Castro-Costa and M Harper
Question: Should donepezil vs. placebo be used for the treatment of Alzheimer's disease?
Bibliography: Bond M, Rogers G, Peteres J, Anderson R, Hoyle M, Miners A, Moxham T, Davis S, Thokala P, Wailoo A, Jeffreys M, Hyde C (2012). The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer´s disease (review of Technology Appraisal no. 111): a systematic review and economic model. Health Technology Assessment.16(1):1-470. doi:10.3310/hta16210.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Donepezil**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Cognitive function (measured with ADAS-cog[vi] at 12 weeks 10mg/day; better indicated by lower values)												
3[1]	Randomized trials	Serious[2]	Very serious[3]	No serious indirectness	Serious[4]	None	522	522	-	MD[vii] 1.97 lower (3.38 to 0.56 lower)	⨁⨁⨁◯ VERY LOW	CRITICAL
Cognitive function (measured with ADAS-cog at 24 weeks/10mg; better indicated by lower values)												

2[5]	Randomized trials	Very serious[6]	No serious inconsistency	No serious indirectness	Serious[4]	None	423	427	-	MD 2.89 lower (3.61 to 2.18 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Cognitive function (measured with MMSE at 12 weeks/ 10mg/day; better indicated by higher values)												
8[7]	Randomized trials	Very serious[2]	No serious inconsistency	No serious indirectness	Serious[4]	None	996	1020	-	MD 1.17 higher (0.88 to 1.45 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Cognitive function (measured with MMSE at 24 weeks/ all dosages; better indicated by higher values)												
7[8]	Randomized trials	Very serious[6]	No serious inconsistency	No serious indirectness	Serious[4]	None	953	780	-	MD 1.21 higher (0.84 to 1.57 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Cognitive function (measured with cognitive function - all cognitive outcomes at 24-26 weeks/ all dosages; better indicated by higher values)												
9[9]	Randomized trials	Very serious[10]	No serious inconsistency	No serious indirectness	No serious imprecision	None	1426	959	-	MD 0.4 higher (0.29 to	⨁◯◯◯ LOW	CRITICAL

										0.5 higher)		
Functional status (measured with all functional outcomes at 24 weeks/ all dosages; better indicated by higher values)												
5[11]	Randomized trials	Very serious[2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	905	642	-	MD 0.30 higher (0.14 to 0.45 higher)	⨁⨁◯◯ LOW	CRITICAL
Behavioural and mood disturbances (measured with NPI[viii] at 12 weeks/10mg/day; better indicated by lower values)												
4[12]	Randomized trials	Very serious[2]	Serious[13]	No serious indirectness	Very serious[4,14]	None	456	397	-	MD 2.25 lower (5.11 lower to 0.61 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Behavioural and mood disturbances (measured with NPI at 24 weeks/ 10mg/day; better indicated by lower values)												
2[15]	Randomized trials	Very serious[6]	Serious[16]	No serious indirectness	Very serious[4,14,17]	None	306	329	-	MD 3.12 lower (8.17 lower to 1.93 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

Global effect (measured with CIBIC-plus[ix] at 12 weeks - 10mg/day; better indicated by lower values)												
3[18]	Randomized trials	Very serious[2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	514	520	-	MD 0.38 lower (0.49 to 0.26 lower)	⨁⨁⨁◯ LOW	IMPORTANT
Global effect (measured with CIBIC-plus at 24 weeks - 10mg/day; better indicated by lower values)												
3[19]	Randomized trials	Very serious[2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	520	531	-	MD 0.43 lower (0.55 to 0.31 lower)	⨁⨁⨁◯ LOW	IMPORTANT
Global effect (measured with CDR[x] at 12 weeks; better indicated by lower values)												
3[20]	Randomized trials	Very serious[2,21]	No serious inconsistency	No serious indirectness	No serious imprecision	None	970	536	-	MD 0.26 lower (0.44 to 0.09 lower)	⨁⨁⨁◯ LOW	IMPORTANT
Global effect (measured with CDR at 24 weeks - all dosages; better indicated by lower values)												

3[22]	Randomized trials	Very serious[2,23]	Serious[24]	No serious indirectness	No serious imprecision	None	965	539	-	MD 0.57 higher (0.85 to 0.29 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Global effect (measured with global outcomes at 24-26 weeks - all dosages; better indicated by lower values)												
6[25]	Randomized trials	Very serious[2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	1285	874	-	MD 0.38 higher (0.27 to 0.48 higher)	⨁◯◯◯ LOW	IMPORTANT

[1] From Figure 7 of Bond et al. (2012). Please note that Di Santo et al. (2013) demonstrated the modest beneficial effects of anti-dementia medications on cognition are independent from dementia severity. The study conclusion was that the modest beneficial effects of anti-dementia medications on cognition are independent from dementia severity. Memantine is more effective on functional incompetence only in severe patients. In the treatment of AD, cholinesterase inhibitors and memantine can modestly improve symptoms in the domains of cognition and activities of daily living, and seem to have beneficial effects on BPSD[xi]. Results also show that patients in different stages of AD retain the ability to respond to treatment with cholinergic agents and memantine. Medication effects are substantially independent from disease severity and patients with a wide range of disease severities can benefit from medications therapy. The severity of a patient's illness should not preclude the treatment with AChE-Is and/or memantine.

[2] None or very few of the primary studies report random allocation and they report no or partial blinding (see Figure 20 of Bond et al. (2012)).

[3] Heterogeneity exceeds 75% (I squared =75.5%).

[4] Wide confidence interval (WHO considers a CI of >0.5 for continuous data and >2 for dichotomous data as wide)..

[5] From Figure 8 of Bond et al. (2012).

[6] No explanation was provided.

[7] From Figure 9 of Bond et al. (2012).

[8] From Figure 10 of Bond et al. (2012).

[9] From Figure 11 of Bond et al. (2012).

[10] Three out of nine studies have a dropout rate between 10- 30%. The studies contributing to more than 30% of the pooled data (Burns et al 1999 and Rogers et al 1998) do not report random allocation and report only partial blinding (see figure 20 of Bond et al. (2012))
[11] From Fig. 12 of Bond et al. (2012).
[12] From Figurere 13 of Bond et al. (2012).
[13] Heterogeneity between 50-75% (I squared= 64.7%).
[14] The 95% CI includes no effect.
[15] From Figure 14 of Bond et al. (2012).
[16] Heterogeneity between 50-75% (I squared= 74.0%).
[17] The 95% CI includes no effect (p=0.226).
[18] From Figure 15 of Bond et al. (2012).
[19] From Figure 16 of Bond et al. (2012).
[20] From Figure 17 of Bond et al. (2012).
[21] Two out of three studies have dropout rate between 10%- 30%.
[22] From Figure 18 of Bond et al. (2012).
[23] Two out of three studies have dropout rate higher than 30%.
[24] Heterogeneity between 50-75% (I squared= 62.7%).
[25] From Figure 18 of Bond et al. (2012).

Table 2. Galantamine vs. placebo for treatment of Alzheimer's disease

Authors: E Castro-Costa and M Harper
Question: Should galantamine vs. placebo be used for treatment of Alzheimer's disease?
Bibliography: Bond M, Rogers G, Peteres J, Anderson R, Hoyle M, Miners A, Moxham T, Davis S, Thokala P, Wailoo A, Jeffreys M, Hyde C (2012). The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer´s disease (review of Technology Appraisal no. 111): a systematic review and economic model. Health Technology Assessment.16(1):1-470. doi:10.3310/hta16210.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Galantamine**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Cognitive function (measured with ADAS-cog at 12 weeks - maximum dose <24mg/day; better indicated by lower values)												
7[1]	Randomized trials	Serious[2]	No serious inconsistency	No serious indirectness	Serious[3]	None	1739	1081	-	MD 2.38 lower (2.8 to 1.96 lower)	⨁⨁⨁◯ LOW	CRITICAL
Cognitive function (measured with ADAS-cog at 21-26 weeks - maximum dose <26mg/day; better indicated by lower values)												
5[4]	Randomized trials	Serious[5]	No serious inconsistency	No serious indirectness	Serious[3]	None	1788	1056	-	MD 2.95 lower (3.41 to	⨁⨁⨁◯ LOW	CRITICAL

										2.51 lower)		
Functional status (measured with ADCS-ADL[xii] at 12-13 weeks - maximum dose < 24mg/day; better indicated by higher values)												
2[6]	Randomized trials	Very serious[7]	No serious inconsistency	No serious indirectness	Serious[3]	None	1085	516	-	MD 1.39 higher (0.59 to 2.19 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Functional status (measured with ADCS-ADL at 21-26 weeks - maximum dose <24mg/day; better indicated by higher values)												
2[8]	Randomized trials	Very serious[7]	No serious inconsistency	No serious indirectness	Serious[3]	None	1124	520	-	MD 2.23 higher (1.32 to 3.14 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Functional status (measured with DAD[xiii] at 21-26 weeks - maximum dose <24mg/day; better indicated by higher values)												
2[9]	Randomized trials	Very serious[10]	No serious inconsistency	No serious indirectness	Serious[3]	None	614	307	-	MD 3.76 higher (1.66 to 3.86 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Functional status (measured with all outcomes at 21-26 weeks - all dosages; better indicated by lower values)												

4[11]	Randomized trials	Very serious[1,2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	1738	827	-	MD 0.27 higher (0.18 to 0.35 higher)	⨁⨁⨁◯ LOW	CRITICAL
Behavioural and mood disturbances (measured with NPI at 13 weeks all dosages; better indicated by lower values)												
2[13]	Randomized trials	Very serious[1,4]	No serious inconsistency	No serious indirectness	Very serious[3,15]	None	770	357	-	MD 0.74 lower (1.83 lower to 0.34 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Behavioural and mood disturbance (measured with NPI at 21-26 weeks - all dosages; better indicated by lower values)												
2[16]	Randomized trials	Very serious[1,7]	No serious inconsistency	No serious indirectness	Serious[3]	None	1124	520	-	MD 1.46 lower (2.59 to 0.34 lower)	⨁◯◯◯ VERY LOW	IMPORTANT
Global effect (measured with CIBIC-plus at 26 weeks - maximum dose <24mg; better indicated by lower values)												
3[18]	Randomized trials	Serious[1,9]	No serious inconsistency	No serious indirectness	No serious imprecision	None	999	712	-	MD 0.20 lower (0.30 to	⨁⨁⨁◯ MODERATE	IMPORTANT

										0.09 lower)		

[1] From Fig. 23 of Bond et al. (2012).
[2] Three out of seven studies have a dropout rate between 10%- 30%.
[3] Wide confidence interval (WHO considers a CI of >0.5 for continuous data and >2 for dichotomous data as wide).
[4] From Fig. 24 of Bond et al. (2012).
[5] Three out of five studies have a dropout rate between 10% - 30% and between 10 and 30% of primary studies are not described as having blinded the assessor.
[6] From Fig. 25 of Bond et al. (2012).
[7] All two studies have a dropout rate between 10% to 30%; and Tariot et al., (contributing to over 30% of pooled effect) did not blind the assessor (see Fig. 32 in Bond et al. (2012)).
[8] From Fig. 26 of Bond et al. (2012).
[9] From Fig. 27 of Bond et al., 2012
[10] One out of two studies have a dropout rate between 10% to 30%; and Bullock et al. (contributing to more than 30% of the pooled evidence) did not blind the assessor (see Fig. 32 from Bond et al. (2012)).
[11] From Fig. 28 of Bond et al. (2012).
[12] All four studies have a dropout rate between 10% to 30%; and Tariot et al. (contributing to over 30% of pooled effect) did not blind the assessor (see Fig. 32 in Bond et al (2012)).
[13] From Fig. 29 of Bond et al. (2012).
[14] All of two studies have a dropout rate between 10% to 30%; and Tariot et al. (contributing to over 30% of pooled effect) did not blind the assessor (see Fig. 32 in Bond et al. (2012)).
[15] The confidence interval crosses the line of no effect (sse Fig. 29 in Bond et al. (2012)).
[16] From Fig. 30 of Bond et al. (2012).
[17] All two studies have a dropout rate between 10% to 30%; and Tariot et al. (contributing to over 30% of pooled effect) did not blind the assessor (see Fig. 32 in Bond et al (2012)).
[18] From Fig. 31 of Bond et al. (2012).
[19] One out of 3 studies have a dropout rate between 10% to 30%.

[Updated 2015]

Table 3. Rivastigmine vs. placebo for treatment of Alzheimer's disease

Authors: E Castro-Costa and M Harper
Question: Should rivastigmine vs. placebo be used for treatment of Alzhimer's disease?
Bibliography: Bond M, Rogers G, Peteres J, Anderson R, Hoyle M, Miners A, Moxham T, Davis S, Thokala P, Wailoo A, Jeffreys M, Hyde C (2012). The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer´s disease (review of Technology Appraisal no. 111): a systematic review and economic model. Health Technology Assessment.16(1):1-470. doi:10.3310/hta16210.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Rivastigmine**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Cognitive function (measured with ADAS-cog at 24-26 weeks maximum dose >12mg/day; better indicated by lower values)												
4[1]	Randomized trials	Very serious[2]	Serious[3]	No serious indirectness	Serious[4]	None	1443	973	-	MD 2.46 lower (3.37 to 1.55 lower)	⨁◯◯◯ VERY LOW	CRITICAL
Cognitive function (measured with MMSE at 24-26 weeks; better indicated by higher values)												
2[5]	Randomized trials	Very serious[2]	No serious inconsistency	No serious indirectness	Serious[4]	None	972	501	-	MD 1.02 higher (0.63 to	⨁◯◯◯ VERY LOW	CRITICAL

										1.41 higher)		
Cognitive function (measured with all cognitive measures at 24-26 weeks - all dosages; better indicated by lower values)												
4[6]	Randomized trials	Very serious[2]	Serious[7]	No serious indirectness	No serious imprecision	None	2144	961	-	MD 0.28 higher (0.14 to 0.42 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Functional status (measured with PDS[xiv] at 24-26 weeks maximum dose >12mg; better indicated by higher values)												
3[8]	Randomized trials	Very serious[2]	No serious inconsistency	No serious indirectness	Serious[4]	None	683	455	-	MD 3.10 higher (1.8 to 4.4 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Functional status (measured with all functional status outcomes at 24-26 weeks all dosages; better indicated by lower values)												
3[9]	Randomized trials	Very serious[2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	1680	736	-	MD 0.21 higher (0.12 to 0.29 higher)	⨁◯◯◯ LOW	CRITICAL

Global effect (measured with CIBIC-plus at 26 weeks - 12mg/day; better indicated by lower values)												
3[10]	Randomized trials	Very serious[2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	894	680	-	MD 0.42 lower (0.55 to 0.29 lower)	⨁⨁⨁◯ LOW	IMPORTANT
Global effect (measured with GDS[xv] at 26 weeks - 12mg/day; better indicated by lower values)												
3[11]	Randomized trials	Very serious[2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	929	694	-	MD 0.19 higher (0.11 to 0.27 higher)	⨁⨁⨁◯ LOW	IMPORTANT
Global effect (measured with all global outcomes - all dosage; better indicated by lower values)												
4[12]	Randomized trials	Very serious[2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	0	-	-	MD 0.23 higher (0.16 to 0.31 higher)	⨁⨁⨁◯ LOW	IMPORTANT

[1] From Fig. 34 of Bond et al. (2012).
[2] Outcome assessment not blinded in more than 30% of the pooled evidence and allocation was not randomized in Fieldman and Lane (2007) (weight more than 10% of pooled evidence).
[3] Heterogeneity between 50-75% (I squared= 62.6%).
[4] Wide confidence interval (WHO considers CI >0.5 for continuous data and >2 for dichotomous data as wide).
[5] From Fig 35 of Bond et al. (2012).

[6] From Fig 36 of Bond et al. (2012).
[7] Heterogeneity between 50-75% (I squared= 70.1%).
[8] From Fig. 37 of Bond et al. (2012).
[9] From Fig. 38 of Bond et al. (2012).
[10] From Fig. 39 of Bond et al. (2012).
[11] From Fig. 40 of Bond et al. (2012).
[12] From Fig. 41 of Bond et al. (2012).

Table 4. Memantine vs. placebo for treatment of Alzheimer's disease

Authors: E Castro-Costa and M Harper
Question: Should memantine vs. placebo be used for treatment of Alzheimer's disease?
Bibliography: Bond M, Rogers G, Peteres J, Anderson R, Hoyle M, Miners A, Moxham T, Davis S, Thokala P, Wailoo A, Jeffreys M, Hyde C (2012). The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer´s disease (review of Technology Appraisal no. 111): a systematic review and economic model. Health Technology Assessment.16(1):1-470. doi:10.3310/hta16210.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Memantine**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Cognitive function (measured with SIB[xvi] at 12 weeks; better indicated by higher values)												
2[1]	Randomized trials	Very serious[2]	Very serious[3]	No serious indirectness	Serious[4]	None	253	256	-	MD 4.15 higher (0.51 to 7.78 higher)	⨁⨁◯◯ VERY LOW	CRITICAL

Cognitive function (measured with SIB at 24-28 weeks; better indicated by lower values)												
2[5]	Randomized trials	Very serious[2]	Very serious[6]	No serious indirectness	Very serious[4,7]	None	294	288	-	MD 3.24 higher (2.23 lower to 8.74 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Functional status (measured with ADCS-ADL at 12 weeks; better indicated by higher values)												
2[8]	Randomized trials	Very serious[2]	No serious inconsistency	No serious indirectness	Very serious[4,7]	None	254	256	-	MD 0.88 higher (0.09 lower to 1.84 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Functional status (measured with ADCS-ADL 24 to 28 weeks; better indicated by higher values)												
2[9]	Randomized trials	Very serious[2]	No serious inconsistency	No serious indirectness	Serious[4]	Reporting bias[10]	295	288	-	MD 1.41 higher (0.04 to 2.78 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Functional status (measured with FAST[xvii] at 24-28 weeks; better indicated by lower values)												

2[11]	Randomized trials	Very serious[2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	272	259	-	MD 0.34 lower (0.55 to 0.12 lower)	⨁⨁⨁◯ LOW	CRITICAL
Behavioural and mood disturbances (measured with NPI at 24-28 weeks; better indicated by lower values)												
2[12]	Randomized trials	Very serious[2]	No serious inconsistency	No serious indirectness	Very serious[4,7]	None	281	273	-	MD 1.61 lower (4.74 lower to 1.52 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Global effect (measured with CIBIC-plus at 24-28 weeks; better indicated by lower values)												
2[13]	Randomized trials	Very serious[2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	289	281	-	MD 0.30 lower (0.47 to 0.13 lower)	⨁⨁⨁◯ LOW	IMPORTANT

[1] From Fig. 43 of Bond et al. (2012).
[2] Neither of the primary studies fully randomly allocated patients nor did either of them blind the assessor (see Fig.50 from Bond et al. (2012)).
[3] Heterogeneity exceeds 75% ($I^2$75.1%).
[4] Wide confidence interval (WHO considers >0.5 for continuous and >2 for dichotomous data as wide).
[5] From Fig. 44 of Bond et al. (2012).
[6] Heterogeneity exceeds 75% (I squared 85.6%).
[7] The 95% CI crosses the line of no effect.

[8] From Fig 45 of Bond et al. (2012).
[9] From Fig 46 of Bond et al. (2012).
[10] Two trials only.
[11] From Fig 47 of Bond et al. (2012).
[12] From Fig 48 of Bond et al. (2012).
[13] From Fig 49 of Bond et al. (2012).

Table 5. Cholinesterase inhibitors vs. placebo for treatment of vascular dementia.

Authors: T Dua and C Barbui
Question: Should cholinesterase inhibitors vs. placebo be used for treatment of vascular dementia?
Bibliography: Kavirajan H and Schneider LS (2007). Efficacy and adverse effects of cholinesterase inhibitors and memantine in vascular dementia: a meta-analysis of randomised controlled trials. Lancet Neurology.6(9):782-792

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Cholinesterase inhibitors**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Cognitive function - ADAS-cog (better indicated by lower values)												
3[1]	Randomized trials	Serious[2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	588	472	-	MD 2.36 lower (3.07 to 1.66 lower)	⨁⨁⨁◯ MODERATE	CRITICAL
Cognitive function - MMSE (better indicated by lower values)												

0	No evidence available					None	0	-	-	MD 0 higher (0 to 0 higher)		CRITICAL
Number of patients improved (global assessment)												
1[3]	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias[4]	140/195 (71.8%)	134/194 (69.1%)	RR 1.04 (0.91 to 1.18)	28 more per 1000 (from 62 fewer to 124 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Behavioural disturbances (better indicated by lower values)												
1[5]	Randomized trials	No serious risk of bias	No serious inconsistency	Serious[6]	Serious[7]	Reporting bias[8]	279	154	-	Weighted mean difference 2.20 lower (4.32 to 0.08 lower)	⨁◯◯◯ VERY LOW	IMPORTANT
Functional status (better indicated by lower values)												

0	No evidence available					none	0	-	-	MD 0 higher (0 to 0 higher)		CRITICAL
Mortality												
3[9]	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[10]	None	12/817 (1.5%)	10/588 (1.7%)	RR 0.88 (0.4 to 1.97)	2 fewer per 1000 (from 10 fewer to 16 more)	⨁⨁◯◯ LOW	IMPORTANT
Treatment acceptability (total dropouts)												
3[11]	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	213/817 (26.1%)	95/588 (16.2%)	RR 1.61 (1.29 to 2.01)	99 more per 1000 (from 47 more to 163 more)	⨁⨁⨁⨁ HIGH	IMPORTANT
Treatment acceptability (dropouts due to adverse events)												

3[11]	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	159/817 (19.5%)	55/588 (9.4%)	RR 2.10 (1.57 to 2.82)	103 more per 1000 (from 53 more to 170 more)	⨁⨁⨁⨁ HIGH	IMPORTANT
Adverse events												
3[12]	Randomized trials	No serious risk of bias	Serious[13]	No serious indirectness	No serious imprecision	None	722/817 (88.4%)	476/588 (81%)	RR 1.11 (1.02 to 1.2)	89 more per 1000 (from 16 more to 162 more)	⨁⨁⨁◯ MODERATE	IMPORTANT

[1] From page 39 of Appendix 20 of NICE (2006).
[2] The analysis adopted an observed-case approach and not an intention-to-treat approach,
[3] From page 37 of Appendix 20 of NICE (2006).
[4] Only one study reported this outcome, so reporting bias is possible,
[5] From page 41 of Appendix 20 of NICE (2006).
[6] Only one study contributed to the analysis.
[7] The confidence interval ranges from appreciable benefit to almost no difference.
[8] Only one study contributed to the analysis so reporting bias might have occurred.
[9] From page 43 of Appendix 20 of NICE (2006).
[10] The 95% confidence interval includes no effect and ranges from appreciable benefit to appreciable harm.
[11] From page 50 of Appendix 20 of NICE (2006).
[12] From page 42 of Appendix 20 of NICE (2006).
[13] Heterogeneity exceeds 50% (I^2 = 73.6%).

Table 6. Memantine vs. placebo for treatment of vascular dementia

Authors: T Dua and C Barbui
Question: Should memantine vs. placebo be used for treatment of vascular dementia?
Bibliography:

- Kavirajan H and Schneider LS (2007). Efficacy and adverse effects of cholinesterase inhibitors and memantine in vascular dementia: a meta-analysis of randomised controlled trials. Lancet Neurology.6(9):782-792; and
- McShane R, Areosa Sastre A, Minakaran N (2006). Memantine for dementia. Cochrane Database of Systematic Reviews.2:CD003154.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Memantine**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Cognitive function - ADAS-cog (Better indicated by higher values)												
2[1]	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	413	402	-	MD 1.85 higher (0.88 to 2.83 higher)[2]	⨁⨁⨁⨁ HIGH	CRITICAL
Cognitive function - MMSE (Better indicated by lower values)												

0	No evidence available					None	0	-	-	MD 0 higher (0 to 0 higher)		CRITICAL
Number of patients improved (global assessment)												
1[3]	Randomized trials	No serious risk of bias	No serious inconsistency	Serious[4]	Serious[5]	None	88/147 (59.9%)	74/141 (52.5%)	OR 1.34 (0.85 to 2.15)	72 more per 1000 (from 41 fewer to 179 more)	⨁◯◯◯ LOW	IMPORTANT
Behavioural disturbances (better indicated by higher values)												
2[6]	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[7]	None	287	254	-	MD 0.48 higher (0.06 to 0.91 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Functional status (activities of daily living) (better indicated by higher values)												
2[8]	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[9]	None	285	257	-	MD 0.12 higher (0.43 lower to	⨁⨁⨁◯ MODERATE	CRITICAL

										0.67 higher)		
Mortality												
0	No evidence available					None	-	-	-	-		IMPORTANT
Treatment acceptability (total dropouts)												
0	No evidence available					None	-	-	-	-		IMPORTANT
Treatment acceptability (dropouts due to adverse events)												
0	No evidence available					None	-	-	-	-		IMPORTANT
Adverse events												
0	No evidence available					None	-	-	-	-		IMPORTANT

[1] From Analysis 3.2 of McShane et al (2006).
[2] Kavirajan and Schneider (2007) identified two trials for memantine and calculated a mean difference of -1.86 (-2.79 to -0.94).
[3] From Figure 3 of Kavirajan and Schneider (2007).

[4] Only one study was included in this analysis.
[5] Estimate ranges from appreciable benefit to appreciable harm.
[6] From Analysis 3.4 of McShane et al (2006).
[7] The confidence interval ranges from appreciable benefit to almost no difference.
[8] From Analysis 3.3 of McShane et al (2006).
[9] The 95% confidence interval ranges from appreciable benefit to appreciable harm.

Table 7. AChEIs vs. placebo for treatment of vascular dementia

Authors: E Castro-Costa and M Harper
Question: Should rivastigmine vs. placebo be used for treatment of vascular dementia?
Bibliography: Birks J, McGuiness B, Craig D (2013). Rivastigmine for vascular cognitive impairment. Cochrane Database of Systematic Reviews.31;5:CD004744. doi:10.1002/14651858.CD004744.pub3.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Rivastigmine**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Cognitive function (measured with VaDAS-change from baseline at 24 weeks; better indicated by lower values)												
1[1]	Randomized trials	No serious risk of bias[2]	No serious inconsistency[3]	No serious indirectness	Very serious[4,5]	None	355	327	-	MD 1.30 lower (2.62 lower to 0.02 higher)	⨁⨁◯◯ LOW	CRITICAL
Congnitive function (measured with MMSE - change from baseline at 24 weeks; better indicated by higher values)												

1[6]	Randomized trials	No serious risk of bias[2]	No serious inconsistency[3]	No serious indirectness	Serious[4]	None	365	345	-	MD 0.60 higher (0.11 to 1.09 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Cognitive function (measured with ADAS-Cog - change from baseline at 24 weeks; better indicated by lower values)												
1[7]	Randomized trials	No serious risk of bias[2]	No serious inconsistency[3]	No serious indirectness	Serious[4]	None	360	338	-	MD 1.10 lower (2.15 to 0.05 lower)	⨁⨁⨁◯ MODERATE	CRITICAL
Global effect (measured with ADS_CGIC 24 weeks; better indicated by higher values)												
1[8]	Randomized trials	No serious risk of bias[2]	No serious inconsistency[3]	No serious indirectness	Very serious[4,5]	None	329	320	-	MD 0.10 lower (3.68 lower to 3.48 higher)	⨁◯◯◯ LOW	IMPORTANT
Global effect (measured with GDS - change from baseline 24 weeks; better indicated by lower values)												
1[9]	Randomized trials	No serious risk	No serious inconsistency[3]	No serious indirectness	Serious[5]	None	365	345	-	MD 0.10 lower (0.21 lower to	⨁⨁⨁◯ MODERATE	IMPORTANT

		of bias[2]								0.01 higher)		
Behavioural disturbance (measured with NPI-12 change from baseline at 24 weeks; better indicated by lower values)												
1[10]	Randomized trials	No serious risk of bias[2]	No serious inconsistency[3]	No serious indirectness	Very serious[4,5]	None	364	342	-	MD 0.40 higher (1.36 lower to 2.16 higher)	⨁⨁◯◯ LOW	IMPORTANT
Withdrawals (assessed with 'due to adverse event by 24 weeks')												
1[11]	Randomized trials	No serious risk of bias[2]	No serious inconsistency[3]	No serious indirectness	Serious[12]	Reporting bias	49/365 (13.4%)	19/345 (5.5%)	OR 2.66 (1.53 to 4.62)	79 more per 1000 (from 27 more to 157 more)	⨁⨁◯◯ LOW	IMPORTANT
								0%		-		
Death (assessed with 'by 24 weeks')												
1[13]	Randomized trials	No serious risk		No serious indirectness	Very serious[5,12]	None	8/365 (2.2%)	4/345 (1.2%)		10 more per 1000	⨁⨁◯◯ LOW	IMPORTANT

		of bias[2]	No serious inconsistency [3]						OR 1.91 (0.57 to 6.4)	(from 5 fewer to 58 more)		
								0%		-		

[1] From analysis 1.1 of Birks et al., 2013
[2] Cochrane have rated the primary study as carrying low risk of bias
[3] Only one study contributing to evidence base (Ballard 2008)
[4] Wide CI (WHO considers for continuous data, 0.5 is wide)
[5] Confidence interval crosses the line of no effect
[6] From analysis 1.2 of Birks et al., 2013
[7] From analysis 1.3 of Birks et al., 2013
[8] From analysis 1.4 of Birks et al., 2013
[9] From analysis 1.5 of Birks et al., 2013
[10] From analysis 1.6 of Birks et al., 2013
[11] From analysis 1.9 of Birks et al., 2013
[12] Wide CI (WHO considers a wide CI as >0.5 for harms data)
[13] . From analysis 1.10 of Birks et al., 2013

[Updated 2015]

Table 8. Rivastigmine vs. placebo for subcortical vascular dementia.

Authors: E Castro Costa and M Harper
Question: Should rivastigmine vs. placebo be used for treatment of subcortical vascular dementia?
Bibliography: Birks J, McGuiness B, Craig D (2013). Rivastigmine for vascular cognitive impairment. Cochrane Database of Systematic Reviews.31;5:CD004744. doi:10.1002/14651858.CD004744.pub3.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Rivastigmine**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Cognitive function (measured with MMSE (change from baseline at 26 weeks; better indicated by higher values)												
1[1,2]	Randomized trials	Serious[3]	No serious inconsistency[2]	No serious indirectness	Very serious[4,5,6]	None	20	20	-	MD 0.70 higher (1.78 lower to 3.18 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Cognitive function (measured with FAB (change from baseline at 26 weeks); better indicated by higher values)												
1[2,7]	Randomized trials	Serious[3]	No serious inconsistency[2]	No serious indirectness	Very serious[4,5,6]	None	20	20	-	MD 0.40 lower (1.52 lower to	⨁◯◯◯ VERY LOW	CRITICAL

										0.72 higher)		
Global function (measured with CDR sum of boxes (change from baseline at 26 weeks); better indicated by lower values)												
1[8]	Randomized trials	Serious[3]	No serious inconsistency[2]	No serious indirectness	Very serious[4,5,6]	None	20	20	-	MD 0.30 higher (3.11 lower to 3.71 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Behavioural disturbances (measured with NPI-12 (change from baseline at 26 weeks); better indicated by lower values)												
1[9]	Randomized trials	Serious[3]	No serious inconsistency[4]	No serious indirectness	Very serious[4,5,6]	None	20	20	-	MD 4.50 lower (13.18 lower to 4.18 higher)	⨁◯◯◯ VERY LOW	IMPORTANT
Functional status (measured with IADL[xviii] (change from baseline at 26 weeks); better indicated by lower values)												
1[10]	Randomized trials	Serious[3]	No serious inconsistency[2]	No serious indirectness	Very serious[4,6]	None	20	20	-	MD 0.10 higher (0.12 lower to	⨁◯◯◯ VERY LOW	CRITICAL

										0.32 higher)		
Withdrawals (assessed with before-end-of-treatment at 26 weeks)												
1[11]	Randomized trials	Serious[3]	No serious inconsistency[2]	No serious indirectness	Very serious[4,5,6]	None	6/20 (30%)	3/20 (15%)	OR 2.43 (0.51 to 11.51)	150 more per 1000 (from 67 fewer to 520 more)	⨁◯◯◯ VERY LOW	IMPORTANT
								0%		-		
Adverse event (assessed with at least one by 26 weeks)												
1[12]	Randomized trials	Serious[3]	No serious inconsistency[2]	No serious indirectness	Very serious[4,5,6]	None	12/20 (60%)	10/20 (50%)	OR 1.50 (0.43 to 5.25)	100 more per 1000 (from 199 fewer to 340 more)	⨁◯◯◯ VERY LOW	IMPORTANT
								0%		-		
Death (assessed with withdrawals)												

1[13]	Randomized trials	Serious[3]	No serious inconsistency[2]	No serious indirectness	Very serious[4,5,6]	None	0/20 (0%)	1/20 (5%)	OR 0.32 (0.01 to 8.26)	33 fewer per 1000 (from 49 fewer to 253 more)	⨁◯◯◯ VERY LOW	IMPORTANT
								0%		-		

[1] From analysis 2.1 of Birks et al. (2013)
[2] The evidence consists of just one study.
[3] Allocation concealment and blinding procedures were rated by Cochrane to give high risk of bias.
[4] Very low number of participants, N=40.
[5] Wide confidence interval.
[6] Confidence interval crosses the line of no effect.
[7] From analysis 2.2 of Birks et al. (2013)
[8] From analysis 2.3 of Birks et al. (2013)
[9] From analysis 2.4 of Birks et al. (2013)
[10] From analysis 2.5 of Birks et al. (2013)
[11] From analysis 2.6 of Birks et al. (2013)
[12] From analysis 2.7 of Birks et al. (2013)
[13] From analysis 2.8 of Birks et al. (2013)

[Updated 2015]

Table 9. Donepezil vs. placebo for treatment of dementia with Lewy bodies

Authors: E Castro-Costa and M Harper
Question: Should donepezil vs. placebo be used for treatment of dementia with Lewy bodies?
Bibliography: Wang HF, Yu JT, Tang SW, Jiang T, Tan CC, Meng XF, Wang C, Tan MS, Tan L (2015). Efficacy and safety of cholinesterase inhibitors and memantine in cognitive impairment in Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies: systematic review with meta-analysis and trial sequential analysis. Journal of Neurology Neurosurgery and Psychiatry.86(2):135-143. doi:10.1136/jnnp-2014-307659. (Accessed via E-pub 2014, ahead of print).

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Donepezil**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Global function (measured with CGIC (change from baseline) 5mg (continuous variable); better indicated by lower values)												
3[1]	Randomized trials	Serious[2]	Very serious[3]	No serious indirectness	Serious[4]	None	220	212	-	MD 0.65 lower (1.28 to 0.01 lower)	⨁⨁◯◯ VERY LOW	CRITICAL
Global function (assessed with CGIC (change from baseline) - donepezil 5mg/day)												
2[5]	Randomized trials	Serious[2]	Very serious[6]	No serious indirectness	Serious[7]	None	92/208 (44.2%)	78/200 (39%)	RR 1.39 (0.66 to 2.94)	152 more per 1000 (from	⨁⨁◯◯ VERY LOW	CRITICAL

										133 fewer to 757 more)		
								0%		-		
Global function (measured with CGIC (change from baseline) - 10mg (continuous variable); better indicated by lower values)												
4[8]	Randomized trials	Serious[2]	Serious[9]	No serious indirectness	no serious imprecision	None	229	231	-	MD 0.30 lower (0.35 to 0.25 lower)	⨁⨁⨁◯ LOW	CRITICAL
Global function (assessed with CGIC (change from baseline) donepezil 10mg/day (dichotomous variable))												
3[10]	Randomized trials	Serious[2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	108/210 (51.4%)	80/212 (37.7%)	RR 1.44 (1.04 to 2.01)	166 more per 1000 (from 15 more to 381 more)	⨁⨁⨁◯ MODERATE	CRITICAL
								0%		-		
Cognitive function (measured with MMSE (change from baseline) - 5mg/day; better indicated by higher values)												

3[11]	Randomized trials	Serious[2]	Very serious[12]	No serious indirectness	Serious[4]	None	227	213	-	MD 2.57 higher (0.90 to 4.23 higher)	⨁◯◯◯ VERY LOW	CRITICAL
Cognitive function (measured with MMSE (change from baseline) - 10mg/day; better indicated by higher values)												
4[13]	Randomized trials	Serious[2]	Serious[14]	No serious indirectness	Very serious[4,15]	None	230	220	-	MD 1.31 higher (0.09 to 2.53 higher)	⨁◯◯◯ VERY LOW	CRITICAL
All-cause dropouts - Donepezil 5mg/day												
3[16]	Randomized trials	Serious[2]	No serious inconsistency	No serious indirectness	Serious[17,18]	None	51/236 (21.6%)	35/213 (16.4%)	RR 1.30 (0.88 to 1.92)	49 more per 1000 (from 20 fewer to 151 more)	⨁⨁◯◯ LOW	IMPORTANT
								0%		-		
All-cause dropouts - Donepezil 10mg/day												

4[19]	Randomized trials	Serious[2]	No serious inconsistency	No serious indirectness	Very serious[15,18]	None	56/239 (23.4%)	37/225 (16.4%)	RR 1.40 (0.96 to 2.04)	66 more per 1000 (from 7 fewer to 171 more)	⨁⨁⨁◯ VERY LOW	IMPORTANT
								0%		-		

[1] From Fig. 2 of Wang et al. (2015).
[2] The systematic review does not include any indication of risk of bias.
[3] Heterogeneity exceeds 75% (I squared 80.0%).
[4] Wide CI (WHO considers for continuous data, 0.5 is wide).
[5] Fig. 3 of Wang et al. (2015)
[6] Heterogeneity exceeds 75% (I squared 83.0%).
[7] Wide confidence interval (for RR values, WHO considered CI of 2 to be wide).
[8] From Fig.2 of Wang et al. (2015).
[9] Heterogeneity between 50-75% (I squared 64.0%).
[10] From Fig.3 of Wang et al. (2015).
[11] From Fig.5 of Wang et al. (2015).
[12] Heterogeneity exceeds 75% (I squared 78.0%).
[13] From Fig.5 of Wang et al. (2015).
[14] Heterogeneity between 50-75% (I squared 65.0%).
[15] 95% CI includes both no effect and benefit.
[16] From Fig.6 of Wang et al. (2015).
[17] 95% CI includes both no effect and benefit.
[18] Wide confidence interval (for RR values concerning harms data, WHO considered CI of 0.5 to be wide).
[19] From Fig.6 of Wang et al. (2015).

[Updated 2015]

Table 10. Rivastigmine vs. placebo for treatment of dementia with Lewy bodies

Authors: E Castro-Costa and M Harper
Question: Should rivastigmine vs. placebo be used for treatment of dementia with Lewy bodies?
Bibliography: Wang HF, Yu JT, Tang SW, Jiang T, Tan CC, Meng XF, Wang C, Tan MS, Tan L (2015). Efficacy and safety of cholinesterase inhibitors and memantine in cognitive impairment in Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies: systematic review with meta-analysis and trial sequential analysis. Journal of Neurology Neurosurgery and Psychiatry.86(2):135-143. doi:10.1136/jnnp-2014-307659. (Accessed via E-pub 2014, ahead of print).

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Rivastigmine**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Global effect (measured with CGIC (change from baseline)-12mg (continuous variable); better indicated by lower values)												
1[1]	Randomized trials	Serious[2]	Serious[3]	No serious indirectness	No serious imprecision	None	329	165	-	MD 0.50 lower (0.77 to 0.23 lower)	⨁⨁⨁◯ LOW	CRITICAL
Global effect (assessed with CGIC (change from baseline) - 12 mg (dichotomous))												
2[4]	Randomized trials	Serious[2]		No serious indirectness	No serious imprecision	None	153/377 (40.6%)	64/221 (29%)		113 more per		CRITICAL

			No serious inconsistency [3]						RR 1.39 (1.09 to 1.77)	1000 (from 26 more to 223 more)	⨁⨁⨁◯ MODERATE	
								0%		-		
Cognitive function (measured with MMSE (change from baseline) - 12mg; better indicated by lower values)												
2[5]	Randomized trials	Serious [2]	No serious inconsistency	No serious indirectness	Serious[6]	None	394	227	-	MD 1.04 higher (0.43 to 1.65 higher)	⨁⨁◯◯ LOW	CRITICAL
All-cause of dropout – Rivastigmine 12mg												
2[7]	Randomized trials	Serious [2]	No serious inconsistency	No serious indirectness	Serious[8]	None	117/421 (27.8%)	42/240 (17.5%)	RR 1.59 (1.16 to 2.19)	103 more per 1000 (from 28 more to 208 more)	⨁⨁◯◯ LOW	IMPORTANT
								0%		-		

[1] From Fig.2 of Wang et al. (2015).

[2] Systematic review does not include details on possible risk of bias of primary studies.

[3] Only one study contributing to evidence.
[4] From Fig. 3 of Wang et al. (2015).
[5] From Fig. 5 of Wang et al. (2015).
[6] Wide CI (WHO considers for continuous data, 0.5 is wide).
[7] From Fig.6 of Wang et al. (2015).
[8] Wide CI (WHO suggests that >0.5 is wide for harms data).

Table 11. Memantine vs. placebo for treatment of dementia with Lewy bodies

Authors: E Castro-Costa and M Harper
Question: Should memantine vs. placebo be used for treatment of dementia with Lewy bodies?
Bibliography: Wang HF, Yu JT, Tang SW, Jiang T, Tan CC, Meng XF, Wang C, Tan MS, Tan L (2015). Efficacy and safety of cholinesterase inhibitors and memantine in cognitive impairment in Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies: systematic review with meta-analysis and trial sequential analysis. Journal of Neurology Neurosurgery and Psychiatry.86(2):135-143. doi:10.1136/jnnp-2014-307659. (Accessed via E-pub 2014, ahead of print).

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Memantine**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Global effect (measured with CGIC (change from baseline) (continuous variable); better indicated by lower values)												
2[1]	Randomized trials	Serious [2]	No serious inconsistency	No serious indirectness	Serious [9]	None	123	130	-	MD 0.40 lower (0.77 to 0.03 lower)	⨁⨁⨁◯ LOW	CRITICAL

Global effect (assessed with CGIC (change from baseline) - 12mg (dichotomous variable))												
3[3]	Randomized trials	Serious[2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	72/133 (54.1%)	61/142 (43%)	RR 1.26 (0.97 to 1.64)	112 more per 1000 (from 13 fewer to 275 more)	⨁⨁⨁◯ MODERATE	CRITICAL
								0%		-		
Cognitive function (measured with MMSE; better indicated by higher values)												
2[4]	Randomized trials	Serious[2]	Serious[5]	No serious indirectness	Very serious[6]	None	41	47	-	MD 0.45 higher (2.76 lower to 3.66 higher)	⨁◯◯◯ VERY LOW	CRITICAL
All-cause dropouts – Memantine 20mg												
3[7]	Randomized trials	Serious[2]	No serious inconsistency	No serious indirectness	Serious[8]	None	31/144 (21.5%)	37/155 (23.9%)	RR 0.90 (0.6 to 1.35)	24 fewer per 1000 (from 95 fewer to 84 more)	⨁◯◯◯ LOW	IMPORTANT

								0%		-		

[1] From Fig.2 of Wang et al. (2015).
[2] Systematic review does not include details on possible risk of bias of primary studies.
[3] From Fig. 3 of Wang et al. (2015).
[4] From Fig. 5 of Wang et al. (2015).
[5] Heterogeneity between 50-75% (I squared 72.0%).
[6] Very low number of participants (pooled N=30) and confidence interval which crosses the line of no effect.
[7] From Fig.6 of Wang et al. (2015).
[8] Confidence interval crosses the line of no effect.
[9] Wide CI (WHO considers for continuous data, 0.5 is wide).

Table 12. Impact of cholinesterase inhibitors vs. placebo on adverse events associated with dementia.

Authors: E Castro-Costa and M Harper
Question: Does treatment of dementia with cholinesterase inhibitors give rise to more adverse events than placebo?
Bibliography: Kim DH, Brown RT, Ding EL, Kiel DP, Berry SD (2011). Dementia medications and risk of falls, syncope, and related adverse events meta-analysis of randomized controlled trials. Journal of the American Geriatric Society.59(6):1019-1031. doi:10.1111/j.1532-5415.2011.03450.x.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Cholinesterase inhibitors**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Falls – All types of dementia												
13[1]	Randomized trials	Serious[2]	No serious inconsistency	Serious[3]	Serious[4]	None	324/5993 (5.4%)	265/3889 (6.8%)	OR 0.88 (0.74 to 1.04)	8 fewer per 1000 (from 17 fewer to 3 more)	⨁⨁⨁◯ VERY LOW	IMPORTANT
								0%		-		
Falls – Alzheimer´s disease												

9[5]	Randomized trials	Serious[2]	No serious inconsistency	No serious indirectness	Serious[4]	None	189/3844 (4.9%)	116/1953 (5.9%)	OR 0.94 (0.74 to 1.2)	3 fewer per 1000 (from 15 fewer to 11 more)	⨁⨁◯◯ LOW	IMPORTANT
								0%		-		
Falls – Vascular dementia												
2[5]	Randomized trials	Serious[2]	No serious inconsistency	No serious indirectness	Very serious[4,6]	None	53/761 (7%)	53/735 (7.2%)	OR 0.99 (0.58 to 1.71)	1 fewer per 1000 (from 29 fewer to 45 more)	⨁◯◯◯ VERY LOW	IMPORTANT
								0%		-		
Falls – Dementia with Lewy bodies												
1[5]	Randomized trials	Serious[2]	Serious[7]	No serious indirectness	Very serious[4,6]	None	21/362 (5.8%)	11/179 (6.1%)	OR 0.94 (0.44 to 2)	3 fewer per 1000 (from 33 fewer to	⨁◯◯◯ VERY LOW	IMPORTANT

										54 more)		
								0%		-		
Syncope –All types of dementia												
13[1]	Randomized trials	Serious[2]	No serious inconsistency	Serious[3]	Serious[6]	None	96/5193 (1.8%)	35/3034 (1.2%)	OR 1.53 (1.02 to 2.30)	6 more per 1000 (from 0 more to 15 more)	⨁◯◯◯ VERY LOW	IMPORTANT
								0%		-		
Syncope – Alzheimer´s disease												
8[5]	Randomized trials	Serious[2]	No serious inconsistency	No serious indirectness	Serious[6]	None[7]	65/3751 (1.7%)	19/2137 (0.89%)	OR 1.90 (1.14 to 3.15)	8 more per 1000 (from 1 more to 19 more)	⨁⨁◯◯ LOW	IMPORTANT

								0%		-		
Syncope – Vascular dementia												
2[5]	Randomized trials	Serious[2]	No serious inconsistency	No serious indirectness	Very serious[4,6]	None	26/827 (3.1%)	10/392 (2.6%)	OR 1.19 (0.56 to 2.52)	5 more per 1000 (from 11 fewer to 36 more)	⨁◯◯◯ VERY LOW	IMPORTANT
								0%		-		
Syncope – Dementia with Lewy bodies												
1[5]	Randomized trials	Serious[2]	Serious[7]	No serious indirectness	Serious[8]	None[7]	1/224 (0.45%)	5/118 (4.2%)	OR 0.10 (0.01 to 0.88)	38 fewer per 1000 (from 5 fewer to 42 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT
								0%		-		
Fracture – All types of dementia												
8[1]	Randomized trials	Serious[2]	No serious inconsistency	Serious[3]	Very serious[4,6]	None[7]	33/2214 (1.5%)	17/1340 (1.3%)	OR 1.39 (0.75 to 2.56)	5 more per 1000 (from 3	⨁◯◯◯ VERY LOW	IMPORTANT

										fewer to 19 more)		
								0%		-		
Fracture – Alzheimer´s disease												
6[5]	Randomized trials	Serious[2]	No serious inconsistency	No serious indirectness	Very serious[4,6]	None[7]	22/1143 (1.9%)	13/821 (1.6%)	OR 1.42 (0.69 to 2.92)	7 more per 1000 (from 5 fewer to 29 more)	⨁⨁◯◯ VERY LOW	IMPORTANT
								0%		-		
Fracture – Vascular dementia												
2[5]	Randomized trials	Serious[2]	No serious inconsistency	No serious indirectness	Very serious[4,6]	None	11/1071 (1%)	4/519 (0.77%)	OR 1.32 (0.42 to 4.16)	2 more per 1000 (from 4 fewer to 24 more)	⨁⨁◯◯ VERY LOW	IMPORTANT
								0%		-		
Accidental Injury – All types of dementia												

19[1]	Randomized trials	Serious[2]	Serious[9]	Serious[3]	Very serious[4,6]	None	505/8024 (6.3%)	323/4977 (6.5%)	OR 1.13 (0.87 to 1.45)	8 more per 1000 (from 8 fewer to 27 more)	⨁◯◯◯ VERY LOW	IMPORTANT
								0%		-		
Accidental Injury – Alzheimer´s disease												
14[1]	Randomized trials	Serious[2]	Serious[10]	No serious indirectness	Very serious[4,6]	None[7]	324/5135 (6.3%)	204/2850 (7.2%)	OR 1.20 (0.84 to 1.71)	13 more per 1000 (from 11 fewer to 45 more)	⨁◯◯◯ VERY LOW	IMPORTANT
								0%		-		
Accidental Injury – Vascular dementia												
4[5]	Randomized trials	No serious risk of bias[2]	Serious[11]	No serious indirectness	Very serious[4,6]	None	160/1863 (8.6%)	104/1105 (9.4%)	OR 0.96 (0.63 to 1.47)	3 fewer per 1000 (from 33 fewer to	⨁◯◯◯ VERY LOW	IMPORTANT

										38 more)		
								0%		-		

[1] From Fig. 2 of Kim et al. (2011).
[2] Systematic review does not include details on possible risk of bias of primary studies.
[3] This analysis includes people with Mild Cognitive Impairment.
[4] CI crosses the line of no effect.
[5] From Table 1 of Kim et al. (2011).
[6] Wide confidence interval (WHO suggests that >0.5 is wide for harms data).
[7] I squared value not available.
[8] No explanation was provided.
[9] Heterogeneity between 50-75% (I squared= 55.0%).
[10] Heterogeneity between 50-75% (I squared= 59.0%).
[11] Heterogeneity between 50-75% (I squared= 58.0%).

Table 13. Impacts of memantine vs. placebo on adverse events associated with dementia

Authors: E Castro-Costa and M Harper
Question: Does treatment of dementia with memantine give rise to more adverse events than placebo?
Bibliography: Kim DH, Brown RT, Ding EL, Kiel DP, Berry SD (2011). Dementia medications and risk of falls, syncope, and related adverse events meta-analysis of randomized controlled trials. Journal of the American Geriatric Society.59(6):1019-1031. doi:10.1111/j.1532-5415.2011.03450.x.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Memantine**	**Placebo**	**Relative (95% CI)**	**Absolute**		
Falls – All types of dementia												
9[1]	Randomized trials	Serious[2]	No serious inconsistency	Serious[3]	No serious imprecision[4]	None	148/1896 (7.8%)	156/1698 (9.2%)	OR 0.92 (0.72 to 1.18)	7 fewer per 1000 (from 24 fewer to 15 more)	⨁⨁◯◯ LOW	IMPORTANT
								0%		-		
Falls – Alzheimer´s disease												

8[5]	Randomized trials	Serious[2]	No serious inconsistency	No serious indirectness	Serious[4]	None	130/1609 (8.1%)	135/1427 (9.5%)	OR 0.94 (0.72 to 1.22)	5 fewer per 1000 (from 25 fewer to 18 more)	⨁⨁⨁◯ LOW	IMPORTANT
								0%		-		
Falls – Vascular dementia												
1[5]	Randomized trials	No serious risk of bias[2]	Serious[6]	No serious indirectness	Very serious[4,7]	none	18/277 (6.5%)	21/271 (7.7%)	OR 0.83 (0.43 to 1.59)	12 fewer per 1000 (from 43 fewer to 40 more)	⨁◯◯◯ VERY LOW	IMPORTANT
								0%		-		
Syncope – Alzheimer´s disease												
4[1]	Randomized trials	Serious[2]	No serious inconsistency	No serious indirectness	Very serious[4,7]	None	8/854 (0.94%)	7/841 (0.83%)	OR 1.04 (0.35 to 3.04)	0 more per 1000 (from 5 fewer to 17 more)	⨁◯◯◯ VERY LOW	IMPORTANT
								0%		-		

Fracture – Alzheimer´s disease												
3[1]	Randomized trials	Serious[2]	No serious inconsistency	No serious indirectness	Serious[7]	None	2/492 (0.41%)	11/484 (2.3%)	OR 0.21 (0.05 to 0.85)	18 fewer per 1000 (from 3 fewer to 22 fewer)	⨁⨁⨁◯ LOW	IMPORTANT
								0%		-		
Accidental Injury – All types of dementia												
7[5]	Randomized trials	Serious[2]	No serious inconsistency	Serious[3]	Very serious[4,7]	None	75/1736 (4.3%)	88/1549 (5.7%)	OR 0.80 (0.56 to 1.12)	11 fewer per 1000 (from 24 fewer to 6 more)	⨁◯◯◯ VERY LOW	IMPORTANT
								0%		-		
Accidental Injury – Alzheimer´s Disease												
6[5]	Randomized trials	Serious[2]	No serious inconsistency	No serious indirectness	Very serious[4,7]	None	58/1459 (4%)	58/1278 (4.5%)	OR 0.93 (0.63 to 1.37)	3 fewer per 1000 (from 16 fewer to	⨁◯◯◯ VERY LOW	IMPORTANT

										16 more)		
								0%		-		
Accidental Injury – Vascular dementia												
1[5]	Randomized trials	Serious[2]	Serious[6]	No serious indirectness	Serious[7]	None	17/277 (6.1%)	30/271 (11.1%)	OR 0.53 (0.28 to 0.98)	49 fewer per 1000 (from 2 fewer to 77 fewer)	⨁⨁◯◯ VERY LOW	IMPORTANT
								0%		-		

[1] From Fig. 3 of Kim et al. (2011).
[2] Systematic review does not include details on possible risk of bias of primary studies.
[3] This analysis includes Mild Cognitive Impairment.
[4] CI crosses line of no effect.
[5] From table 2 of Kim et al. (2011).
[6] I squared value not available.
[7] Wide confidence interval (WHO suggests that >0.5 is wide for harms data).

Additional evidence not mentioned in GRADE tables

The following studies were identified as relevant to the scoping question.

Aarsland D, Ballard C, Rongove A, Broadstock M, Svenningsson P. Clinical Trials of Dementia with Lewy Bodies and Parkinson´s Disease Dementia. Current Neurology and Neuroscience Reports. 2012;12(5):492-501. doi:10.1007/s11910-012-0290-7.

The review carried out by Aarsland et al. (2012) included six placebo-controlled studies that included patients with dementia with Lewy bodies (DLB) and five placebo-controlled studies that included patients with Parkinson´s Disease dementia. The DLB studies focused on cognition (two studies), psychosis (two studies), or global changes (two studies, with one study focused on cognition and psychiatric symptoms). A total of 231 DLB patients were included and three medications groups (two studies each) were used including cholinesterase inhibitors, atypical antipsychotics and memantine. Of these, five studies reported significant findings, as compared with placebo. In addition, one double-blind study with 31 DLB patients compared risperidone and citalopram but did not include a placebo group. Evidence from meta-analysis suggests that **rivastigmine can improve cognition and functioning in DLB**.

Craig D and Birks J. Galantamine for vascular cognitive impairment. Cochrane Database of Systematic Reviews. 2006;1:CD004746.

The review carried out by Craig and Birks (2006) included two trials and 1378 participants, employing randomized, double-blind and parallel-group methodology. Both trials were of 6-months duration and were testing a galantamine dose of 16-24mg/day in two divided doses. Both trials had an overall low risk of bias. The results showed:

1. Statistically significant treatment **effects in favour of galantamine compared with placebo in cognition, activities of daily living and behaviour**; and
2. Significantly **higher numbers of patients dropped out** (102/396 galantamine, 33/196 placebo OR 1.71, 95% CI 1.11 to 2.65, p=0.02) **and withdrew due to an adverse event from the group treated with galantamine** compared with the placebo group.

The authors concluded that **limited data were available when considering the impact of galantamine on vascular dementia or vascular cognitive impairment**. The available data suggest **some advantage over placebo in the areas of cognition and global clinical state**. **Galantamine produced higher rates of gastrointestinal side-effects** in both of the included trials.

Molino I, Colucci L, Fasanaro AM, Traini E, Amenta F. Efficacy of Memantine, donepezil, or their association in moderate-severe Alzheimer´s Disease: A review of clinical trials. The Scientific World Journal. 2013:eCollection Article ID 925702. doi:10.1155/2013/925702.

Molino et al. (2013) reviewed evidence from clinical trials of effectiveness of memantine, donepezil or twomedications in association on managing moderate-severe Alzheimer´s Disease. Only 13 studies met the criterion of "adequacy and representativeness" indicated by the Newcastle-Ottawa score. They included six RCTs with memantine as monotherapy, five RCTs with donepezil as monotherapy, and two RCTs with donepezil plus memantine treatment. **Memantine and donepezil lead to improvements in moderate-to-severe AD** and the **choice** between the compounds **should be based on their contraindications** more than on disease severity. No evidence was found on the advantages of the association of memantine-donepezil. The heterogeneity of the conditions explored by the RCTs, the relatively short time of observation (24-52 weeks) and the different cognitive assessment tools used **did not allow comparing properly different trials**.

Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer´s disease. In: NICE technology appraisal guidance [TA217] [website]. London: National Institute of Clinical Excellence (NICE); March 2011. Accessed from: http://www.nice.org.uk/guidance/ta217.

These recommendations were developed using the NICE multiple technology appraisal process for the use of new and existing medicines and treatments in the NHS in England and Wales. It updates and replaces the NICE Technology Appraisal Guidance 111 (published November 2006; amended September 2007, August 2009). **The review and re-appraisal** of donepezil, galantamine, rivastigmine and memantine for treatment of AD **has resulted in a change in the recommendations. Specifically, donepezil, galantamine and rivastigmine are now recommended as options for managing mild, as well as moderate AD, and memantine is now recommended as an option for managing moderate AD for people who cannot take AChEIs, and as an option for managing severe AD.** The NICE recommendations also proposes that the treatment should be administered under the following conditions:

1. Only specialists in the care of patients with dementia should initiate treatment (i.e., psychiatrists, including those specializing in learning disability, neurologists and physicians specializing in the care of older people). Caregivers' views on the patient's condition at baseline should be sought.
1. Treatment should be continued only when it is considered to be having a worthwhile effect on cognitive, global, functional or behavioural symptoms.
2. Patients who continue on treatment should be reviewed regularly using cognitive, global, functional and behavioural assessments. Treatment should be reviewed by an appropriate specialist team, unless there are locally-agreed protocols for shared care. Caregivers' views on the patient's condition at follow-up should be sought.

Methods: The Assessment Group conducted a systematic review of RCTs published since 2004 and those included in 'Donepezil, galantamine, rivastigmine (review) and memantine for the treatment of Alzheimer's disease (amended)' (from NICE Technology Appraisal Guidance 111). The Assessment Group reviewed the clinical effectiveness of donepezil, galantamine, rivastigmine and memantine in accordance with their marketing authorizations. For the population with mild Alzheimer's disease (defined as MMSE 21–26), the AChEIs (i.e., donepezil, galantamine and rivastigmine) were compared with each other and with best supportive care (i.e., without treatment with any AChEIs or memantine). For the population with moderate Alzheimer's disease (defined as MMSE 10–20), the AChEIs and memantine were compared with each other and with best supportive care. For the population with severe Alzheimer's disease (defined as MMSE less than 10), memantine was compared with best supportive care. The Assessment Group considered cognition, function, behaviour, global outcomes, mortality, institutionalization, health-related quality of life and adverse effects. If possible, new evidence was pooled with the evidence from before 2004, using random effects meta-analysis compared with placebo.

Summary of results: The NICE Guidance Committee considered the results from the new placebo-controlled RCTs, which continued to show the small but definite clinical benefit of the AChEIs in mild and moderate Alzheimer's disease compared with best supportive care. The Committee noted that the evidence was almost exclusively based on 6-month long RCTs because few of these trials had follow-up of over 6 months. The Committee heard from clinical specialists and patient experts that the benefits of treatment appeared to last for 23 years in some patients in open-label studies. The Committee concluded that the new evidence provided additional support to the conclusions from 2004, that each of the AChEIs offers benefits over best supportive care for cognitive, functional and global outcomes, and AChEIs may also offer some benefit in behavioural outcomes, although the nature and extent of behavioural benefits are uncertain owing to mixed results from the available evidence. As well, there was insufficient evidence to differentiate between the AChEIs in terms of clinical effectiveness.

Regarding memantine, the NICE Guidance Committee concluded that it had a different mode of action from the AChEIs and in practice would be used later in the treatment pathway in people with more severe Alzheimer's disease, which is also a time when a higher proportion of people develop behavioural symptoms.

O´Brien JT and Burns A. Clinical practice with anti-dementia drugs: a revised (second) consensus statement from the British Association for Psychopharmacology. Journal of Psychopharmacology. 2011;25(8):997-1019. doi:10.1177/0269881110387547.

The British Association for Psychopharmacology (BAP) coordinated a meeting of experts to review and revise its first (2006) Guidelines for clinical practice with anti-dementia medications. As before, levels of evidence were rated using accepted standards, which were then translated into grades of recommendation from A to D, with A having the strongest evidence base (using RCTs) and D having the weakest evidence base (using case studies or expert opinion). O'Brien and Burns' (2011) findings were as follows:

1. **Cholinesterase inhibitors (i.e., donepezil, rivastigmine and galantamine) are effective for mild to moderate AD (A) and memantine for moderate to severe AD (A);**
2. **Neither cholinesterase inhibitors nor memantine are effective in those with mild cognitive impairment** (A);

3. **Cholinesterase inhibitors are not effective in frontotemporal dementia and may cause agitation** (A); and
4. **Cholinesterase inhibitors should be used for treatment of people with Lewy body dementias** (e.g., Parkinson´s disease dementia), **especially for neuropsychiatric symptoms** (A).

van de Glind EM, van Enst WA, van Munster BC, Olde Rikkert MG, Scheltens P, Scholten RJ, Hooft L. Pharmacological treatment of Dementia: A scoping review of Systematic reviews. Dementia and Geriatric Cognitive Disorders. 2013;36(3-4):211-228. doi:10.1159/000353892.

Van de Glind et al. (2013) performed a scoping review that aimed to give an overview of the subjects and methodological quality of available systematic reviews on the pharmacological treatment of the most prevalent forms of dementia. It comprised 62 studies, including 34 Cochrane reviews. The most prevalent reason for excluding a review was that the reported intervention was not FDA or EMA registered. Out of the 62 reviews, 55(90%) reviews were assessed as having a low risk of bias. The reviews by Craig and Birks (2006) (also reported above) showed that cholinesterase inhibitors are effective for mild to moderate AD and for Parkinson's dementia. They are also cost-effective. **With regard to effects, the different medications are comparable; however, in terms of side-effects, donepezil might be the better choice**. Memantine proved to be effective for patients with moderate to severe AD, although not for other forms of dementia.For vascular dementia, the efficacy of galantamine showed mixed results across two studies. For rivastigmine, no proper RCTs were available. Thus, **cholinesterase inhibitors are not recommended for vascular dementia**. For **behavioural problems, no distinction between the different types of dementia was made**.The use of memantine resulted in a consistent, small reduction in the incidence of agitation in patients with dementia. However, there was no available evidence addressing the question as to whether prevalent agitation can be treated with memantine.

Additional evidence: Cost effectiveness and feasibility

Hyde C, Peters J, Bond M, Rogers G, Hoyle M, Anderson R, Jeffreys M, Davis S, Thokala P, Moxham T. Evolution of the evidence on the effectiveness and cost-effectiveness of acetylcholinesterase inhibitors and memantine for Alzheimer's disease: systematic review and economic model. Age and Ageing. 2013;42(1):14-20. doi:10.1093/ageing/afs165.

As part of a *Health Technology Assessment* cost-effectiveness study, Hyde et al. (2013) investigated the effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of AD to re-consider and update the evidence base that was used to inform the 2007 NICE guidelines. The systematic review of effectiveness targeted RCTs. The cost-effectiveness was assessed using a cohort-based model with three health states: pre-institutionalised, institutionalised and dead. The perspective was NHS and Personal Social Services and the cost year was 2009. The study demonstrated improved cost-effectiveness. For donepezil, galantamine and rivastigmine, the incremental cost per quality-adjusted life year (QALY) in 2004 was above £50,000. In 2010, the same medications 'dominated' best supportive care (i.e., improved clinical

outcome at reduced cost). This was primarily because of changes in the modelled costs of introducing the medications. For memantine, the cost-effectiveness also improved from a range of £37,000–53,000 per QALY gained to a base-case of £32,000.

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Summary of evidence table

ALZHEIMER´S DISEASE				
OUTCOME	**Donepezil vs. placebo** *(Number of studies, mean difference [95% CI], quality)*	**Galantamine vs. placebo** *(Number of studies, mean difference [95% CI], quality)*	**Rivastigmine vs. placebo** *(Number of studies, mean difference [95% CI], quality))*	**Memantine vs. placebo** *(Number of studies, mean difference [95% CI], quality)*
Cognitive Function (all cognitive outcomes at 21-28 weeks)	9 studies, SMD[xix] 0.40 (0.29 to 0.50) Favouring active treatment, LOW quality	5 studies, WMD[xx]-2.96 (-3.41 to -2.51)(ADAS-COG) Favouring active treatment, LOW quality	4 studies, SMD 0.28 (0.14 to 0.42) Favouring active treatment, VERY LOW quality	2 studies, WMD 3.24 (-2.23 to 8.74)(SIB) No difference, VERY LOW quality
Global effect assessment (global outcomes all dosages)	6 studies, SMD 0.38 (0.27 to 0.48) Favouring active treatment, LOW quality	3 studies, WMD-0.20 (-0.30 to -0.09) (CIBIC) Favouring active treatment, MODERATE quality	4 studies, SMD 0.23 (0.16 to 0.31) Favouring active treatment, LOW quality	2 studies, WMD-0.30 (-0.47 to -0.13) (CIBIC-Plus) Favouring active treatment, LOW quality
Behavioural Disturbances (NPI at 12 or 13 weeks)	4 studies, WMD -2.25 (-5.11 to 0.61) No difference,	2 studies, WMD -0.74 (-1.83 to 0.34) No difference,	_____	_____

(NPI at 24-28 weeks)	VERY LOW quality 2 studies, WMD -3.12 (-8.17 to 1.93) No difference, VERY LOW quality	VERY LOW quality 2 studies, WMD 1.46 (-2.59 to -0.34) Favouring active treatment, MODERATE quality	_____	2 studies, WMD -1.61 (-4.74 to 1.52) No difference, VERY LOW quality
Functional Status (all outcomes at 21-26 weeks)	5 studies, SMD 0.30 (0.14 to 0.45) Favouring active treatment, LOW quality	4 studies, SMD 0.27 (0.18 to 0.35) Favouring active treatment, LOW quality	3 studies, SMD 0.21 (0.12 to 0.29) Favouring active treatment, LOW quality	Outcome measures not combined : -ADCS-ADL [xxi]MD 1.41 higher (0.04 to 2.78 higher), VERY LOW quality -FAST MD 0.34 lower (0.55 to 0.12 lower), LOW quality
VASCULAR DEMENTIA				
OUTCOME	**ChEIs (as a group) vs. placebo** *(Number of studies, mean difference [95% CI], quality)*	**Memantine vs. placebo** *(Number of studies, Mean difference [95% CI] and Quality)*	**Rivastigimine (3 -12mg/day) vs. placebo** *(Number of studies, Mean difference [95% CI] and Quality)*	**Rivastigmine (6mg/day) vs. placebo** *(Number of studies, Mean difference [95% CI] and Quality)* (SUBCORTICAL VASCULAR DEMENTIA)
Cognitive Function at 24 – 26 weeks VaDAS[xxii]	_____	_____	1 study, MD -1.30 (-2.62 to 0.02) No difference, LOW quality	_____

MMSE	_____	_____	1 study, MD 0.60 (0.11 to 1.09) Favoring active treatment, MODERATE quality	1 study, MD 0.70 (-1.71 to 3.18) No difference, VERY LOW quality
FAB	_____	_____	_____	1 study, MD -0.40 (-1.52 to 0.72) No difference, VERY LOW quality
ADAS[xxiii]	3 studies (last observation), MD 2.36 lower (3.07 to 1.66 lower) Favouring active treatment, MODERATE quality	2 studies, MD 1.85 (0.88 to 2.83) Favouring active treatment, HIGH quality	1 study, MD -1.10 (-2.15 to -0.05) Favouring active treatment, MODERATE quality	_____
Global effect assessment at 24 weeks				
ADCS-CGIC	_____	_____	1 study, MD -0.10 (-3.68 to 3.48) No difference, LOW quality	_____
GDS	_____	_____	1 study, MD -0.10 (-3.68 to 3.48) No difference, MODERATE quality	1 study,
	_____	_____	_____	

CDR sum of boxes				MD 0.30 (-3.11 to 3.71) No difference, VERY LOW quality
CIBIC-plus or CGIC	1 study (last observation), RR[xxiv] 1.04 (0.91 to 1.18) No difference, MODERATE quality	1 study (last observation), OR[xxv] 1.34 (0.85 to 2.15) No difference, LOW quality	_____	_____
Behavioural Disturbances at 24 weeks	1 study WMD -2.20 (-4.32 to -0.08) Favouring control, VERY LOW quality	2 studies, MD 0.48 (0.06 to 0.91) Favouring active treatment, MODERATE quality	1 study, MD 0.40 (-1.36 to 2.16) No difference, LOW quality	1 study, MD -4.50 (-13.18 to 4.18) No difference, LOW quality
Functional Status	_____	2 studies MD 0.12 higher (0.43 lower to 0.67 higher) No difference, MODERATE quality	_____	1 study, MD 0.10 (-0.12 to 0.32) No difference, VERY LOW quality
At least one adverse event by 26 weeks	3 studies, RR 1.11 (1.02 to 1.2) Favouring control, MODEARTE quality	_____	_____	1 study, OR 1.50 (0.43 to 5.25) No difference, VERY LOW quality
Dropouts due to adverse events (proxy)	3 studies RR 2.10 (1.57 to 2.82) Favouring control,	_____	_____	_____

	HIGH quality			
Death	3 studies, RR 0.88 (0.4 to 1.97) No difference, LOW quality	_____	1 study, OR 1.91 (0.57 to 6.40) No difference, LOW quality	1 study, OR 0.32 (0.01 to 8.26) No difference, VERY LOW quality
DEMENTIA WITH LEWY BODIES				
OUTCOME	**Donepezil 5mg vs. placebo** *(Number of studies, mean difference [95% CI], quality)*	**Donepezil 10mg vs. placebo** *((Number of studies, mean difference [95% CI], quality)*	**Rivastigmine 12mg vs. placebo** *(Number of studies, mean difference [95% CI], quality)*	**Memantine 20mg vs. placebo** *(Number of studies, mean difference [95% CI], quality)*
Cognitive Function (no follow up time stated) – MMSE	3 studies, SMD 2.57 (0.90 to 4.23) Favouring active treatment, VERY LOW quality	4 studies, SMD 1.31 (0.09 to 2.53) Favouring active treatment, VERY LOW quality	2 studies, SMD 1.04 (0.43 to 1.65) Favoruing active treatment, LOW quality	2 studies, SMD 0.45 (-2.76 to 3.66) No difference, LOW quality
Global effect assessment	3 studies, SMD -0.65 (-1.28 to -0.01) Favouring active treatment, VERY LOW quality	4 studies, SMD -0.30 (-0.35 to -0.25) Favouring active treatment, VERY LOW quality	1 study, SMD -0.50 (-0.77 to -0.23) Favouring active treatment, LOW quality	2 studies, SMD -0.40 (-0.77 to -0.03) Favouring active treatment, VERY LOW quality
ALL TYPES OF DEMENTIA: ADVERSE EVENTS				
OUTCOME	**Cholinesterase inhibitors** *(Number of studies, mean difference [95% CI], quality)*	**Memantine** *(Number of studies, mean difference [95% CI], quality)*		

Fall	13 studies, OR 0.88 (0.74 to 1.04) No difference, VERY LOW quality	9 studies, OR 0.92 (0.72 to 1.18) No difference, LOW quality		
Syncope	13 studies, OR 1.53 (1.02 to 2.30) Increased risk, VERY LOW quality	_____		
Fracture	8 studies, OR 1.39 (0.75 to 2.56) No difference, VERY LOW quality	_____		
Accidental injury	19 studies, OR 1.13 (0.87 to 1.45) No difference, VERY LOW quality	7 studies OR 0.80 (0.56 to 1.12) No difference, VERY LOW quality		
ALZHEIMEIR'S DISEASE				
OUTCOME	**Cholinesterase inhibitors** *(Number of studies, mean difference [95% CI], quality)*	**Memantine** *(Number of studies, mean difference [95% CI], quality)*		
Fall	9 studies, OR 0.94	8 studies, OR 0.94		

	(0.74 to 1.20) No difference, LOW quality	(0.72 to 1.22) No difference, LOW quality		
Syncope	8 studies, OR 1.90 (1.14 to 3.15) Increased risk, LOW quality	4 studies, OR 1.04 (0.35 to 3.04) No difference, VERY LOW quality		
Fracture	6 studies, OR 1.42 (0.69 to 2.92) No difference, VERY LOW quality	3 studies, OR 0.21 (0.05 to 0.85) Decreased risk in memantine, LOW quality		
Accidental injury	14 studies, OR 1.20 (0.84 to 1.71) No difference, VERY LOW quality	6 studies, OR 0.93 (0.63 to 1.37) No difference, VERY LOW quality		
VASCULAR DEMENTIA				
OUTCOME	**Cholinesterase inhibitors** *(Number of studies, mean difference [95% CI], quality)*	**Memantine** *(Number of studies, mean difference [95% CI], quality)*		
Fall	2 studies, OR 0.99 (0.58 to 1.71) No difference,	1 study, OR 0.83 (0.43 to 1.59) No difference,		

	VERY LOW quality	VERY LOW quality		
Syncope	2 studies, OR 1.19 (0.56 to 2.52) No difference, VERY LOW quality	_____		
Fracture	2 studies, OR 1.32 (0.42 to 4.16) No difference, VERY LOW quality	_____		
Accidental injury	4 studies, OR 0.96 (0.63 to 1.47) No difference, VERY LOW quality	1 study, OR 0.53 (0.28 to 0.98) Decreased risk, VERY LOW quality		
DEMENTIA WITH LEWY BODIES				
OUTCOME	**Cholinesterase inhibitors** *(Number of studies, mean difference [95% CI], quality)*	**Memantine** *(Number of studies, mean difference [95% CI], quality)*		
Fall	1 studies, OR 0.94 (0.44 to 2.00) No difference, VERY LOW quality	_____		
Syncope	1 studies,	_____		

	OR 0.10 (0.01 to 0.88) No difference, VERY LOW quality			
Fracture	_____	_____		
Accidental injury	_____	_____		

Evidence to recommendation table

Benefits	The additional clinical effectiveness evidence identified by Bold et al. (2012) in an updated systematic review suggests that there is clinical benefit of cholinesterase inhibitors used to alleviate Alzheimer's disease symptoms (particularly in cognition function, global effect and functional status); however, the quality of the evidence is low and there is considerable debate about the magnitude of the effect. Although there is also new evidence on the effectiveness of memantine, it remains less supportive of this medication's use than the evidence for cholinesterase inhibitors. As well, evidence shows that cholinesterase inhibitors are effective in improving the outcomes investigated among people with dementia with Lewy bodies. According to the UK's National Institute of Clinical Excellence (NICE) technological guidance summary of evidence, there is small but definite clinical benefit of the cholinesterase inhibitors in mild and moderate Alzheimer's disease compared with best supportive care. Memantine offers symptomatic benefits in cognitive, functional, global and behavioural outcomes, although the size of this benefit is uncertain.

	Moderate to high quality evidence concerning the effect of cholinesterase inhibitors and memantine on vascular dementia suggests that all treatments are more effective than placebo with regards to cognitive function, but the pooled evidence is somewhat dated. Where other clinical outcomes are concerned, cholinesterase inhibitors are found to be no more effective than placebo, but memantine was found to have beneficial effects on behavioural disturbance.
Harms	Treatment with cholinesterase inhibitors is associated with higher rates of adverse events than with placebo across all types of dementia, particularly increased risk of syncope in Alzheimer' disease. Meta-analysis of 54 placebo-controlled randomized trials and extension studies of cholinesterase inhibitors and memantine that reported falls, syncope and related events in cognitively-impaired older adults. Compared to placebo, cholinesterase inhibitor use was associated with an increased risk of syncope, but not with other events (i.e., falls, fracture and accidental injury). Memantine use was associated with fewer fractures, but not with other events (i.e., fall, syncope and accidental injury). There was no differential effect by type and severity of cognitive impairment, residential status, nor length of follow-up. However, due to underreporting and small number of events, a potential benefit or risk cannot be excluded.
Summary of the quality of evidence	The quality of the evidence included in this evidence profile is very low to moderate. Heterogeneity of outcome measures in trials was noted, as well as limitations of some of the instruments used in the clinical trials, including cognitive and behavioural scales. Moreover, most of the trials had only short-term follow-up (up to 6 months).

Value and preferences

In favour	Cognitive decline and lack of functioning (e.g., activities of daily living) seen in people with dementia represent a serious burden for patients and their families.
Against	Adverse effects and safety in the long-term may represent serious concerns. Adherence to treatment may be particularly problematic in patient populations that may require complex treatment regimes.
Uncertainty or variability?	Patients and their families must make informed choices based on benefit/harms profiles of the medications for their needs.

Feasibility (including resource use considerations)	The evidence suggests that the efficacy of cholinesterase and memantine varies according to dementia sub-type; however, there is clear evidence of clinical benefit for Alzheimer's disease and emerging evidence for some medications and some outcomes for vascular dementia and dementia with Lewy bodies. Dementia diagnosis and subtype definition requires training, supervision and support, but may be feasible in non-specialist settings. However, the accuracy of such diagnoses may be open to question. It may be particularly challenging to distinguish mild dementia from normal ageing. It is best if treatment is initiated and continued with specialist involvement, which may not be available. In all cases, regular clinical monitoring is required. In some health care systems cholinesterase inhibitors and memantine are associated with high acquisition costs. However, cholinesterase inhibitors are increasingly available in generic forms at lower costs and out-of-pocket costs are reimbursed in some health systems. Cholinesterase inhibitors and memantine are not included in the WHO list of essential medicines.
Uncertainty or variability?	There is variability in the efficacy of these interventions according to dementia sub-type. There is variability in country capacity to deliver cholinesterase inhibitors and memantine treatment due to potential resource constraints. There is uncertainty with regards to the accuracy of dementia diagnosis in non-specialist health care settings.

Recommendation and remarks

Recommendation

Cholinesterase inhibitors and memantine may be offered to people with dementia in non-specialist health settings. Non-specialists need to be trained and supervised to ensure competence in diagnosis and monitoring.
The use of cholinesterase inhibitors should be focused upon those with mild to moderate Alzheimer's disease, where the majority of evidence is available.
Memantine may be considered for those with moderate to severe Alzheimer's disease and vascular dementia.
Memantine should not be prescribed for Lewy Body dementia.

Rationale: Cholinesterase inhibitors and memantine offer symptomatic benefits in cognitive, functional, global and behavioural outcomes, although the size of this benefit is uncertain and the quality of the evidence very low. Adverse effects and safety in the long-term may represent serious concerns. Dementia diagnosis and subtype definition and management with the above medications require training, supervision and support. Moreover these medications are associated with high acquisition costs.

Remarks

Consideration should be given to adherence and monitoring of adverse effects.

[Updated 2015]

Judgements about the strength of a recommendation

Factor	Decision
Quality of the evidence Very low to moderate	□ High □ Moderate □ Low **X Very low**
Balance of benefits versus harms	**X Benefits clearly outweigh harms** □ Benefits and harms are balanced □ Potential harms clearly outweigh potential benefits
Values and preferences	**X No major variability** □ Major variability
Resource use	□ Less resource-intensive **X More resource-intensive**
Strength	**CONDITIONAL**

OTHER REFERENCES

Blanke ML and VanDongen AMJ. Chapter 13: Activation Mechanisms of the NMDA Receptor. In Van Dongen AM (Ed). Biology of the NMDA Receptor. Boca Raton, Florida, USA: CRC Press; 2009.

Prince M, Guerchet M,Prina M. The Global Impact of Dementia 2013–2050. London, UK: Alzheimer's Disease International; 2013 (http://www.alz.co.uk/research/GlobalImpactDementia2013.pdf, accessed on 1 May 2014).

Sousa RM, Ferri CP, Acosta D, Albanese E, Guerra M, Huang Y, Jacob KS, Jotheeswaran AT, Rodriguez JJ, Pichardo GR, Rodriguez MC, Salas A, Sosa AL, Williams J, Zuniga T, Prince M (2009). Contribution of chronic diseases to disability in elderly people in countries with low and middle incomes: a 10/66 Dementia Research Group population-based survey. The Lancet.28(374):1821-30. doi:10.1016/S0140-6736(09)61829-8.

Sousa RM, Ferri CP, Acosta D, Albanese E, Guerra M, Huang Y, Jacob KS, Jotheeswaran AT, Rodriguez JJ, Pichardo GR, Rodriguez MC, Salas A, Sosa AL, Williams J, Zuniga T, Prince M (2012). The contribution of chronic diseases to the prevalence of dependence among older people in Latin, America, China and India: A 10/66 Dementia Research Group population-based survey. BioMed Central Geriatrics.10:53. doi:10.1186/1471-2318-10-53.

United Nations. World Population Prospects: The 2012 Revision, Highlights and Advance Tables. New York, USA: United Nations, Department of Economic and Social Affairs, Population Division; 2013 (http://esa.un.org/unpd/wpp/Documentation/pdf/WPP2012_highlights.pdf, accessed on 1 May 2014).

Wimo A and Prince M (2010). World_Alzheimer_Report: The Global Economic Impact of Dementia. Alzheimer's Disease International: Illinois, USA

---

[i] McMaster University search strategy details: http://hiru.mcmaster.ca/hiru/HIRU_Hedges_MEDLINE_Strategies.aspx.
[ii] Acetylcholinesterase inhibitors (AChEIs)
[iii] Randomized controlled trials (RCTs)
[iv] US Food and Drug Administration (FDA)
[v] European Medicines Agency (EMA)
[vi] Alzheimer's Disease Assessment Scale-cognitive (ADS-cog)
[vii] Mean difference (MD)
[viii] Neuropsychiatric Inventory (NPI)

[ix] Clinician Interview Based Impression of Change plus Caregiver Input (CIBIC-plus)
[x] Clinical Dementia Rating (CDR)
[xi] Behavioural and psychological symptoms of dementia (BPSD)
[xii] Alzheimer's Disease Co-operative Study-Activities of Daily Living (ADCS-ADL)
[xiii] Disability Assessment for Dementia (DAD)
[xiv] Post diagnostic support (PDS)
[xv] Global Deterioration Scale (GDS)
[xvi] Severe Impairment Battery (SIB)
[xvii] Functional Assessment Staging (FAST)
[xviii] Instrumental Activities of Daily Living (IADLs)
[xix] Standardized mean difference (SMD)
[xx] Weighted mean difference (WMD)
[xxi] ADCS-ADL
[xxii] Vascular Dementia Assessment Scale (VaDAS)
[xxiii] Alzheimer's Disease Assessment Scale (ADAS)
[xxiv] Relative risk (RR)
[xxv] Odds ratio (OR)