The effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease (review of TA111): a systematic review and economic model

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APPENDICES

Appendix 1: Outcome measures

These Tables of outcome measures have been copied from the previous TAR, TA 111, Appendix 6.[1]

Global outcome measures

Type	Construct measure and scoring	Critical appraisal
Clinical Dementia Rating (CDR) and Clinical Dementia Rating Sum of Boxes (CDR-SB)	Cognitive impairment in memory, orientation, judgement/problem-solving, community affairs, home/hobbies, and personal care 0=none, 0.5=questionable, 1=mild, 2=moderate, 3=severe CDR-SB is a modified form which sums the ratings in the six performance categories to give a global dementia ranking.	Provides physicians with a global rating that encompasses a broad range of patient characteristics and can be used by neurologists, psychiatrists, and psychologists and focuses on cognition, not on items that may be related to other medical, emotional or social conditions. Good inter-rater reliability and fair to good concurrent validity. Although no work has been done on test-retest reliability, nothing so far suggests that researchers should avoid this scale when trying to stage AD. The CDR can be used as an eligibility criterion for trial participation or as an outcome measure.
Global Deterioration Scale (GDS)	Progressive stages of cognitive impairment 1 (no cognitive decline)-7 (very severe cognitive decline)	Most frequently used but ratings can misstate a patient's severity. Problems might arise when the GDS is used as an inclusion criterion for participation in an RCT. The ability to enrol desired patients could be threatened if the GDS misidentifies the stages of dementia. The GDS should not be used to stage dementia in Alzheimer's Disease drug trials.
Clinical Global Impression of Change scale (CGIC) and the global improvement index with interviewing of patients Clinician Interview-Based Impression of Change (CIBIC) and with caregiver input	Overall improvement in patient health status assessed by clinician (-with caregiver) 1 (very much improved) - 7 (very much worse) A number of different variations are available Scale is nonparametric and of a non-interval nature.	Fair to good test-retest and inter-rater reliability and concurrent validity. Results may arise from fact that groups providing global assessments do not base their ratings on the same domains. Physicians take clinical psychopathology as the basis of determining global improvement, nurses believe the amount of work needed to care for patients was important. This instrument also

Type	Construct measure and scoring	Critical appraisal
(CIBIC-M or –Plus)		includes a caregiver opinion, results may differ depending on whether the rater first interviews the patient or caregiver. The number of different variations may have reduced the validity.
Gottfries-Bråne-Steen (GBS)	Motor function, intellectual function, emotional function and symptoms common to demented patients. 0 (normal function or absence of symptoms) to 6 (maximal disturbance or presence of symptoms)	Psychometric properties range from fair to good. Scale is useful mean of quantifying dementia in drug trials. GBS should not be used as a diagnostic tool.
Mental Function Impairment Scale (MENFIS)	A modification of the GBS prepared by the study authors for a previous study. Scores range from 0 to 78, with a higher score indicating a greater degree of deficit.	Unable to source data on reliability and validity.
Patient Global Assessment (PGA)	7 point Likert scale ranges from 1 (very much improved) to 4 (no change) to 7 (very much worse)	Unable to source data on reliability and validity.

Cognitive outcome measurement scales

Type	Construct measure and scoring	Critical appraisal
Alzheimer's Disease Assessment Scale-cognitive (ADAS-cog)	Orientation, memory, language and praxis 0-70, with higher scores indicating greater impairment	Limited in its ability to detect change at one end or the other of the severity continuum. For many subtests, detection of improvement appears only possible for a restricted range of severity levels. Limitations should be considered when used as a drug efficacy measure. The rate of decline of AD using ADAS-cog suggests that the decline is non-linear and not a constant but is dependent on the stage of the disease. Content and ecological validity are lacking.
Benton Visual Retention Test (BVRT)	Assesses visual perception, visual memory, and visuoconstructive abilities. The test has three alternate forms, each consisting of ten designs. In addition, there are four possible modes of administration. Scoring is based on an assessment of the number and types of errors made compared with the expected scores found in the norm tables. The wider	The interscorer agreement for total error score is high and for major categories of errors reliability is moderate to high. A correlation of 0.42 was found between the Benton and the Digit Span WAIS subtest. This low correlation indicates discriminate validity since the Benton was created to supplement the Digit Span test.

Type	Construct measure and scoring	Critical appraisal
	the discrepancy in favour of the expected score, the more probable it is that the participant has suffered neurological impairment.	Educational level may influence a participant's score on the test. Participants with higher educational levels tend to use a more exhaustive exploration strategy during the recognition phase of the test, allowing them to perform better than participants with lower educational levels. The executive working memory component is more efficient in participants with higher educational levels.
Computerised Memory Battery (CMBT)	A computerized version of the Memory Assessment Clinical Battery (MAC) designed to simulate critical cognitive tasks: Name-Face Association (delayed recall and total acquisition);First and Last Names (total acquisition), Facial Recognition (first miss and total correct); Telephone Number Recall (7-digit and 10-digit number correct); House and Object Placement Task (total acquisition and first trial)	The MAC-Q questionnaire demonstrates internal consistency and test-retest reliability.
Clinical Global Impression-item 2 (CGI- 2)	This rating instrument expresses the global change in observable cognitive functioning directly on a transitional scale ranging from 1 (very much improved) to 7 (very much deteriorated) as rated by a clinician.	This is a sub-test of the CGI, it is easy and quick to administer and is widely used in clinical and trial settings.
Digit symbol substitution subtest (DSST) of the Wechsler Adult Intelligence Scale-Revised	Participants fill in a grid of 100 blank squares, each paired with a randomly assigned number from 1 to 9, using a key that pairs each number with a different symbol. The score is the number of correct answers after 90 seconds.	Performance on this test is affected by many different components, so the test lacks specificity. Participants with impaired vision or visuomotor coordination, pronounced motor slowing or low education levels are at a disadvantage.
Fuld object-memory evaluation (FOME)	Ten item assessment with ten common objects in a bag are presented "to determine whether the patient can identify objects by touch" (stereognosis). The test was developed while testing large samples of aged adults, nursing home residents and community active people, for whom norms are provided.	Unable to source data on reliability and validity.
Mini-Mental State Examination (MMSE)	11 questions on orientation, memory, concentration, language and praxis.	Good reliability and validity for its original purpose of screening for

Type	Construct measure and scoring	Critical appraisal
	Scale ranges from 0-30. Higher score indicates less impairment. There is no range of scores that can be rigidly and universally applied to indicate dementia severity i.e. as a marker of mild, moderate and severe dementia. In clinical trials often a score of 21-26 is associated with mild AD, moderate AD is associated with an MMSE of 10 to 20 and severe AD is usually associated with an MMSE of less than 10. This may be less suitable within routine daily practice.	dementia, short screening scales are not designed to measure more subtle aspects of cognition. Short scales such as the MMSE may indicate little or no change over time in subjects who would otherwise be shown to have declined substantially if another scale had been used to measure change in status. Not an ideal outcome measure for AD drug trials, especially if the expected benefits are not large. It has dependence on intact language ability and there are no available validated versions in languages suitable for use with ethnic minorities. It cannot be used effectively in people with low IQs or learning disabilities.
Severe Impairment Battery (SIB)	A measure of cognition that was developed to assess a range of cognitive functioning in individuals who are too impaired to complete standard neuropsychological tests and takes into account specific behavioural and cognitive deficits associated with severe dementia. It is composed of 40 simple one-step commands which are scored on a three point scale and are presented in conjunction with gestural cues. The SIB also allows for non-verbal and partially correct responses. The six major subscales are attention, orientation, language, memory, visuo-spatial ability, and construction. Overall scores range from 0-1000 with positive scores indicating clinical improvement	The SIB has been shown to be psychometrically reliable and clinical norms are available. No further details of reliability and validity have been sourced.
Syndrom Kurz Test (SKT)	A psychometric test battery for the assessment of memory and attention. The SKT consists of nine 1 minute subtests that are partly speed oriented and partly span orientated: scaled subtest scores are aggregated to an SKT total status score ranting from 1 (very good) to 27 (very poor).	This test has shown good test-retest reliability. Correlations with other cognitive measures support its validity as a cognitive outcome measure for AD.
Ten Point Clock Drawing Test	This is a screening test for dementia in particular for assessing visuospatial and executive functions. Patients have to drawn in the numbers of digits placed in a pre drawn circle.	This test has been shown to be both reliable and valid and is simple and easy to administer with good sensitivity and specificity.

Type	Construct measure and scoring	Critical appraisal
Trail Making Test (TMT)	Assesses speed of visual search, attention, mental flexibility and motor function. The test has two parts: A) drawing a line linking numbers in sequence and B) drawing a line linking letters in sequence. The reviewer calls any mistakes to the attention of the participant, and these must be corrected before progressing. The score is the time taken to successfully complete a test.	Reliability is reported to be higher for part A than for part B, which requires more information-processing ability and is more sensitive to brain damage. Reliability is restricted due to the use of time scores rather than both error counts and time scores, since error correction may take longer in some participants than others. Scores are strongly affected by the participant's education level.
Wechsler logical memory test	This test is one of 13 subtests of the Wechsler Memory Scale-Revised. The first subtest is for screening purposes, and the other 12 are grouped into five separate memory areas. The test manual provides guidelines for scoring and weighting, and provides norms for individuals aged 16-74 with information about significant differences between any two scores.	Test-retest reliability and concurrent validity with a verbal learning test are adequate for the whole WMS-R test. Level of education affects a participant's score. Normative data for those aged 75 and over is lacking. The score is more heavily influenced by verbal memory performance than by other memory components.

Functional and quality of life outcome measurement scales

Type	Construct measure and scoring	Critical appraisal
Alzheimer's Disease Cooperative Study-Activities of Daily Living ADCS-ADL	This rating scale is a 23-item assessment of ADLs that is scored from 0 (greatest impairment) to 78. It evaluates Activities of daily living.	The ADCS-ADL is a structured questionnaire originally created to assess functional capacity over a broad range of severity of dementia. The ADAS-ADL_{19} is a subset of the original inventory and focuses on items appropriate for the assessment of later stages of dementia. The sensitivity and reliability of this modification has been established.
Alzheimer's Disease Functional assessment and Change Scale (ADFACS)	Scale consists of 10 items for instrumental ADL: ability to use the telephone, performing household tasks, using household appliances, handling money, shopping, preparing food, ability to get around both inside and outside the home, pursuing hobbies and leisure activities, handling personal mail, grasping situations or explanations. Scale has a range of 0 to 54 where lower scores correspond to better function. Test takes approximately 20 minutes to complete.	Full assessment of psychometric properties not yet published. Has face validity for those with mild-moderate AD. The ADL items chosen for this scale have been demonstrated to be sensitive to change over 12 months, correlate well with MMSE scores, and have good test-retest reliability (although several questions have been modified in the scale).

Type	Construct measure and scoring	Critical appraisal
Behavioural Rating Scale for Geriatric Patients (BGP)	Consists of 35 items (scored 0, 1, or 2) assessing observable aspects of cognition, function and behaviour. A high score indicates worse function.	Unable to source data on reliability and validity.
Bristol Activities of Daily Living scale (BADL)	Caregiver assessment of 20 ADLs. Categories included are food, eating, drinks, drinking, dressing, hygiene, teeth, bath, toilet, transferring, mobility, orientation to time and space, communication, telephone, housework/gardening, shopping, finances, hobbies, and transport. Scores range from 0 - 60 with higher scores indicating better function.	Designed specifically for use with patients with dementia. Face validity was measured by asking carers whether items were important, and construct validity was confirmed by principal components analysis. Concurrent validity was assessed by observed performance, the test has good content validity, and there is good test-retest reliability. The test is shown to correlate well with performance ADLs and tests of cognitive function.
Caregiver-rated Modified Crichton Scale (CMCS)	A modified Crichton Geriatric Rating Scale (CGRS). This a seven-item scale using a Likert-type scoring method. Questions include comprehension to time and place, carrying out conversation, cooperation, restlessness, dressing, social activities and leisure. Negative change relates to clinical improvement.	Reliability demonstrated. Unable to source data on validity.
Disability Assessment for Dementia (DAD)	This rating scale is a 46-item structured interview or questionnaire for the caregiver that is scored from 0 to 100 (least impairment). It evaluates ADLs and takes approximately 20 minutes to complete. It is based on a recognised conceptual definition of disability from the WHO	The DAD scale demonstrates a high degree of internal consistency and excellent interrater and test-retest reliability. Full details of concurrent and construct validity not yet published.
Functional Assessment Staging scale (FAST)	Assesses the magnitude of progressive functional deterioration in patients with dementia by identifying characteristic progressive disabilities. Seven major stages range from normal (stage 1) to severe dementia (Stage 7).	FAST has been shown to be a reliable and valid assessment technique for evaluating functional deterioration in AD patients throughout the entire course of the illness. Because the elements of functional capacity incorporated in FAST are relatively universal and readily ascertainable, as well as characteristic of the course of AD, FAST can serve as a strong diagnostic and differential diagnostic aid for clinicians.
General Health Questionnaire (GHQ-30)	GHQ-30 The GHQ is a self-report psychiatric screening test, and items include questions on: depression and	GHQ-30 is based on Medical Outcomes Study Short Form-36, which is extensively validated

Type	Construct measure and scoring	Critical appraisal
	unhappiness, anxiety and felt psychological disturbance, social impairment, and hypochondriasis. Participants rate themselves on a four-point severity scale, according to how they have recently experienced each GHQ item: better than usual, same as usual, worse than usual, or much worse than usual. Normally each item is scored either 0 or 1, depending on which severity choice is selected. Individual items are summed to give the total score.	
Instrumental Activities of Daily Living (IADL)	For women, the set of behaviour assessed include telephoning, shopping, food preparation, housekeeping, laundering, use of transport, use of medicine and ability to handle money. For men, the areas of food preparation, housekeeping and laundering are excluded. Each of the behavioural areas is given a score of 0 or 1, leading to an overall score that ranges from 0 to 8 for women and from 0 to 5 for men.	The IADL is a very frequently used and often cited instrument for assessing the instrumental competence of elderly patients. The scale is well anchored from a theoretical point of view and the behaviours that are included are likely to be affected in the first stages of dementia.
The Interview for Deterioration in Daily Living in Dementia (IDDD)	The IDDD measures functional disability in self-care (16 items such as washing, dressing and eating) and complex activities (17 items such as shopping, writing, and answering the telephone) Severity of impairment is rated on a 7-point scale, where 1-2=no or slight impairment, 3-4=mild impairment, 5-6=moderate impairment, 7=severe impairment, giving a total range score of 22-231.	This scale appears to be appropriate to assess community-living patients with mild and moderate levels of dementia. It assesses a substantial proportion of complex activities likely to be affected during the first stages of the AD. The number of non-redundant items in the scale is viewed positively since it may increase the sensitivity of the tool. Empirical info on the testing of the IDDD and its measurement properties is seriously lacking.
Physical Self-Maintenance Scale (PSMS)	Measured through competence of 6 behaviours: toileting, feeding, dressing, grooming, locomotion and bathing. It can be completed by untrained staff based on information from subjects, caregivers, friends etc. Each behavioural area is given a score of 1 or 0, with over score ranging from 0 to 6. Using Guttman scaling, each scale point has 5 descriptive scale points.	Brief assessment of activities of daily living. Theoretically well grounded, it has been proven useful for evaluation of institutionalised elderly but has a ceiling effect for those living in the community. Testing of psychometric properties is incomplete.
The Progressive Deterioration Scale (PDS)	PDS examines activities of daily living and instrumental activities of daily living. Examples are: extent to which a patient can leave the immediate neighbourhood, use of familiar household implements, involvement	This scale has been shown to be sensitive to three severity stages of dementia although some debate whether the content is adequate to assess those with moderately-severe

Type	Construct measure and scoring	Critical appraisal
	in family finances, budgeting. Each question is scored by measuring the distance along the line on a scale from 0 to 100, with higher scores reflecting better functionality. A composite score is derived from averaging across the items for a maximal score of 100. The scale is sometimes classified as a measure of quality of life.	AD. The scale was systematically developed and tested on a fairly large sample of AD patients (although the mean age of the final test group was only 69.5 years). Test-retest reliability was determined in 123 patients, giving stage correlations (rs) of 0.889 for early AD (14 participants), 0.775 for 44 middle stage participants and 0.775 for 65 late stage participants. A moderate degree of correlation has been demonstrated between PDS and ADAS-cog scores (rp= -0.57 to -0.64). There is considerable reduplication within the scale – 4 questions relate to handling finances but there are no items pertaining to basic activities such as washing, dressing and toileting. The scale is therefore not thought to have adequate content to assess people with moderately severe AD as it does not assess the wide range of daily living skills affected at different stages of the disease. There are high levels of between and within patient variability (in the order of 12 points) which may make it less suited to detect differences over short time periods.
QOL (patient and caregiver scales)	This assessment was a 7-item patient-rated scale evaluating the patients perceptions of their well-being in terms of relationships, eating and sleeping, and social and leisure activities. The tests is conducted by interview. Scored on an analogue scale between 0 (worst quality) to 50 (best quality).	This instrument has not been validated in patients with Alzheimer's disease but was selected because no QOL instrument has been validated in this population.
Unified Activities of Daily Living Form (Unified ADL)	All self-care and mobility variables commonly used to assess patient's functional status. A 20-item scale was produced. The need for assistance is scored for every item, on a 10-point scale.	The psychometric properties of this scale, resulting from the combination of existing evaluations, have not been published.

Behaviour and mood outcome measurement scales

Type	Construct measure and scoring	Critical appraisal
Behavioural Pathology in Alzheimer's Disease rating scale (BEHAVE-AD)	A measure of the severity of behavioural symptoms in AD. It consists of 25 symptoms group onto seven categories. Each symptom is scored on the basis of severity on a four point scale.	The BEHAVE-AD has been shown to be reliable and valid.
Behavioural Rating Scale for Geriatric patients (BGP)	A 35 item rating scale more commonly used in European trials.	No information about the reliability or validity of this scale was found.
NOSGER - Nurses Observation Scale for Geriatric Patients	Contains 30 items of behaviour, each rated on a 5-point scale according to frequency of occurrence. Item scores are summarized into 6 dimension scores (memory, instrumental activities of daily life, self-care, mood, social behaviour, and disturbing behaviour).	This scale has been validated, and has high inter-rater and test-retest reliability. The test correlates well with clinician's global rating of change.
Neuro-psychiatric Inventory (NPI)	Currently evaluates 12 items: delusions, hallucinations, dysphoria, anxiety, agitation, euphoria, apathy, irritability, disinhibition, aberrant motor behaviour, night-time behaviour and changes in appetite/eating behaviour. Psychometric properties were established on first 10 items. Total score for each domain is calculated by multiplying frequency rating by severity rating, adding domain scores to get a total score. Higher scores represent more problems. Maximum scores is 12 per domain, with either 10 or 12 domains assessed.	Content validity has been established, reliability and validity are satisfactory. Limitations included: poor description of appraisal period for behavioural symptoms; no justification for scoring system; and, inter-rater reliability was poorly deserved.

Appendix 2: Literature search strategies

Clinical effectiveness search strategy

The Medline search strategy below was translated and run in:

DATABASE	Search Date
MEDLINE (Ovid) and Medline In Process : 1950 to present	16/11/2009
EMBASE (Ovid): 1980 to 2009 week 46	16/11/2009
PsycINFO (OVID): 2002 to November Week 2 2009	16/11/2009
Cochrane CENTRAL Register of Controlled Trials (CCTR): 2009 Issue 4	13/11/2009
Cochrane Database of Systematic Reviews (CDSR):2009 Issue 4	13/11/2009
CRD databases: NHSEED, HTA, DARE	16/11/2009
ISI Web of Science: Science Citation Index	16/11/2009
ISI Web of Science : Conference Proceedings Citation Index	16/11/2009
BIOSIS – via ISI Web of Science	16/11/2009

All searches were then rerun on March 31, 2010

MEDLINE OVID 1950 to present

Search Date: 16/11/2009 re-run search date: 31/03/2010

1-Alzheimer Disease/

2-alzheimer*.tw.

3-1 or 2

4-Memantine/

5-Memantine.mp.

6-ebixa.mp.

7-axura.mp.

8-namenda*.mp.

9-or/4-8

10-Galantamine/

11-galantamin*.mp.

12-galanthamine.mp.

13-Epigalanthamin.mp.

14-Jilkon*.mp.

15-Lycoremin*.mp.

16-Nivalin*.mp.

17-Razadyne*.mp.

18-Reminyl*.mp.

19-or/10-18

20-donepezil*.mp.

21-donezepil*.mp.

22-aricept*.mp.

23-Memac*.mp.

24-Memorit*.mp.

25-Eranz*.mp.

26-or/20-25

27-rivastigmin*.mp.

28-exelon*.mp.

29-prometax*.mp.

30-or/27-29

31-30 or 26 or 19 or 9

32-3 and 31

33-Randomized controlled trial.pt.

34-randomized controlled trial/

35-(random$ or placebo$).ti,ab,sh.

36-((singl$ or double$ or triple$ or treble$) and (blind$ or mask$)).tw,sh.

37-or/33-36

38-clinical trial/

39-"controlled clinical trial".pt.

40-(retraction of publication or retracted publication).pt.

41-37 or 38 or 39 or 40

42-32 and 41

43-(animals not humans).sh.

44-42 not 43

45-limit 44 to (english language and yr="2004 -Current")

Cost-effectiveness search strategy

This following Medline search strategy was translated and run in:

DATABASE	Search Date
MEDLINE (Ovid) and Medline In Process : 1950 to present	05/02/2010
EMBASE (Ovid): 1980 to 2009 week 46	05/02/2010
PsycINFO (OVID): 2002 to November Week 2 2009	04/02/2010
Cochrane CENTRAL Register of Controlled Trials (CCTR): 2009 Issue 4	04/02/2010
Cochrane Database of Systematic Reviews (CDSR):2009 Issue 4	13/11/2009
CRD databases: NHSEED, HTA, DARE	05/02/2010
ISI Web of Science: Science Citation Index	05/02/2010
ISI Web of Science : Conference Proceedings Citation Index	05/02/2010
BIOSIS – via ISI Web of Science	05/02/2010

EconLIT	05/02/2010

MEDLINE (Ovid) 1950 – Present

Searched 04/02/2010

1 exp Alzheimer Disease/

2 alzheimer$.ti,ab.

3 1 or 2

4 Economics, Medical/

5 Economics, Nursing/

6 exp economics, hospital/

7 economics pharmaceutical/

8 ec.fs.

9 exp "Costs and Cost Analysis"/

10 exp Cost-Benefit Analysis/

11 "Value of Life"/

12 exp Models, Economic/

13 exp "Fees and Charges"/

14 Resource Allocation/

15 exp Budgets/

16 budget*.tw.

17 (economic$ or price$ or pricing or financ$ or fee$ or pharmacoeconomic$ or pharma economic$).tw.

18 (expenditure$ not energy).tw.

19 (value$5 adj2 (money or monetary or life or lives or cost$2)).tw.

20 (economic adj2 burden).tw.

21 (resource$2 adj2 (use* or utili* or allocat*)).tw.

22 (cost$2 adj2 (benefit$ or consequence* or analys* or saving* or breakdown* or lowering or estimat* or variable* or allocation* or control* or illness* or affordable* or instrument* or technolog* or fee* or charge$2 or utilit$ or minim$ or effective$ or effective* or efficac*)).ab.

23 cost.ti.

24 22 or 23

25 or/4-24

26 Memantine/

27 Memantine.mp.

28 ebixa.mp.

29 axura.mp.

30 namenda*.mp.

31 Galantamine/

32 galantamin*.mp.

33 galanthamine.mp.

34 Epigalanthamin.mp.
35 Jilkon*.mp.
36 Lycoremin*.mp.
37 Nivalin*.mp.
38 Razadyne*.mp.
39 Reminyl*.mp.
40 donepezil*.mp.
41 donezepil*.mp.
42 aricept*.mp.
43 Memac*.mp.
44 Memorit*.mp.
45 Eranz*.mp.
46 rivastigmin*.mp.
47 exelon*.mp.
48 prometax*.mp.
49 or/26-48
50 3 and 25 and 49
51 limit 50 to (english language and yr="2004 -Current")

Quality of Life and Utilities Search Strategy

This following Medline search strategy was translated and run in:

DATABASE	Search Date
MEDLINE (Ovid) and Medline In Process : 1950 to present	06/01/2010
EMBASE (Ovid): 1980 to 2009 week 46	05/02/2010
PsycINFO (OVID): 2002 to November Week 2 2009	04/02/2010
Cochrane CENTRAL Register of Controlled Trials (CCTR): 2009 Issue 4	04/02/2010
Cochrane Database of Systematic Reviews (CDSR):2009 Issue 4	13/11/2009
CRD databases: NHSEED, HTA, DARE	05/02/2010
ISI Web of Science: Science Citation Index	05/02/2010
ISI Web of Science : Conference Proceedings Citation Index	05/02/2010
BIOSIS – via ISI Web of Science	05/02/2010
EconLIT	05/02/2010

1 "Quality of Life"/
2 "Value of Life"/
3 ((qualit$3 or value) adj2 life).tw.
4 quality-adjusted life years/
5 quality adjusted.tw.
6 (qaly* or qald* or qale* or qtime* or qualy).tw.
7 sickness impact profile/
8 (disabilit$3 adj2 life).tw.

9 daly.tw.

10 Health Status Indicators/

11 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirstysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).tw.

12 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.

13 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).tw.

14 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.

15 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).tw.

16 (euroqol or euro qol or eq5d or eq 5d).tw.

17 (hql or hqol or qol or hrqol).tw.

18 (hye or hyes).tw.

19 health$ year$ equivalent$.tw.

20 (health utilit* or utilities or utility value*).tw.

21 hui$1.tw.

22 disutil$.tw.

23 rosser.tw.

24 (quality adj3 well).tw.

25 quality of wellbeing.tw.

26 qwb.tw.

27 willingness to pay.tw.

28 standard gamble$.tw.

29 (time trade off or time tradeoff or tto).tw.

30 (health adj3 (utilit$3 or value$2 or preference$2)).tw.

31 (visual analog$3 scale or VAS).tw.

32 (health adj2 (utilit$3 or value$2 or preference$2)).tw.

33 patient preference$2.tw.

34 or/1-33

35 mini mental state exam$.ti,ab.

36 ((mmse or mmmse) adj5 alzheimer*).ti,ab.

37 modified mmse.ti,ab.

38 alzheimer$ disease assessment scale$.ti,ab.

39 adas.ti,ab.

40 adas cog$.ti,ab.

41 cibic$.ti,ab.

42 progressive deterioration scale$.ti,ab.

43 (pds adj5 alzheimer*).ti,ab.

44 (clinical global impression of change or CGIC).tw.

45 clinic* interview based impression of change.tw.

46 (CDR or clinical dementia rating).tw.
47 alzheimer$.tw.
48 Alzheimer Disease/
49 47 or 48
50 34 and 49
51 (cognitive adj (scale* or rating or rate)).tw.
52 49 and 51
53 or/35-46
54 49 and 53
55 50 or 52 or 54
56 limit 55 to (english language and yr="2004 -Current")

Additional searches for economic modelling parameters:

This below Medline search strategy was translated and run in:

DATABASES	Search Date
Ovid MEDLINE: 1950 to present	07/01/2010
Ovid MEDLINE In Process and other non-indexed citations	07/01/2010
BIOSIS via Web of Science	08/01/2010
EMBASE 1980 to 2009 week 46	07/01/2010
ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED)	08/01/2010
ISI Web of Science: conference Proceedings Citation Index- Science (CPCI-S)-	08/01/2010
NHSEED via CRD databases	08/01/2010
Econlit via First Search	08/01/2010

Ovid MEDLINE(R) <1950 to October Week 2 2007>.

Searched 24/10/07

1 Alzheimer Disease/
2 alzheimer$.tw.
3 1 or 2
4 exp Models, Economic/
5 *Models, Theoretical/
6 *Models, Organizational/
7 economic model$.ti,ab.
8 Markov Chains/
9 markov$.ti,ab.
10 Monte Carlo Method/
11 monte carlo.ti,ab.
12 exp Decision Theory/
13 (decision$ adj2 (tree$ or analy$ or model$)).ti,ab.

14 or/4-13

15 3 and 14

16 limit 15 to (english language and yr="2004 -Current")

Additional searches for Dementia model parameter, quality of life and utilities:

This (below) Medline search strategy was translated and run in:

DATABASES	Search Date
Ovid MEDLINE 1950 to present	19/02/2010
Ovid MEDLINE In Process and other non-indexed citations	19/02/2010
EMBASE – 1980 to 2009 week 46	19/02/2010
PsycINFO (OVID): 2002 to November Week 2 2009	19/02/2010
NHSEED via CRD databases	19/02/2010

Ovid MEDLINE(R) <1950 to October Week 2 2007>.

Search Date: 19/02/2010

1 Dementia/ (29095)
2 *Dementia/ (22077)
3 dementia.ti. (22047)
4 2 or 3 (30348)
5 exp Models, Economic/ (6944)
6 (economic next model* or markov* or monte next carlo).ti. (1847)
7 (economic next model* or markov* or monte next carlo).ab. (7968)
8 or/5-7 (14883)
9 4 and 8 (28)
10 1 and 8 (29)
11 9 or 10 (33)
12 "Quality of Life"/ (79428)
13 (quality adj2 life).ti. (26019)
14 (quality adj2 life).ab. (87761)
15 quality-adjusted life years/ (4171)
16 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirstysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).tw. (9883)
17 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1012)
18 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).tw. (1382)
19 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (19)
20 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).tw. (288)
21 (euroqol or euro qol or eq5d or eq 5d).tw. (1832)
22 utilit*.ti. (12510)
23 or/12-22 (141512)
24 4 and 23 (1064)
25 9 or 24 (1085)
26 limit 25 to english language (905)
27 from 26 keep 1-905 (905)

Additional citation searching and ad-hoc searches were performed for model parameters.

Appendix 3: Data extraction forms

Design	Participants	Arms	OUTCOMES
Brodaty et al. (2005){245 /id} **Study design:** Parallel double-blind RCT **Country:** United States, Australia, Canada, South Africa, and New Zealand **No. of centres:** 93 **Funding:** none reported **Length of follow-up (wk):** 26 **Notes** -	**Number randomised:** 971 **MMSE min:** 10 **MMSE max:** 24 **Inclusion criteria:** mild to moderate probable AD (NINCDS-ADRDA) MMSE 10–24 ADAS-cog/11 ≥18 history of cognitive decline that was gradual in onset and progressive over a period of ≥6mo living with or regular daily visits from a responsible caregiver (≥5d/wk) **Exclusion criteria:** other neurodegenerative disorders or cognitive impairment due to acute cerebral trauma, hypoxic cerebral damage, vitamin deficiency states, infection, primary or metastatic cerebral neoplasia, significant endocrine or metabolic disease, or mental retardation vascular dementia or evidence of clinically active cerebrovascular disease history of epilepsy or convulsions; current clinically significant psychiatric disease; active peptic ulcer; clinically significant hepatic, renal, pulmonary, metabolic, or endocrine disturbances; clinically significant urinary outflow obstruction; clinically significant cardiovascular disease use of any agent for the treatment of dementia (approved, experimental, or over the counter) including, but not limited to, nootropic agents, cholinomimetic agents, estrogens taken without medical need, chronic nonsteroidal anti-infl ammatory agents or cycloxygenase-2 inhibitors (>30 consecutive days, regardless of indication), and vitamin E (unless a stable dose had been taken for ≥6mo prior to trial initiation). **Therapy common to all participants:** 1mo placebo run-in prior to treatment allocation **Sample attrition / dropout:** 768 of 971 completed study. 203 withdrew after allocation: did not receive treatment (n=6); adverse event (n=67); withdrew consent (n=62); noncompliance (n=29); lost to follow-up (n=10); insufficent response (n=10); death (n=5); other reasons (n=3). No differences between groups.	**Arm No:** 1 **Name:** Galantamine prolonged release od **N:** 320 **Drug:** Galantamine **Starting daily dose (mg):** 8 **Dosage details:** prolonged release formulation titrated from an initial dosage of 8mg/d for the first 4wk up to a maximum of 24mg/d in increments of 8 mg/day every 4wk after the placebo run-in whole dose given in single capsule in am; placebo given in pm **Arm No:** 2 **Name:** Galantamine bd **N:** 327 **Drug:** Galantamine **Starting daily dose (mg):** 8 **Dosage details:** titrated from an initial dosage of 8mg/d for the first 4wk up to a maximum of 24mg/d in increments of 8 mg/day every 4wk after the placebo run-in single capsules in am and pm **Arm No:** 3 **Name:** Placebo **N:** 324 **Drug:** Placebo **Starting daily dose (mg):** - **Dosage details:** single placebo dose in am and pm	Participants attended clinic visits scheduled for day 0 (baseline) and weeks 4, 8, 12, and 26. **Cognitive** ▪ ADAS-cog (assessment of 11 items on the cognitive subscale of the ADAS) **Functional** ▪ ADCS-ADL (measured using a 23-item subscale of the ADCS-ADL appropriate for subjects in the mild to moderate category of AD) **Behavioural** ▪ NPI (severity and frequency of each symptom rated on the basis of scripted questions administered to the subject's caregiver) **Global severity** ▪ CIBIC-plus **Adverse events**

Baseline characteristics

	Galantamine prolonged release od	Placebo

		N	K	MEAN	N	K	MEAN	*P*
Demographics:								
Age	C	319		76.6 (SD 7.64)	320		76.3 (SD 8.03)	0.629[a]
Sex (n male)	D	319	114	(35.7%)	320	115	(35.9%)	0.976[b]
Weight (kg)	C	318		68.6 (SD 14.2)	319		67.8 (SD 14.6)	0.472[a]
Race (n white)	D	319	297	(93.1%)	320	289	(90.3%)	0.256[b]
Cognitive:								
Mini Mental State Examination	C	319		18 (SD 3.97)	320		18.1 (SD 4.08)	

[a] student's t-test (calculated by reviewer)

[b] chi-square test (Yates's correction) (calculated by reviewer)

		Galantamine bd			Placebo			
		N	K	MEAN	N	K	MEAN	*P*
Demographics:								
Age	C	326		76.5 (SD 7.77)	320		76.3 (SD 8.03)	0.748[a]
Sex (n male)	D	326	118	(36.2%)	320	115	(35.9%)	0.989[b]
Weight (kg)	C	326		68.3 (SD 15.9)	319		67.8 (SD 14.6)	0.671[a]
Race (n white)	D	326	293	(89.9%)	320	289	(90.3%)	0.957[b]
Cognitive:								
Mini Mental State Examination	C	326		17.8 (SD 4.14)	320		18.1 (SD 4.08)	

[a] student's t-test (calculated by reviewer)

[b] chi-square test (Yates's correction) (calculated by reviewer)

Results

		Galantamine prolonged release od			Placebo			
		N	K	MEAN	N	K	MEAN	*P*
Study medication:								
Duration of treatment – 26wk	C	319		152 (SD 46.9)	320		161 (SD 46.9)	
ITT population								
Disposition of participants:								
Discontinued treatment due to AEs – 26wk	D	320	28	(8.8%)	324	15	(4.6%)	
Discontinued treatment before end of trial – 26wk	D	320	68	(21.3%)	324	54	(16.7%)	
LOCF analysis								
Cognitive:								
ADAS-cog – 8wk	MC	287		-1.5 (SD 5.08)	293		0 (SD 5.14)	
ADAS-cog – 12wk	MC	290		-2 (SD 5.28)	296		0.2 (SD 5.33)	
ADAS-cog – 26wk	MC	240		-1.3 (SD 5.29)	248		1.2 (SD 5.68)	<0.001[a]
ADAS-cog – 26wk	MC	291		-1.3 (SD 5.29)	296		1.2 (SD 5.68)	<0.001[a]
Functional:							-2.7 (SD	
ADCS-ADL – 26wk[b]	MC	245		0 (SD 7.51)	258		8.99)	<0.001[a]
Behavioural:							0.6 (SD	
NPI – 26wk[b]	MC	245		-0.6 (SD 10.3)	258		9.96)	0.941[a]
Global severity:							4.35 (SD	
CIBIC-plus score – 26wk	C	291		4.21 (SD 1.1)	301		1.14)	NS[c]
CIBIC-plus: markedly improved – 26wk	D	291	3	(1.0%)	301	3	(1.0%)	0.712[d]
CIBIC-plus: moderately improved – 26wk	D	291	14	(4.8%)	301	11	(3.7%)	0.621[d]
CIBIC-plus: minimally improved – 26wk	D	291	49	(16.8%)	301	48	(15.9%)	0.856[d]
CIBIC-plus: no change – 26wk	D	291	114	(39.2%)	301	111	(36.9%)	0.623[d]
CIBIC-plus: minimally worse – 26wk	D	291	81	(27.8%)	301	80	(26.6%)	0.802[d]
CIBIC-plus: moderately worse – 26wk	D	291	24	(8.2%)	301	41	(13.6%)	0.050[d]
CIBIC-plus: markedly worse – 26wk	D	291	6	(2.1%)	301	7	(2.3%)	0.951[d]

OC population								
Cognitive:								
ADAS-cog – 8wk	MC	284		-1.5 (SD 5.06)	289		0 (SD 5.1)	
ADAS-cog – 12wk	MC	269		-2.2 (SD 5.25)	275		0 (SD 5.14)	
ADAS-cog – 26wk	MC	240		-1.4 (SD 5.27)	248		1.3 (SD 5.67)	<0.001[a]
Functional:								
ADCS-ADL – 8wk	MC	280		0.8 (SD 6.86)	294		-0.7 (SD 7.72)	
ADCS-ADL – 12wk	MC	276		0.4 (SD 6.65)	281		-0.3 (SD 7.71)	
ADCS-ADL – 26wk	MC	245		0 (SD 8.61)	258		-2.4 (SD 9.64)	0.003[a]
Behavioural:								
NPI – 26wk	MC	245		-0.6 (SD 10.8)	258		0.1 (SD 13.2)	0.451[a]
Global severity:								
CIBIC-plus score – 26wk	C	246		4.19 (SD 1.13)	259		4.36 (SD 1.15)	NS[c]
CIBIC-plus: markedly improved – 26wk	D	246	3	(1.2%)	259	3	(1.2%)	0.728[d]
CIBIC-plus: moderately improved – 26wk	D	246	14	(5.7%)	259	9	(3.5%)	0.327[d]
CIBIC-plus: minimally improved – 26wk	D	246	43	(17.5%)	259	41	(15.8%)	0.705[d]
CIBIC-plus: no change – 26wk	D	246	90	(36.6%)	259	94	(36.3%)	0.981[d]
CIBIC-plus: minimally worse – 26wk	D	246	69	(28.0%)	259	70	(27.0%)	0.875[d]
CIBIC-plus: moderately worse – 26wk	D	246	23	(9.3%)	259	36	(13.9%)	0.146[d]
CIBIC-plus: markedly worse – 26wk	D	246	4	(1.6%)	259	6	(2.3%)	0.812[d]
Safety population								
Adverse events:								
Any AE – 0wk	D	319	253	(79.3%)	320	224	(70.0%)	0.009[d]
Any gastrointestinal – 0wk	D	319	111	(34.8%)	320	80	(25.0%)	0.009[d]
Any psychiatric – 0wk	D	319	73	(22.9%)	320	66	(20.6%)	0.551[d]
Any general – 0wk	D	319	76	(23.8%)	320	60	(18.8%)	0.141[d]
Any central/peripheral nervous system – 0wk	D	319	77	(24.1%)	320	52	(16.3%)	0.017[d]
Any respiratory – 0wk	D	319	45	(14.1%)	320	43	(13.4%)	
Any metabolic/nutritional – 0wk	D	319	42	(13.2%)	320	36	(11.3%)	
Any urinary – 0wk	D	319	40	(12.5%)	320	38	(11.9%)	
Any secondary term – 0wk	D	319	28	(8.8%)	320	39	(12.2%)	
Anorexia – 0wk	D	319	19	(6.0%)	320	8	(2.5%)	
Nausea – 0wk	D	319	54	(16.9%)	320	16	(5.0%)	
Diarrhoea – 0wk	D	319	15	(4.7%)	320	22	(6.9%)	
Vomiting – 0wk	D	319	21	(6.6%)	320	7	(2.2%)	
Agitation – 0wk	D	319	22	(6.9%)	320	21	(6.6%)	
Depression – 0wk	D	319	18	(5.6%)	320	8	(2.5%)	
Injury – 0wk	D	319	24	(7.5%)	320	18	(5.6%)	
Dizziness – 0wk	D	319	33	(10.3%)	320	14	(4.4%)	
Headache – 0wk	D	319	29	(9.1%)	320	18	(5.6%)	
Upper respiratory tract infection – 0wk	D	319	15	(4.7%)	320	16	(5.0%)	
Weight decrease – 0wk	D	319	14	(4.4%)	320	4	(1.3%)	
Urinary tract infection – 0wk	D	319	22	(6.9%)	320	26	(8.1%)	
Fall – 0wk	D	319	20	(6.3%)	320	19	(5.9%)	

[a] ANOVA with factors for treatment and pooled country (United States vs. ex-United States)

[b] sample size not provided (must presumably be greater than the 26wk observed data cases)

[c] Cochrane-Mantel-Haenszel statistic using modified ridit scores, derived from rank score (the Van Elteren test) and controlling for country effect (United States vs. ex-United States)

[d] chi-square test (Yates's correction) (calculated by reviewer)

		Galantamine bd			Placebo			
		N	**K**	**MEAN**	**N**	**K**	**MEAN**	***P***
Study medication:								
Duration of treatment – 26wk	C	326		156 (SD 51.3)	320		161 (SD 46.9)	
ITT population								
Disposition of participants:								
Discontinued treatment due to AEs – 26wk	D	327	25	(7.6%)	324	15	(4.6%)	
Discontinued treatment before end of trial – 26wk	D	327	75	(22.9%)	324	54	(16.7%)	

LOCF analysis							
Cognitive:							
ADAS-cog – 8wk	MC	294		-1.7 (SD 4.97)	293	0 (SD 5.14)	
ADAS-cog – 12wk	MC	296		-2.5 (SD 5.16)	296	0.2 (SD 5.33)	
ADAS-cog – 26wk	MC	227		-1.6 (SD 6.19)	248	1.2 (SD 5.68)	<0.01[a]
ADAS-cog – 26wk	MC	296		-1.6 (SD 6.19)	296	1.2 (SD 5.68)	<0.01[a]
Functional:							
ADCS-ADL – 26wk[b]	MC	242		-1 (SD 0.778)	258	-2.7 (SD 8.99)	0.018[a]
Behavioural:							
NPI – 26wk[b]	MC	242		-0.9 (SD 11.4)	258	0.6 (SD 9.96)	0.102[a]
Global severity:							
CIBIC-plus score – 26wk	C	302		4.21 (SD 1.07)	301	4.35 (SD 1.14)	NS[c]
CIBIC-plus: markedly improved – 26wk	D	302	3	(1.0%)	301	3 (1.0%)	0.685[d]
CIBIC-plus: moderately improved – 26wk	D	302	15	(5.0%)	301	11 (3.7%)	0.553[d]
CIBIC-plus: minimally improved – 26wk	D	302	46	(15.2%)	301	48 (15.9%)	0.897[d]
CIBIC-plus: no change – 26wk	D	302	127	(42.1%)	301	111 (36.9%)	0.224[d]
CIBIC-plus: minimally worse – 26wk	D	302	78	(25.8%)	301	80 (26.6%)	0.907[d]
CIBIC-plus: moderately worse – 26wk	D	302	30	(9.9%)	301	41 (13.6%)	0.201[d]
CIBIC-plus: markedly worse – 26wk	D	302	3	(1.0%)	301	7 (2.3%)	0.336[d]
OC population							
Cognitive:							
ADAS-cog – 8wk	MC	286		-1.7 (SD 5.07)	289	0 (SD 5.1)	
ADAS-cog – 12wk	MC	268		-2.6 (SD 5.07)	275	0 (SD 5.14)	
ADAS-cog – 26wk	MC	227		-1.8 (SD 6.33)	248	1.3 (SD 5.67)	<0.001[a]
Functional:							
ADCS-ADL – 8wk	MC	292		0.9 (SD 7.18)	294	-0.7 (SD 7.72)	
ADCS-ADL – 12wk	MC	279		1.1 (SD 7.85)	281	-0.3 (SD 7.71)	
ADCS-ADL – 26wk	MC	242		-1 (SD 8.87)[e]	258	-2.4 (SD 9.64)	0.088[a]
Behavioural:							
NPI – 26wk	MC	242		-1.2 (SD 12.9)	258	0.1 (SD 13.2)	0.203[a]
Global severity:							
CIBIC-plus score – 26wk	C	240		4.21 (SD 1.11)	259	4.36 (SD 1.15)	NS[c]
CIBIC-plus: markedly improved – 26wk	D	240	3	(1.3%)	259	3 (1.2%)	0.751[d]
CIBIC-plus: moderately improved – 26wk	D	240	14	(5.8%)	259	9 (3.5%)	0.298[d]
CIBIC-plus: minimally improved – 26wk	D	240	36	(15.0%)	259	41 (15.8%)	0.895[d]
CIBIC-plus: no change – 26wk	D	240	93	(38.8%)	259	94 (36.3%)	0.636[d]
CIBIC-plus: minimally worse – 26wk	D	240	67	(27.9%)	259	70 (27.0%)	0.903[d]
CIBIC-plus: moderately worse – 26wk	D	240	25	(10.4%)	259	36 (13.9%)	0.294[d]
CIBIC-plus: markedly worse – 26wk	D	240	2	(0.8%)	259	6 (2.3%)	0.336[d]
Safety population							
Adverse events:							
Any AE – 0wk	D	326	235	(72.1%)	320	224 (70.0%)	
Any gastrointestinal – 0wk	D	326	114	(35.0%)	320	80 (25.0%)	
Any psychiatric – 0wk	D	326	58	(17.8%)	320	66 (20.6%)	
Any general – 0wk	D	326	62	(19.0%)	320	60 (18.8%)	
Any central/peripheral nervous system – 0wk	D	326	69	(21.2%)	320	52 (16.3%)	
Any respiratory – 0wk	D	326	41	(12.6%)	320	43 (13.4%)	
Any metabolic/nutritional – 0wk	D	326	43	(13.2%)	320	36 (11.3%)	
Any urinary – 0wk	D	326	39	(12.0%)	320	38 (11.9%)	
Any secondary term – 0wk	D	326	30	(9.2%)	320	39 (12.2%)	
Anorexia – 0wk	D	326	22	(6.7%)	320	8 (2.5%)	
Nausea – 0wk	D	326	45	(13.8%)	320	16 (5.0%)	
Diarrhoea – 0wk	D	326	22	(6.7%)	320	22 (6.9%)	
Vomiting – 0wk	D	326	28	(8.6%)	320	7 (2.2%)	
Agitation – 0wk	D	326	20	(6.1%)	320	21 (6.6%)	
Depression – 0wk	D	326	16	(4.9%)	320	8 (2.5%)	
Injury – 0wk	D	326	12	(3.7%)	320	18 (5.6%)	
Dizziness – 0wk	D	326	24	(7.4%)	320	14 (4.4%)	
Headache – 0wk	D	326	18	(5.5%)	320	18 (5.6%)	
Upper respiratory tract infection – 0wk	D	326	12	(3.7%)	320	16 (5.0%)	
Weight decrease – 0wk	D	326	17	(5.2%)	320	4 (1.3%)	
Urinary tract infection – 0wk	D	326	22	(6.7%)	320	26 (8.1%)	
Fall – 0wk	D	326	20	(6.1%)	320	19 (5.9%)	

[a] ANOVA with factors for treatment and pooled country (United States vs. ex-United States)

[b] sample size not provided (must presumably be greater than the 26wk observed data cases)

[c] Cochrane-Mantel-Haenszel statistic using modified ridit scores, derived from rank score (the Van Elteren test) and controlling

for country effect (United States vs. ex-United States)

[d] chi-square test (Yates's correction) (calculated by reviewer)

[e] different values for SE given in Table 2 (1.12) and Figure 4 (0.57) of publication; latter used as closer to range of dispersion reported in other arms

Methodological issues

Randomisation and allocation: Randomization to treatment was determined by calling an interactive voice response system. The subject number and treatment code

(which corresponded to a specific medication kit) was randomly generated after the caller at the site provided the requested subject details. All treatments were supplied in opaque, size-0 gelatin capsules that were identical in appearance, taste and smell. All subjects received 1 capsule twice daily.

Data analysis: * ADAS-cog/11, ADCS-ADL, NPI, ADAS-cog/13, nonmemory ADAS-cog, & memory ADAS-cog scores: ANOVA model with factors for treatment and pooled country (USA vs. non-USA)

* CIBIC-plus: Cochrane-Mantel-Haenszel statistic using modified ridit scores, derived from rank score (the Van Elteren test) and controlling

for country effect (USA vs. non-USA) was used to compare the distribution of subjects with scores on the 7-point scale between groups as well as subgroups

* percentage of responders for ADAS-cog/11 and CIBIC-plus were analyzed via Cochrane-Mantel-Haenszel test using modified ridit scores derived from rank scores

The primary efficacy analyses were based on the observed case (OC) population at week 26. The ITT population was defined as all randomized subjects who received ≥1 dose of study medication and who provided ≥1 postbaseline primary efficacy measurement (ADAS-cog or CIBIC-plus). OC data were defined as data slotted into the last scheduled time interval. Analyses based on ITT last observation

carried forward (LOCF) method for missing data also were performed to demonstrate the robustness of results

Power calculation: Powered at >95% to detect a 2.5-point (SD 6.2) difference in ADAS-cog/11 score and at 90% to detect a 15% difference between

active and placebo groups in their CIBIC-plus responder rates, assuming a 55% placebo responder rate (no change/improved CIBIC-plus

score). Required sample size not explicitly reported.

Conflicts of interest: Lead author declares consultancy fees, a grant, and sponsored speaking engagements from Janssen

Quality appraisal

1. **Was the assignment to the treatment groups really random?** ADEQUATE
2. **Was the treatment allocation concealed?** ADEQUATE
3. **Were the groups similar at baseline in terms of prognostic factors?** REPORTED - YES
4. **Were the eligibility criteria specified?** ADEQUATE
5. **Were outcome assessors blinded to the treatment allocation?** ADEQUATE
   treating healthcare providers + caregivers contributed to outcome assessment, though no reason to suspect blinding was compromised
6. **Was the care provider blinded?** ADEQUATE
7. **Was the patient blinded?** ADEQUATE
8. **Were the point estimates and measure of variability presented for the primary outcome measure?** PARTIAL
   in one instance, data are repeated with different measures of dispersion
9. **Did the analyses include an intention-to-treat analysis?** PARTIAL
   LOCF analyses attempted; however, LOCF cohort is less than full sample size and decreases as follow-up extends
10. **Were withdrawals and dropouts completely described?** ADEQUATE

Design	Participants	Arms	OUTCOMES
Bullock et al. (2004){257 /id} **Study design:** Parallel double-blind RCT **Country:** 'Including' Canada, Denmark, Finland, France, Germany, Israel, The	**Number randomised:** 285 **MMSE min:** 10 **MMSE max:** 25 **Inclusion criteria:** Probable vascular dementia (NINDS-	**Arm No:** 1 **Name:** Galantamine **N:** 152 **Drug:** Galantamine	**Cognitive** ▪ ADAS-cog (not defined) ▪ ADAS-cog/13 (methods note as secondary efficacy variable, but outcome data not

Netherlands, Poland, UK **No. of centres:** 62 **Funding:** None reported **Length of follow-up (wk):** 26 **Notes** **Notes:** Follow-up also at 32 and 52 weeks during the open-label phase of the trial Unable to calculate attrition n, as using percentages quoted in the text gives non-whole numbers	AIREN definition) or AD + CVD (NINCDS-ADRDA definition) (with CVD evidenced by CT or MRI) Mild-to-moderate dementia (MMSE 10-25) Score >=12 on 11-item subscale of of AD assessment scale presence of focal neurological signs disease onset at between 40 and 90 years of age **Exclusion criteria:** neurogenerative disorders cognitive impairmentresulting from other cerebral trauma cerebral neoplasia mental retardation vitamin deficiency significant endocrine or metabolic disease clinically significant coexitsng medical conditions significant cardiovascular disease that would likely limit the patinet's ability to complete the study current use of agents for the treatment of dementia recent history (within 30 days) of treatment with other investigational agents history of alcohol or drug abuse **Therapy common to all participants:** 1mo single-blind placebo run-in prior to treatment allocation **Sample attrition / dropout:** 230 of 285 completed study	**Starting daily dose (mg):** 4 **Dosage details:** Titrated upwards in weekly 4mg increments over a period of 6 wks, and then continued at this maintenance dose (24mg/day) for an additional 4.5mo **Arm No:** 2 **Name:** Placebo **N:** 86 **Drug:** Placebo **Starting daily dose (mg):** - **Dosage details:** single placebo dose am and pm	reported) **Functional** ▪ Disability Assessment for Dementia (outcome data only available from study including IPD in a pooled analysis (Feldman et al. 2005{523 /id})) **Behavioural** ▪ NPI (methods note as secondary efficacy variable, but outcome data not reported)

Baseline characteristics

		Galantamine			Placebo			
		N	K	MEAN	N	K	MEAN	*P*
Demographics:								
Age	C	152		75.8 (SD 6.78)	86		77.6 (SD 6.12)	0.043[a]
Sex (n male)	D	152	73	(48.0%)	86	42	(48.8%)	0.988[b]
Height (cm)	C	152		164 (SD 10.4)	86		164 (SD 10.6)	0.943[a]
Weight (kg)	C	152		69.9 (SD 12.9)	86		67 (SD 13)	0.099[a]
Cognitive:								
ADAS-cog – 0wk	C	148		22.7 (SD 9.25)	85		23.9 (SD 9.86)	0.358[a]
Mini Mental State Examination	C	152		20.5 (SD 3.95)	86		20.2 (SD 3.52)	0.559[a]

[a] student's t-test (calculated by reviewer)

[b] chi-square test (Yates's correction) (calculated by reviewer)

Results

		Galantamine			Placebo			
		N	K	MEAN	N	K	MEAN	*P*
ITT population								
Disposition of participants:								
Discontinued treatment due to AEs[a]	D	188	49	(26.1%)	97	16	(16.5%)	
LOCF analysis								
Functional:								
Disability Assessment for Dementia – 26wk	MC	188		-1 (SD 15.8)	97		-6 (SD 14.5)	<0.01[c]
OC population								
Cognitive:								
ADAS-cog – 6wk[d]	MC	148		-0.5 (SD 4.62)	85		0.15 (SD 6.26)	0.366[e]
ADAS-cog – 13wk[d]	MC	148		-1.48 (SD 4.32)	85		0 (SD 6.03)	0.031[e]
ADAS-cog – 26wk	C	147		21.5 (SD 10.5)	83		25.7 (SD 12)	0.006[f]
ADAS-cog – 26wk	MC	147		-1.1 (SD 5.79)	83		2 (SD 5.56)	<0.001[f]

[a] approximated to nearest integer (percentages only presented in text); poor rounding suggests true denominator may be less than full sample size

[b] 523 /id})

[c] test not specified

[d] estimated from figure

[e] student's t-test (calculated by reviewer)

[f] student's t-test (two-tailed) (calculated by reviewer)

Safety data not presented for RCT alone - conflated with data from subsequent open-label follow-up. >10% of participants experienced nausea, fall, dizziness, diarrhoea, and/or vomiting; >5% experienced injury, insomnia, abdominal pain, confusion, agitation headache, back pain, depression, constipation, flu-like symptoms, URTI, UTI, fatigue, pain, anorexia, hypertension, anaemia, and/or urinary incontinence

Methodological issues

Randomisation and allocation: Randomisation was conducted using a 'computer-generated code' (no further details provided).

No details provided about appearance, taste, or smell of placebo.

Data analysis: ADAS-cog/11 change from baseline with treatment and country as factors, treatment groups compared using 2-way ANOVA.

Paired t test for comparisons within treatment groups (baseline vs. each visit) of ADAS-COG/11, vital signs, ECG results and body weight.

Wilcoxon signed-rank test used for within-group comparisons if data not distributed normally.

Primary efficacy analysis based on observed case population at 26 weeks. Reported as ITT analysis, but no further details about this or how missing data were handled is reported..

Power calculation: Not reported

Conflicts of interest: None reported

Quality appraisal

1. **Was the assignment to the treatment groups really random?** PARTIAL
   Randomised using a computer-generated code (but not generated from a central office)
2. **Was the treatment allocation concealed?** UNKNOWN
3. **Were the groups similar at baseline in terms of prognostic factors?** REPORTED - YES
4. **Were the eligibility criteria specified?** UNKNOWN
5. **Were outcome assessors blinded to the treatment allocation?** UNKNOWN
6. **Was the care provider blinded?** UNKNOWN
7. **Was the patient blinded?** PARTIAL
8. **Were the point estimates and measure of variability presented for the primary outcome measure?** ADEQUATE

9.	**Did the analyses include an intention-to-treat analysis?** PARTIAL ITT claimed, but n<original sample size
10.	**Were withdrawals and dropouts completely described?** ADEQUATE

Design	Participants	Arms	OUTCOMES
Bullock et al. (2005){264 /id} **Study design:** Parallel double-blind RCT **Country:** Australia, Canada, France, Germany, Italy, Spain, UK **No. of centres:** 94 **Funding:** Study supported by Novartis Pharma AG 4 of the study authors (YH, JN, GR, RL) are employees of Novartis The remaining 4 authors (RB, JT, HB, GG) did not receive remuneration for taking part in the study or writing the manuscript **Length of follow-up (wk):** 104 **Notes** -	**Number randomised:** 998 **MMSE min:** 10 **MMSE max:** 20 **Inclusion criteria:** Male or female outpatients aged 50-85yrs AD (DSM-IV criteria) or probable AD (NINCDS-ADRDA criteria) MMSE 10-20 Contact with a responsible caregiver at least once a day (Patients with AD who also had symptoms suggestive of concomitant Lewy body disease (McKeith et al criteria) were also permitted to enter the study **Exclusion criteria:** Current diagnosis of any primary neurodegenerative disorder other than AD (including Parkinson's disease) Any advance, severe, progressive or unstable disease or disability A major depressive episode Active, uncontrolled seizure disorder or peptic ulceration Acute, severe or unstable asthmatic conditions Severe or unstable cardiovascular disease History or diagnosis of cerebrovascular disease Known hyperensitivity to drugs similar to rivastigmine or donezepil in structure or pharmacologic action Use of any cholinesterase inhibitor or other approved treatment for AD in the 6 weeks prior to randomisation Use of any investigational drug, any drug or treatment known to cause major organ system toxicity, or any new psychotropic medication during the 4 weeks prior to randomisation Anticholinergic drugs at randomisation	**Arm No:** 1 **Name:** Rivastigmine **N:** 498 **Drug:** Rivastigmine **Starting daily dose (mg):** 3 **Dosage details:** Titrated from an initial dosage of 3mg/d for the first 4wk up to a maximum of 12mg/d in increments of 3mg/d every 4wk **Arm No:** 2 **Name:** Donepezil **N:** 499 **Drug:** Donepezil **Starting daily dose (mg):** 5 **Dosage details:** Titrated from an initial dosage of 5mg/d for the first 8wk up to 10mg/d in weeks 9-16 **Notes:** For patients who did not achieve the maximum dose during the titration period, investigators were asked to make at least one attempt during the maintenance period to increase the dose to the next highest dose level. The overall dosing strategy was to treat patients at the highest doses that were individually well-tolerated, but dose adjustments were permitted.	**Cognitive** ▪ Mini Mental State Examination (not defined) ▪ Severe impairment battery (consists of six subscales (attention, orientation, language, memory, visuoperception and construction) including brief assessments of social skills, praxis and responding to name. (score range 0-100, lower scores indicating a greater degree of cognitive impairment)) **Functional** ▪ ADCS-ADL (not defined) **Behavioural** ▪ NPI (not defined) **Global severity** ▪ Global deterioration scale (not defined) **Adverse events** An adverse event was defined as any undesirable sign, symptom or medical condition occurring after starting study drug even if the event was not considered to be related to study drug. A serious adverse event was classed as one that was considered one of the following: fatal, life-threatening, necessitating prolonged hospitalisation, resulting in significant disability or requiring medical intervention to prevent any of these outcomes. Information about all adverse events was recorded at each follow-up visit, whether volunteered by the subject or carer, or discovered through investigator questioning or examination, laboratory test, ECG or other means. Adverse events were coded with a standard glossary.

	Therapy common to all participants: None **Sample attrition / dropout:** 578 of 994 (58.1%) completed study (rivastigmine 261 of 495 (52.7%), donezepil 317 of 499 (63.5%) (998 were randomised, 4 withdrew before receiving treatment) Reasons for non-completion: rivastigmine - adverse events (n=129); abnormal lab values (n=1); unsatisfactory therapeutic effect (n=19); protocol violation (n=12); withdrawn consent (n=34); lost to follow-up (n=10); admiistrative problems (n=4); death (n=26) donezepil - adverse events (n=80); abnormal lab values (n=1); unsatisfactory therapeutic effect (n=17); protocol violation (n=9); withdrawn consent (n=22); lost to follow-up (n=13); admiistrative problems (n=6); death (n=34)		

Baseline characteristics

		Rivastigmine			Donepezil			
		N	K	MEAN	N	K	MEAN	*P*
Demographics:								
Age	C	495		75.9 (SD 6.6)	499		75.8 (SD 6.8)	0.814[a]
Age ≥75	D	495	318	(64.2%)	499	314	(62.9%)	0.715[b]
Sex (n male)	D	495	154	(31.1%)	499	157	(31.5%)	0.959[b]
Disease characteristics:								
Duration of dementia (mo)	C	495		33.6 (SD 22.2)	499		34.2 (SD 26.5)	0.699[a]
Probable concomitant Lewy body dementia	D	495	18	(3.6%)	499	22	(4.4%)	0.647[b]
Family history: mother	D	495	55	(11.1%)	499	63	(12.6%)	0.522[b]
Family history: father	D	495	17	(3.4%)	499	18	(3.6%)	0.981[b]
Family history: sibling	D	495	37	(7.5%)	499	50	(10.0%)	0.191[b]
Domestic circumstances:								
Living alone	D	495	92	(18.6%)	499	85	(17.0%)	0.578[b]
Living with caregiver or other	D	495	370	(74.7%)	499	393	(78.8%)	0.155[b]
Assisted living/group home	D	495	33	(6.7%)	499	21	(4.2%)	0.116[b]
Cognitive:								
Mini Mental State Examination – 0wk	C	495		15.1 (SD 3)	499		15.1 (SD 2.9)	1.000[a]
Mini Mental State Examination: ≥15	D	495	280	(56.6%)	499	283	(56.7%)	0.986[b]
LOCF analysis								
Cognitive:								
Mini Mental State Examination – 0wk	C	471		15.2 (SD 3)	484		15.1 (SD 2.9)	0.917[a]
Severe impairment battery – 0wk	C	471		87.8 (SD 10.9)	483		87.8 (SD 11.2)	
Functional:								
ADCS-ADL – 0wk	C	454		46.6 (SD 17.2)	475		48.4 (SD 16.6)	
Behavioural:								
NPI – 0wk	C	471		14.5 (SD 12.9)	484		14.4 (SD 13.9)	
Global severity:								
Global deterioration scale – 0wk	C	471		4.39 (SD 0.7)	483		4.27 (SD 0.8)	

[a] student's t-test (calculated by reviewer)

[b] chi-square test (Yates's correction) (calculated by reviewer)

Results

		Rivastigmine			Donepezil			
		N	K	MEAN	N	K	MEAN	P
ITT population								
Disposition of participants:								
Discontinued treatment due to AEs	D	498	128	(25.7%)	500	80	(16.0%)	<0.001[a]
Discontinued treatment before end of trial	D	498	237	(47.6%)	500	183	(36.6%)	<0.001[a]
LOCF analysis								
Cognitive:								
Mini Mental State Examination – 104wk	MC	471		-2.35 (SD 6.51)	484		-2.85 (SD 6.6)	0.089[b]
Mini Mental State Examination – 104wk	MC	471		-2.35 (SD 6.51)	484		-2.85 (SD 6.6)	0.106[c]
Severe impairment battery – 104wk	MC	471		-9.3 (SD 23.9)	483		-9.91 (SD 24.2)	0.609[b]
Severe impairment battery – 104wk	MC	471		-9.3 (SD 23.9)	483		-9.91 (SD 24.2)	0.738[c]
Functional:								
ADCS-ADL – 104wk	MC	454		-12.8 (SD 19.2)	475		-14.9 (SD 19.6)	0.007[c]
ADCS-ADL – 104wk	MC	454		-12.8 (SD 19.2)	475		-14.9 (SD 19.6)	0.047[b]
Behavioural:								
NPI – 104wk	MC	471		2.4 (SD 17.4)	484		2.94 (SD 17.6)	0.505[c]
NPI – 104wk	MC	471		2.4 (SD 17.4)	484		2.94 (SD 17.6)	0.554[b]
Global severity:								
Global deterioration scale – 104wk	MC	471		0.58 (SD 0.9)	483		0.69 (SD 0.9)	0.049[c]
Safety population								
Adverse events:								
Any serious AE – 104wk	D	495	157	(31.7%)	499	162	(32.5%)	0.854[a]
Safety population - titration phase								
Adverse events:								
Any AE – 16wk	D	495	406	(82.0%)	499	323	(64.7%)	<0.001[a]
Anorexia – 16wk	D	495	45	(9.1%)	499	20	(4.0%)	0.002[a]
Nausea – 16wk	D	495	163	(32.9%)	499	76	(15.2%)	<0.001[a]
Diarrhoea – 16wk	D	495	41	(8.3%)	499	34	(6.8%)	0.449[a]
Vomiting – 16wk	D	495	138	(27.9%)	499	29	(5.8%)	<0.001[a]
Agitation – 16wk	D	495	35	(7.1%)	499	50	(10.0%)	0.121[a]
Depression – 16wk	D	495	19	(3.8%)	499	10	(2.0%)	0.126[a]
Headache – 16wk	D	495	27	(5.5%)	499	23	(4.6%)	0.642[a]
Weight decrease – 16wk	D	495	30	(6.1%)	499	9	(1.8%)	<0.001[a]
Urinary tract infection – 16wk	D	495	8	(1.6%)	499	13	(2.6%)	0.388[a]
Fall – 16wk	D	495	25	(5.1%)	499	10	(2.0%)	0.015[a]
Hypertension – 16wk	D	495	20	(4.0%)	499	7	(1.4%)	0.018[a]
Aggression – 16wk	D	495	7	(1.4%)	499	11	(2.2%)	0.486[a]
Safety population - maintenance phase								
Adverse events:								
Any AE – 104wk	D	404	318	(78.7%)	453	349	(77.0%)	0.613[a]
Anorexia – 104wk	D	404	26	(6.4%)	453	14	(3.1%)	0.031[a]
Nausea – 104wk	D	404	52	(12.9%)	453	24	(5.3%)	<0.001[a]
Diarrhoea – 104wk	D	404	26	(6.4%)	453	30	(6.6%)	0.978[a]
Vomiting – 104wk	D	404	62	(15.3%)	453	20	(4.4%)	<0.001[a]
Agitation – 104wk	D	404	34	(8.4%)	453	47	(10.4%)	0.389[a]
Depression – 104wk	D	404	21	(5.2%)	453	16	(3.5%)	0.303[a]
Headache – 104wk	D	404	13	(3.2%)	453	12	(2.6%)	0.771[a]
Weight decrease – 104wk	D	404	36	(8.9%)	453	43	(9.5%)	0.861[a]
Urinary tract infection – 104wk	D	404	18	(4.5%)	453	26	(5.7%)	0.487[a]
Fall – 104wk	D	404	33	(8.2%)	453	44	(9.7%)	0.503[a]
Hypertension – 104wk	D	404	21	(5.2%)	453	18	(4.0%)	0.487[a]
Aggression – 104wk	D	404	19	(4.7%)	453	25	(5.5%)	0.700[a]

[a] chi-square test (Yates's correction) (calculated by reviewer)

[b] ANCOVA, covarying country, MMSE category, and baseline score

[c] Wilcoxon rank sum test

Methodological issues

Randomisation and allocation: Performed using Interactive Voice Response System that automated the random assignment of treatment groups to randomisation numbers. Randomisation was stratified with respect to severity, i.e. was done separately with MMSE scores of 10-14 and 15-20.

All treatments were supplied as capsules that were identical in size, shape and colour, and all patients received the same number of capsules per day.

Data analysis: Primary: SIB. Secondary: GDS, ADCS-ADL, MMSE, NPI. ANCOVA and/or Wilcoxon rank sum test conducted with treatment, country, MMSE category and baseline scores as explanatory variables.

Additional analyses on SIB, NPI, ADCS-ADL where patients had different baseline disease severities, genders, ages, and vascular risk profiles.

Exploratory analyses conducted on pharmacogenetic sub-population (for BuChE - the more common BuChE wild type (wt/wt) and those with one or two BuChE-K variants - and by apiloprotein E[APOE}E4 carrier status). Additional secondary analysis conducted in patients with AD who had symptoms suggestive of concomitant Lewy body disease (DLB diagnosed accoridng to McKeith et al criteria, or receiving Parkinsonian medication but not formally diagnosed with PD). ANCOVA and/or Wilcoxon rank sum test conducted with treatment, country, MMSE category and baseline scores as explanatory variables. Exploratory analyses of pharmacogenetic data assessed by ANCOVA with age, gender, and baseline values as explanatory variables.

ITT population defined as all randomised patinets who received study medication and from whom at least one efficacy measurement was obtained while on treatment. Missing values were impited with LOCF data. In addition, supportive analyses comprised an evaluable patients population of all patients who were treated with study medication for at least 16 weeks (with a LOCF imputation), and an observed case population of patients who had evaluations on treatment at designated assessment times, with no imputation of missing values, whether they had completed the study or not.

Power calculation: Powered at 85% to detect a statistically significant (significance level 5%, two-sided) difference in SIB of 4 points between the two groups (assuming a SD of 20 on change from baseline in mean SIB scores, as observed in previous trials), sample size of 450 patients per treatment group was required.

Conflicts of interest: Study supported by Novartis Pharma AG

4 of the study authors (YH, JN, GR, RL) are employees of Novartis

The remaining 4 authors (RB, JT, HB, GG) did not receive remuneration for taking part in the study or writing the manuscript

Quality appraisal

1. **Was the assignment to the treatment groups really random?** ADEQUATE
2. **Was the treatment allocation concealed?** ADEQUATE
3. **Were the groups similar at baseline in terms of prognostic factors?** REPORTED - YES
4. **Were the eligibility criteria specified?** INADEQUATE
5. **Were outcome assessors blinded to the treatment allocation?** PARTIAL
6. **Was the care provider blinded?** ADEQUATE
7. **Was the patient blinded?** ADEQUATE
8. **Were the point estimates and measure of variability presented for the primary outcome measure?** ADEQUATE
9. **Did the analyses include an intention-to-treat analysis?** ADEQUATE
10. **Were withdrawals and dropouts completely described?** ADEQUATE

Design	Participants	Arms	OUTCOMES
Cumbo (2005){364 /id} **Study design:** - **Country:** Funded by an Italian health agency, but not stated whether study conducted in Italy or elsewhere. **No. of centres:** Not stated. Small sample size suggests single centre. **Funding:** Supported by Department of Neuroscience	**Number randomised:** 101 **MMSE min:** 10 **MMSE max:** 27 **Inclusion criteria:** Probable AD (NINCS-ARDRA) MMSE 10-27 >=3yr duration of disease No behavioural symptoms Carer who could ensure	**Arm No:** 1 **Name:** Rivastigmine **N:** 37 **Drug:** Rivastigmine **Starting daily dose (mg):** 9 **Dosage details:** No details reported of titration. **Notes:** Starting daily dose is only reported as the mean for	**Behavioural** ▪ NPI ▪ Developing BPSD ▪ Time to BPSD ▪ BEHAVE-AD **Adverse events**

(NHS District of Caltanissetta) Novartis Farma SpA supported the English editing of the manuscript **Length of follow-up (wk):** 78 **Notes** -	compliance to treatment and attendance and provide the information required for psychometric and behavioural assessments **Exclusion criteria:** History of primary neurological or psychiatric disease other than AD Drug or alcohol abuse Clinically significant medical or surgical disorders independently of stability Previous therapy for dementia Concomitant treatment with cholinomimetic or anticholinergic drugs, investigational drugs, tricyclic antidepressants or neuroleptics Refusal to give informed consent in writing **Therapy common to all participants:** None **Sample attrition / dropout:** None	the whole arm. No maximum dose reported. **Arm No:** 2 **Name:** Galantamine **N:** 33 **Drug:** Galantamine **Starting daily dose (mg):** 16 **Dosage details:** No details reported of titration. **Notes:** Starting daily dose is only reported as the mean for the whole arm. No maximum dose reported. **Arm No:** 3 **Name:** Donepezil **N:** 31 **Drug:** Donepezil **Starting daily dose (mg):** 10 **Dosage details:** No details reported of titration. **Notes:** Starting daily dose is only reported as the mean for the whole arm. No maximum dose reported.	

Baseline characteristics

	All study participants		
	N	**K**	**MEAN**
Demographics:			
Age	101		76.35 [rng 66–83]
Sex (n male)	101	43	(42.6%)
Education (yrs)	101		5 [rng 3–12]
Disease characteristics:			
Duration of dementia (mo)	101		61.08 [rng 36–108]
Cognitive:			
Mini Mental State Examination	101		16.6
Functional:			
ADL	101		3.7
Instrumental Activities of Daily Living	101		5.3
Behavioural:			
NPI	101		0
NPI - caregiver distress	101		0
BEHAVE-AD	101		0
Global severity:			
Global deterioration scale	101		5

Results

	Rivastigmine			Galantamine			
	N	**K**	**MEAN**	**N**	**K**	**MEAN**	***P***

Behavioural:								
NPI - delusions – 78wk	D	37	1	(2.7%)	33	4	(12.1%)	0.288[a]
NPI - hallucinations – 78wk	D	37	0	(0.0%)	33	0	(0.0%)	0.341[a]
NPI - agitation/aggression – 78wk	D	37	4	(10.8%)	33	9	(27.3%)	0.144[a]
NPI - depression/dysphoria – 78wk	D	37	13	(35.1%)	33	10	(30.3%)	0.861[a]
NPI - anxiety – 78wk	D	37	14	(37.8%)	33	15	(45.5%)	0.687[a]
NPI - elation/euphoria – 78wk	D	37	0	(0.0%)	33	0	(0.0%)	0.341[a]
NPI - apathy/indifference – 78wk	D	37	7	(18.9%)	33	7	(21.2%)	0.952[a]
NPI - disinhibition – 78wk	D	37	0	(0.0%)	33	3	(9.1%)	0.252[a]
NPI - irritability/lability – 78wk	D	37	12	(32.4%)	33	14	(42.4%)	0.538[a]
NPI - aberrant motor behaviour – 78wk	D	37	0	(0.0%)	33	0	(0.0%)	0.341[a]
NPI - night-time behaviour – 78wk	D	37	1	(2.7%)	33	9	(27.3%)	0.010[a]
NPI - appetite/eating change – 78wk	D	37	0	(0.0%)	33	1	(3.0%)	0.936[a]
Developing BPSD – 78wk	D	37	14	(37.8%)	33	15	(45.5%)	0.687[a]
BEHAVE-AD - delusional and paranoid ideation – 78wk	D	37	1	(2.7%)	33	4	(12.1%)	0.288[a]
BEHAVE-AD - hallucinations – 78wk	D	37	0	(0.0%)	33	0	(0.0%)	0.341[a]
BEHAVE-AD - activity disturbances – 78wk	D	37	0	(0.0%)	33	0	(0.0%)	0.341[a]
BEHAVE-AD - aggression – 78wk	D	37	4	(10.8%)	33	9	(27.3%)	0.144[a]
BEHAVE-AD - diurnal cycle disturbances – 78wk	D	37	1	(2.7%)	33	9	(27.3%)	0.010[a]
BEHAVE-AD - affective disturbances – 78wk	D	37	13	(35.1%)	33	10	(30.3%)	0.861[a]
BEHAVE-AD - anxiety and phobias – 78wk	D	37	14	(37.8%)	33	15	(45.5%)	0.687[a]
Adverse events:								
Anorexia – 78wk	D	37	1	(2.7%)	33	1	(3.0%)	0.524[a]
Nausea – 78wk	D	37	3	(8.1%)	33	2	(6.1%)	0.894[a]
Vomiting – 78wk	D	37	1	(2.7%)	33	1	(3.0%)	0.524[a]
Headache – 78wk	D	37	1	(2.7%)	33	0	(0.0%)	0.936[a]
Weight decrease – 78wk	D	37	0	(0.0%)	33	1	(3.0%)	0.936[a]
Disposition of participants:								
Discontinued treatment due to AEs – -1wk	D	37	0	(0.0%)	33	0	(0.0%)	0.341[a]
Discontinued treatment before end of trial – -1wk	D	37	0	(0.0%)	33	0	(0.0%)	0.341[a]

[a] chi-square test (Yates's correction) (calculated by reviewer)

		Rivastigmine			Donepezil			
		N	**K**	**MEAN**	**N**	**K**	**MEAN**	***P***
Behavioural:								
NPI - delusions – 78wk	D	37	1	(2.7%)	31	5	(16.1%)	0.130[a]
NPI - hallucinations – 78wk	D	37	0	(0.0%)	31	3	(9.7%)	0.226[a]
NPI - agitation/aggression – 78wk	D	37	4	(10.8%)	31	7	(22.6%)	0.326[a]
NPI - depression/dysphoria – 78wk	D	37	13	(35.1%)	31	13	(41.9%)	0.746[a]
NPI - anxiety – 78wk	D	37	14	(37.8%)	31	14	(45.2%)	0.716[a]
NPI - elation/euphoria – 78wk	D	37	0	(0.0%)	31	1	(3.2%)	0.902[a]
NPI - apathy/indifference – 78wk	D	37	7	(18.9%)	31	8	(25.8%)	0.698[a]
NPI - disinhibition – 78wk	D	37	0	(0.0%)	31	1	(3.2%)	0.902[a]
NPI - irritability/lability – 78wk	D	37	12	(32.4%)	31	15	(48.4%)	0.276[a]
NPI - aberrant motor behaviour – 78wk	D	37	0	(0.0%)	31	0	(0.0%)	0.355[a]
NPI - night-time behaviour – 78wk	D	37	1	(2.7%)	31	0	(0.0%)	0.902[a]
NPI - appetite/eating change – 78wk	D	37	0	(0.0%)	31	1	(3.2%)	0.902[a]
Developing BPSD – 78wk	D	37	14	(37.8%)	31	16	(51.6%)	0.371[a]
BEHAVE-AD - delusional and paranoid ideation – 78wk	D	37	1	(2.7%)	31	5	(16.1%)	0.130[a]
BEHAVE-AD - hallucinations – 78wk	D	37	0	(0.0%)	31	3	(9.7%)	0.226[a]
BEHAVE-AD - activity disturbances – 78wk	D	37	0	(0.0%)	31	0	(0.0%)	0.355[a]
BEHAVE-AD - aggression – 78wk	D	37	4	(10.8%)	31	7	(22.6%)	0.326[a]
BEHAVE-AD - diurnal cycle disturbances – 78wk	D	37	1	(2.7%)	31	10	(32.3%)	0.003[a]
BEHAVE-AD - affective disturbances – 78wk	D	37	13	(35.1%)	31	13	(41.9%)	0.746[a]
BEHAVE-AD - anxiety and phobias – 78wk	D	37	14	(37.8%)	31	15	(48.4%)	0.529[a]
Adverse events:								
Anorexia – 78wk	D	37	1	(2.7%)	31	0	(0.0%)	0.902[a]
Nausea – 78wk	D	37	3	(8.1%)	31	2	(6.5%)	0.837[a]
Vomiting – 78wk	D	37	1	(2.7%)	31	0	(0.0%)	0.902[a]
Headache – 78wk	D	37	1	(2.7%)	31	2	(6.5%)	0.875[a]
Weight decrease – 78wk	D	37	0	(0.0%)	31	0	(0.0%)	0.355[a]
Disposition of participants:								
Discontinued treatment due to AEs – -1wk	D	37	0	(0.0%)	31	0	(0.0%)	0.355[a]
Discontinued treatment before end of trial – -1wk	D	37	0	(0.0%)	31	0	(0.0%)	0.355[a]

[a] chi-square test (Yates's correction) (calculated by reviewer)

		Galantamine			Donepezil			
		N	K	MEAN	N	K	MEAN	*P*
Behavioural:								
NPI - delusions – 78wk	D	33	4	(12.1%)	31	5	(16.1%)	0.919[a]
NPI - hallucinations – 78wk	D	33	0	(0.0%)	31	3	(9.7%)	0.274[a]
NPI - agitation/aggression – 78wk	D	33	9	(27.3%)	31	7	(22.6%)	0.885[a]
NPI - depression/dysphoria – 78wk	D	33	10	(30.3%)	31	13	(41.9%)	0.479[a]
NPI - anxiety – 78wk	D	33	15	(45.5%)	31	14	(45.2%)	0.820[a]
NPI - elation/euphoria – 78wk	D	33	0	(0.0%)	31	1	(3.2%)	0.965[a]
NPI - apathy/indifference – 78wk	D	33	7	(21.2%)	31	8	(25.8%)	0.890[a]
NPI - disinhibition – 78wk	D	33	3	(9.1%)	31	1	(3.2%)	0.651[a]
NPI - irritability/lability – 78wk	D	33	14	(42.4%)	31	15	(48.4%)	0.820[a]
NPI - aberrant motor behaviour – 78wk	D	33	0	(0.0%)	31	0	(0.0%)	0.328[a]
NPI - night-time behaviour – 78wk	D	33	9	(27.3%)	31	0	(0.0%)	0.008[a]
NPI - appetite/eating change – 78wk	D	33	1	(3.0%)	31	1	(3.2%)	0.500[a]
Developing BPSD – 78wk	D	33	15	(45.5%)	31	16	(51.6%)	0.808[a]
BEHAVE-AD - delusional and paranoid ideation – 78wk	D	33	4	(12.1%)	31	5	(16.1%)	0.919[a]
BEHAVE-AD - hallucinations – 78wk	D	33	0	(0.0%)	31	3	(9.7%)	0.274[a]
BEHAVE-AD - activity disturbances – 78wk	D	33	0	(0.0%)	31	0	(0.0%)	0.328[a]
BEHAVE-AD - aggression – 78wk	D	33	9	(27.3%)	31	7	(22.6%)	0.885[a]
BEHAVE-AD - diurnal cycle disturbances – 78wk	D	33	9	(27.3%)	31	10	(32.3%)	0.871[a]
BEHAVE-AD - affective disturbances – 78wk	D	33	10	(30.3%)	31	13	(41.9%)	0.479[a]
BEHAVE-AD - anxiety and phobias – 78wk	D	33	15	(45.5%)	31	15	(48.4%)	0.988[a]
Adverse events:								
Anorexia – 78wk	D	33	1	(3.0%)	31	0	(0.0%)	0.965[a]
Nausea – 78wk	D	33	2	(6.1%)	31	2	(6.5%)	0.651[a]
Vomiting – 78wk	D	33	1	(3.0%)	31	0	(0.0%)	0.965[a]
Headache – 78wk	D	33	0	(0.0%)	31	2	(6.5%)	0.519[a]
Weight decrease – 78wk	D	33	1	(3.0%)	31	0	(0.0%)	0.965[a]
Disposition of participants:								
Discontinued treatment due to AEs – -1wk	D	33	0	(0.0%)	31	0	(0.0%)	0.328[a]
Discontinued treatment before end of trial – -1wk	D	33	0	(0.0%)	31	0	(0.0%)	0.328[a]

[a] chi-square test (Yates's correction) (calculated by reviewer)

Time to BPSD data unextractable, because it is not possible to distinguish treatment groups

Methodological issues

Randomisation and allocation: No details of randomisation procedure reported.

Open-label trial.

Data analysis: Primary outcome: Time to onset of BPSD (Behavioural and psychosocial symptoms of dementia), analysed using survival analysis according to the actuarial method, grouping events with onset in the same predefined time interval. The first time interval comprised the first 6mo, thereafter the intervals were monthly. Curves related to the probability of survival without BPSD were compared using Wilcoxon's test between pairs of treatments. The remaining parameters were analysed descriptively in view of the small sample size.

Power calculation: None reported

Conflicts of interest: Supported by Department of Neuroscience (NHS District of Caltanissetta)

Novartis Farma SpA supported the English editing of the manuscript

Quality appraisal

1. **Was the assignment to the treatment groups really random?** UNKNOWN
2. **Was the treatment allocation concealed?** UNKNOWN
3. **Were the groups similar at baseline in terms of prognostic factors?** UNKNOWN
   Mean or range across all trial arms only given
4. **Were the eligibility criteria specified?** UNKNOWN
5. **Were outcome assessors blinded to the treatment allocation?** UNKNOWN
6. **Was the care provider blinded?** UNKNOWN
   Open-label trial

7. **Was the patient blinded?** UNKNOWN
Open-label trial

8. **Were the point estimates and measure of variability presented for the primary outcome measure?** ADEQUATE

9. **Did the analyses include an intention-to-treat analysis?** ADEQUATE
All patients completed follow-up

10. **Were withdrawals and dropouts completely described?** ADEQUATE
No dropouts occurred

Design	Participants	Arms	OUTCOMES
Moraes et al. (2006){438 /id} **Study design:** Parallel double-blind RCT **Country:** Brazil **No. of centres:** 1 **Funding:** FAPESP (Fundacao de Amparoa Pesquisa do Estado de Sao Paulo) AFIP (Associacao Fundo de Incentivo a Psicofarmacolgia) **Length of follow-up (wk):** 26	**Number randomised:** 35 **MMSE min:** - **MMSE max:** - **Inclusion criteria:** Probable AD (AD and Related Disorders Association criteria) Clinical Dementia Rating (Brazilian version) 1-2 (mild to moderate) **Exclusion criteria:** Other causes of dementia Other current severe medical or psychiatric disease Evidence of moderate to severe sleep disorders, based on medical, sleep, and psychiatric interviews Apnoea-hypoapnoea index >10/h and periodic leg movement index >5/h at baseline polysomnographic recording Psychoactive drugs in the month prior to entering the study **Therapy common to all participants:** 2 nights of polysomnographic recording (for purposes of habituation) **Sample attrition / dropout:** 8 patients left the study due to technical difficulties in polysomnography recordings	**Arm No:** 1 **Name:** Donepezil **N:** 17 **Drug:** Donepezil **Starting daily dose (mg):** 5 **Dosage details:** Starting daily dose of 5mg for the first month, increased to 10mg/d in the second month **Arm No:** 2 **Name:** Placebo **N:** 18 **Drug:** Placebo **Starting daily dose (mg):** - **Dosage details:** Single daily dose	▪ ADAS-cog (selected aspects of cognitive performance, including elements of memory, orientation, reasoning, language, and praxis)
Notes -			

Baseline characteristics

		Donepezil			Placebo			
		N	K	MEAN	N	K	MEAN	*P*
OC population								
Demographics:								
Age	C	17		77.4 (SD 6.6)	18		74.5 (SD 9.8)	0.32[a]
Sex (n male)	D	17	4	(23.5%)	18	7	(38.9%)	0.34[a]
BMI (kg/m2)	C	17		26 (SD 4.8)	18		24.9 (SD 4.5)	0.48[a]
Education (yrs)	C	17		4.4 (SD 3.6)	18		6 (SD 5.2)	0.30[a]
Cognitive:								
ADAS-cog – 0wk	C	17		35.6 (SD 13.7)	18		39 (SD 18.5)	0.543[b]

Global severity:						
Clinical Dementia Rating	C	17	1.2 (SD 0.4)	18	1.5 (SD 0.5)	0.11[a]

[a] one-way ANOVA

[b] student's t-test (two-tailed) (calculated by reviewer)

Results

		Donepezil			Placebo			
		N	K	MEAN	N	K	MEAN	*P*
OC population								
Cognitive:								
ADAS-cog – 13wk	C	17		30.7 (SD 13.9)	18		40.9 (SD 19.4)	0.085[a]
ADAS-cog – 26wk	C	17		28.3 (SD 12.3)	18		42.8 (SD 18.7)	<0.01[b]

[a] student's t-test (calculated by reviewer)

[b] two-way ANOVA, with treatment group and treatment time as the main factors

Mild and transitory side-effects involving nausea and headache occurred in 3 patients receiving donepezil.

Methodological issues

Randomisation and allocation: Randomisation process not reported. Individual responsible for the random allocation of patinets to the trial arms was blind to the treatment code (how blinding was attained is not reported). Appearance of donepezil and placebo tablets is not described.

Data analysis: Polysomnographic and cognitive data were analysed using 2-way ANOVA for repeated measures with treatment group and treatment time as the main factors and time/treatment interaction effect. Posthoc Duncan multiple range test performed, with p level set at <=.01. Spearman test to assess correlation between cognitive improvement rate and REM sleep and EEG parameters.

Power calculation: Data from 10 patients was initially analysed for sample size estimation (procedure not reported). Based on this analysis, a sample size of 15 subjects in each group was calculated to set out a difference of 8 percentage points in REM sleep percentage (significance level of 1% and power of 95%). To assess the interaction term in the ANOVA model, 27 subjects were required in each group (sample size not attained) - power of 80% was possible with the sample size analysed.

Conflicts of interest: Authors state no financial conflicts of interest.

No financial support from industry for study.

Quality appraisal

1. **Was the assignment to the treatment groups really random?** UNKNOWN
2. **Was the treatment allocation concealed?** INADEQUATE
3. **Were the groups similar at baseline in terms of prognostic factors?** REPORTED - YES
4. **Were the eligibility criteria specified?** INADEQUATE
5. **Were outcome assessors blinded to the treatment allocation?** PARTIAL
6. **Was the care provider blinded?** PARTIAL
7. **Was the patient blinded?** PARTIAL
8. **Were the point estimates and measure of variability presented for the primary outcome measure?** ADEQUATE
9. **Did the analyses include an intention-to-treat analysis?** UNKNOWN
10. **Were withdrawals and dropouts completely described?** PARTIAL

Design	Participants	Arms	OUTCOMES
Feldman & Lane (2007){526 /id} **Study design:** Parallel	**Number randomised:** 678 **MMSE min:** 10	**Arm No:** 1 **Name:** Rivastigmine td	**Cognitive** ▪ ADAS-cog (11-item

double-blind RCT **Country:** Australia, Canada, Ireland, Italy, South Africa, UK **No. of centres:** 37 **Funding:** Commissioned by Novartis Pharma AG (Switzerland) **Length of follow-up (wk):** 26	**MMSE max:** 26 **Inclusion criteria:** AD (DSM-IV criteria) and probable AD (NINCDS-ADRDA) MMSE 10-26 Responsible caregiver **Exclusion criteria:** Severe and unstable cardiac disease Severe and obstructuive pulmonary disease Other life-threatening conditions Use of anticholoinergic drugs, health food supplements containing ACh precursors, putative memory enhancers, or insulin Use of psychotropic drugs, with the exception of chloral hydrate, short acting benzodiazepines and haloperidol (<=3d in succession and not <72h before any efficacy assessment) **Therapy common to all participants:** None **Sample attrition / dropout:** 553 of 678 completed study. 125 withdrew after allocation: adverse events (n=83); ECG abnormalities (n=4); laboratory abnormalities (n=1); withdrawn consent (n=14); protocol violation (n=8); treatment failure (n=2); failure to attend (n=7); other reasons (n=6). Differences between groups was only on adverse events (rivastigmine TID 11%; rivastigmine BID 17%; placebo 9%)	**N:** 227 **Drug:** Rivastigmine **Starting daily dose (mg):** 2 **Dosage details:** Dose administered three times a day. Titrated from an initial dose of 2mg/d for the first week up to a maximum of 12mg in 1mg/d steps at weekly intervals. Patients unable to tolerate 2mg/d by day 10 were withdrawn from the study. Tolerability could be optimised by maintaining a dose level for periods of up to 2wk. **Arm No:** 2 **Name:** Rivastigmine bd **N:** 229 **Drug:** Rivastigmine **Starting daily dose (mg):** 2 **Dosage details:** Dose administered two times a day (plus one placebo tablet). Titrated from an initial dose of 2mg/d for the first week up to a maximum of 12mg in 1mg/d steps at weekly intervals. Patients unable to tolerate 2mg/d by day 10 were withdrawn from the study. Tolerability could be optimised by maintaining a dose level for periods of up to 2wk. **Arm No:** 3 **Name:** Placebo **N:** 222 **Drug:** Placebo **Starting daily dose (mg):** - **Dosage details:** -	assessment of memory, language, praxis, orientation, total score range 0-70, with decreasing score indicating improved cognitive function) ▪ ADAS-cogA (ADAS-cog with an added item of attention (concentration/distractability), total score range 0-75, where decreasing score indicated improved cognitive function) ▪ Mini Mental State Examination (recent memory, attention, concentration, naming, repetition, comprehension and ability to formulate a sentence (10 item assessment, with a range of 0-30 points, with higher score representing better cognitive function) **Functional** ▪ Progressive Deterioration Scale (activities of daily living, 29 item score on a visual analogue scale 0-100, where an increase in score indicated improvement in the patient's ability to perform activities of daily living) **Global severity** ▪ CIBIC-plus score (Overall global assessment of patient response on 7 point Likert scale where 1=markedly improved and 7=markedly worsened) ▪ Global deterioration scale (overall staging of AD severity, 7 stage scale where a higher stage indicates more advanced AD) **Adverse events**
Notes -			

Baseline characteristics

		Rivastigmine td			Placebo			
		N	K	MEAN	N	K	MEAN	*P*
Demographics:								
Age	C	227		71.4 (SD 7.9)	222		71.7 (SD 8.7)	0.702[a]
Sex (n male)[b]	D	227	91	(40.1%)	222	89	(40.1%)	1.000[c]
Height (cm)	C	227		164 (SD 10.7)	222		164 (SD 10.3)	1.000[a]
Weight (kg)	C	227		65.9 (SD 12.9)	222		65.9 (SD 12.3)	1.000[a]
Disease characteristics:								
Duration of dementia (mo)	C	227		38.4 (SD 25.5)	222		39.7 (SD 28.2)	0.608[a]
Disease severity (NINCDS-ADRDA): mild	D	227	43	(18.9%)	222	45	(20.3%)	0.723[c]
Disease severity (NINCDS-ADRDA): moderate	D	227	55	(24.2%)	222	52	(23.4%)	0.841[c]
Disease severity (NINCDS-ADRDA): severe	D	227	3	(1.3%)	222	3	(1.4%)	0.978[c]

Cognitive:						
Mini Mental State Examination – 0wk	C	227	18.3 (SD 4.5)	222	18.7 (SD 4.6)	0.352[a]
Global severity:						
Global deterioration scale – 0wk	C	227	4.1 (SD 0.8)	222	4.1 (SD 0.9)	1.000[a]
ITT population						
Cognitive:						
ADAS-cog – 0wk	C	227	28.1 (SD 12.5)	220	28.5 (SD 12.3)	0.733[a]
ADAS-cogA – 0wk	C	227	29.1 (SD 13.1)	220	29.4 (SD 13)	0.808[a]
Mini Mental State Examination – 0wk	C	227	18.1 (SD 4.7)	220	18.8 (SD 4.6)	0.112[a]
Functional:						
Progressive Deterioration Scale – 0wk	C	225	49.2 (SD 19.8)	221	49 (SD 19.6)	0.915[a]
Global severity:						
Global deterioration scale – 0wk	C	227	4.1 (SD 0.9)	222	4.1 (SD 0.9)	1.000[a]
LOCF analysis						
Cognitive:						
ADAS-cog – 0wk	C	209	28.3 (SD 12.2)	208	28.5 (SD 12.2)	0.867[a]
ADAS-cogA – 0wk	C	209	29.2 (SD 12.9)	208	29.4 (SD 12.8)	0.874[a]
Mini Mental State Examination – 0wk	C	193	18.1 (SD 4.5)	198	18.8 (SD 4.6)	0.129[a]
Functional:						
Progressive Deterioration Scale – 0wk	C	207	49 (SD 19.6)	209	48.9 (SD 19.4)	0.958[a]
Global severity:						
Global deterioration scale – 0wk	C	195	4.1 (SD 0.9)	202	4.1 (SD 0.9)	1.000[a]
OC population						
Cognitive:						
ADAS-cog – 0wk	C	180	27.9 (SD 11.8)	183	27.7 (SD 11.9)	0.872[a]

[a] student's t-test (calculated by reviewer)

[b] approximated to nearest integer (percentages only presented in text)

[c] chi-square test (calculated by reviewer)

		Rivastigmine bd			Placebo			
		N	**K**	**MEAN**	**N**	**K**	**MEAN**	***P***
Demographics:								
Age	C	229		71 (SD 8.2)	222		71.7 (SD 8.7)	0.380[a]
Sex (n male)[b]	D	229	98	(42.8%)	222	89	(40.1%)	0.560[c]
Height (cm)	C	229		164 (SD 10.7)	222		164 (SD 10.3)	0.480[a]
Weight (kg)	C	229		66.7 (SD 12.2)	222		65.9 (SD 12.3)	0.488[a]
Disease characteristics:								
Duration of dementia (mo)	C	229		40.6 (SD 31.2)	222		39.7 (SD 28.2)	0.748[a]
Disease severity (NINCDS-ADRDA): mild	D	229	45	(19.7%)	222	45	(20.3%)	0.869[c]
Disease severity (NINCDS-ADRDA): moderate	D	229	53	(23.1%)	222	52	(23.4%)	0.944[c]
Disease severity (NINCDS-ADRDA): severe	D	229	2	(0.9%)	222	3	(1.4%)	0.628[c]
Cognitive:								
Mini Mental State Examination – 0wk	C	229		18.8 (SD 4.6)	222		18.7 (SD 4.6)	0.818[a]
Global severity:								
Global deterioration scale – 0wk	C	229		4 (SD 0.9)	222		4.1 (SD 0.9)	0.239[a]
ITT population								
Cognitive:								
ADAS-cog – 0wk	C	228		27.7 (SD 12.3)	220		28.5 (SD 12.3)	0.492[a]
ADAS-cogA – 0wk	C	228		28.6 (SD 13)	220		29.4 (SD 13)	0.515[a]
Mini Mental State Examination – 0wk	C	227		18.7 (SD 4.6)	220		18.8 (SD 4.6)	0.818[a]
Functional:								
Progressive Deterioration Scale – 0wk	C	227		48.7 (SD 19.5)	221		49 (SD 19.6)	0.871[a]
Global severity:								
Global deterioration scale – 0wk	C	229		4 (SD 0.9)	222		4.1 (SD 0.9)	0.239[a]
LOCF analysis								
Cognitive:								
ADAS-cog – 0wk	C	199		27.7 (SD 12.3)	208		28.5 (SD 12.2)	0.510[a]
ADAS-cogA – 0wk	C	199		28.5 (SD 13)	208		29.4 (SD 12.8)	0.482[a]
Mini Mental State Examination – 0wk	C	186		18.7 (SD 4.6)	198		18.8 (SD 4.6)	0.832[a]
Functional:								
Progressive Deterioration Scale – 0wk	C	195		48.6 (SD 19.7)	209		48.9 (SD 19.4)	0.878[a]

Global severity:						
Global deterioration scale – 0wk	C	188	4 (SD 0.9)	202	4.1 (SD 0.9)	0.274[a]
OC population						
Cognitive:						
ADAS-cog – 0wk	C	173	28.6 (SD 12.1)	183	27.7 (SD 11.9)	0.480[a]

[a] student's t-test (calculated by reviewer)

[b] approximated to nearest integer (percentages only presented in text)

[c] chi-square test (calculated by reviewer)

Results

		Rivastigmine td			Placebo			
		N	K	MEAN	N	K	MEAN	*P*
ITT population								
Cognitive:								
ADAS-cog – 12wk[a]	MC	227		-1.9 (SD 6.66)	220		0.9 (SD 5.93)	<0.001[b]
ADAS-cog – 18wk[a]	MC	227		-1.6 (SD 6.66)	220		1.8 (SD 6.67)	<0.001[b]
ADAS-cog – 26wk	MC	227		-0.2 (SD 7.3)	220		2.8 (SD 7.2)	≤0.001[c]
ADAS-cog: any improvement – 12wk[a]	D	227	68	(30.0%)	220	36	(16.4%)	≤0.001[d]
ADAS-cog: any improvement – 18wk[a]	D	227	75	(33.0%)	220	28	(12.7%)	≤0.001[d]
ADAS-cog: any improvement – 26wk[a]	D	227	52	(22.9%)	220	28	(12.7%)	
ADAS-cogA – 26wk	MC	227		-0.1 (SD 7.9)	220		3.2 (SD 7.8)	≤0.001[c]
Mini Mental State Examination – 26wk	MC	227		0.3 (SD 3.6)	220		-1.4 (SD 3.6)	≤0.001[b]
Functional:								
Progressive Deterioration Scale – 26wk	MC	225		-1.5 (SD 11.3)	221		-4.9 (SD 11.2)	≤0.001[c]
Global severity:								
CIBIC-plus score – 12wk[a]	C	220		3.9	213		4.3	≤0.001[b]
CIBIC-plus score – 18wk[a]	C	220		3.9 (SD 1.04)	213		4.5 (SD 1.02)	≤0.001[b]
CIBIC-plus score – 26wk	C	222		3.9 (SD 1.3)	216		4.5 (SD 1.3)	≤0.001[e]
CIBIC-plus: any improvement – 12wk[a]	D	220	66	(30.0%)	213	34	(16.0%)	≤0.001[d]
CIBIC-plus: any improvement – 18wk[a]	D	220	68	(30.9%)	213	40	(18.8%)	≤0.001[d]
CIBIC-plus: any improvement – 26wk[a]	D	220	68	(30.9%)	213	40	(18.8%)	<0.05[d]
Global deterioration scale – 26wk	MC	227		0 (SD 0.7)	222		-0.3 (SD 0.7)	<0.05[b]
Disposition of participants:								
Discontinued treatment due to AEs – 26wk	D	227	24	(10.6%)	222	20	(9.0%)	
Discontinued treatment before end of trial – 26wk	D	227	38	(16.7%)	222	33	(14.9%)	
LOCF analysis								
Cognitive:								
ADAS-cog – 26wk	MC	209		-0.7 (SD 6.9)	208		2.7 (SD 6.8)	≤0.001[c]
ADAS-cogA – 26wk	MC	209		-0.6 (SD 7.5)	208		3.1 (SD 7.4)	≤0.001[c]
Mini Mental State Examination – 26wk	MC	193		0.4 (SD 3.4)	198		-1.4 (SD 3.5)	≤0.001[b]
Functional:								
Progressive Deterioration Scale – 26wk	MC	207		-1 (SD 11.4)	209		-4.7 (SD 11.3)	≤0.001[c]
Global severity:								
CIBIC-plus score – 26wk	C	206		3.9 (SD 1.2)	205		4.5 (SD 1.2)	≤0.001[e]
Global deterioration scale – 26wk	MC	195		0 (SD 0.7)	202		-0.3 (SD 0.7)	<0.05[b]
OC population								
Cognitive:								
ADAS-cog – 26wk	MC	180		-0.9 (SD 6.8)	183		2.1 (SD 6.8)	≤0.001[c]
Global severity:								
CIBIC-plus score – 26wk	C	177		3.9 (SD 1.2)	179		4.4 (SD 1.2)	≤0.001[e]
Safety population								
Adverse events:								
Any AE – 0wk	D	227	208	(91.6%)	222	169	(76.1%)	<0.05[f]
Any serious AE – 0wk	D	227	40	(17.6%)	222	33	(14.9%)	NS[f]
Anorexia – 0wk	D	227	42	(18.5%)	222	6	(2.7%)	<0.05[f]
Nausea – 0wk	D	227	109	(48.0%)	222	31	(14.0%)	<0.05[f]
Diarrhoea – 0wk	D	227	38	(16.7%)	222	20	(9.0%)	<0.05[f]
Vomiting – 0wk	D	227	68	(30.0%)	222	14	(6.3%)	<0.05[f]
Abdominal pain – 0wk	D	227	26	(11.5%)	222	12	(5.4%)	<0.05[f]

Agitation – 0wk	D	227	14	(6.2%)	222	26	(11.7%)	<0.05[f]
Anxiety – 0wk	D	227	8	(3.5%)	222	3	(1.4%)	NS[f]
Dizziness – 0wk	D	227	39	(17.2%)	222	16	(7.2%)	<0.05[f]
Headache – 0wk	D	227	36	(15.9%)	222	23	(10.4%)	NS[f]
Flatulence – 0wk	D	227	15	(6.6%)	222	4	(1.8%)	<0.05[f]
Haemorrhoids – 0wk	D	227	2	(0.9%)	222	6	(2.7%)	NS[f]

[a] estimated from figure

[b] t-test using pooled error term from ANCOVA/ANOVA (SAS Type III analysis)

[c] Mantel–Haenszel test blocking for centre

[d] Mantel–Haenszel test

[e] t-test using pooled error term from ANOVA (SAS Type III)

[f] Fisher's exact test

		Rivastigmine bd			Placebo			
		N	**K**	**MEAN**	**N**	**K**	**MEAN**	***P***
ITT population								
Cognitive:								
ADAS-cog – 12wk[a]	MC	228		-0.8 (SD 6.04)	220		0.9 (SD 5.93)	<0.05[b]
ADAS-cog – 18wk[a]	MC	228		-0.1 (SD 6.79)	220		1.8 (SD 6.67)	<0.001[b]
ADAS-cog – 26wk	MC	228		1.2 (SD 7.2)	220		2.8 (SD 7.2)	<0.05[c]
ADAS-cog: any improvement – 12wk[a]	D	228	52	(22.8%)	220	36	(16.4%)	<0.05[d]
ADAS-cog: any improvement – 18wk[a]	D	228	57	(25.0%)	220	28	(12.7%)	≤0.001[d]
ADAS-cog: any improvement – 26wk[a]	D	228	41	(18.0%)	220	28	(12.7%)	NS[d]
ADAS-cogA – 26wk	MC	228		1.5 (SD 7.8)	220		3.2 (SD 7.8)	<0.05[c]
Mini Mental State Examination – 26wk	MC	227		-0.6 (SD 3.6)	220		-1.4 (SD 3.6)	<0.05[b]
Functional:								
Progressive Deterioration Scale – 26wk	MC	227		-2.6 (SD 11.1)	221		-4.9 (SD 11.2)	<0.05[c]
Global severity:								
CIBIC-plus score – 12wk[a]	C	215		3.9	213		4.3	≤0.001[b]
CIBIC-plus score – 18wk[a]	C	215		4.1 (SD 1.03)	213		4.5 (SD 1.02)	≤0.001[b]
CIBIC-plus score – 26wk	C	222		4.1 (SD 1.3)	216		4.5 (SD 1.3)	<0.05[e]
CIBIC-plus: any improvement – 12wk[a]	D	215	62	(28.8%)	213	34	(16.0%)	<0.05[d]
CIBIC-plus: any improvement – 18wk[a]	D	215	47	(21.9%)	213	40	(18.8%)	NS[d]
CIBIC-plus: any improvement – 26wk[a]	D	215	49	(22.8%)	213	40	(18.8%)	NS[d]
Global deterioration scale – 26wk	MC	229		-0.2 (SD 0.7)	222		-0.3 (SD 0.7)	NS[b]
Disposition of participants:								
Discontinued treatment due to AEs – 26wk	D	229	39	(17.0%)	222	20	(9.0%)	
Discontinued treatment before end of trial – 26wk	D	229	54	(23.6%)	222	33	(14.9%)	
LOCF analysis								
Cognitive:								
ADAS-cog – 26wk	MC	199		0.8 (SD 6.9)	208		2.7 (SD 6.8)	<0.05[c]
ADAS-cogA – 26wk	MC	199		1 (SD 7.5)	208		3.1 (SD 7.4)	<0.05[c]
Mini Mental State Examination – 26wk	MC	186		-0.4 (SD 3.5)	198		-1.4 (SD 3.5)	<0.05[b]
Functional:								
Progressive Deterioration Scale – 26wk	MC	195		-2.3 (SD 11.5)	209		-4.7 (SD 11.3)	<0.05[c]
Global severity:								
CIBIC-plus score – 26wk	C	198		4.1 (SD 1.2)	205		4.5 (SD 1.2)	<0.05[e]
Global deterioration scale – 26wk	MC	188		-0.1 (SD 0.7)	202		-0.3 (SD 0.7)	NS[b]
OC population								
Cognitive:								
ADAS-cog – 26wk	MC	173		0.9 (SD 7)	183		2.1 (SD 6.8)	NS[c]
Global severity:								
CIBIC-plus score – 26wk	C	167		4.1 (SD 1.2)	179		4.4 (SD 1.2)	<0.05[e]
Safety population								
Adverse events:								
Any AE – 0wk	D	228	208	(91.2%)	222	169	(76.1%)	<0.05[f]
Any serious AE – 0wk	D	228	40	(17.5%)	222	33	(14.9%)	NS[f]
Anorexia – 0wk	D	228	47	(20.6%)	222	6	(2.7%)	<0.05[f]
Nausea – 0wk	D	228	123	(53.9%)	222	31	(14.0%)	<0.05[f]
Diarrhoea – 0wk	D	228	40	(17.5%)	222	20	(9.0%)	<0.05[f]
Vomiting – 0wk	D	228	88	(38.6%)	222	14	(6.3%)	<0.05[f]
Abdominal pain – 0wk	D	228	34	(14.9%)	222	12	(5.4%)	<0.05[f]

Agitation – 0wk	D	228	21	(9.2%)	222	26	(11.7%)	NS[f]
Anxiety – 0wk	D	228	13	(5.7%)	222	3	(1.4%)	<0.05[f]
Dizziness – 0wk	D	228	42	(18.4%)	222	16	(7.2%)	<0.05[f]
Headache – 0wk	D	228	40	(17.5%)	222	23	(10.4%)	<0.05[f]
Flatulence – 0wk	D	228	11	(4.8%)	222	4	(1.8%)	NS[f]
Haemorrhoids – 0wk	D	228	0	(0.0%)	222	6	(2.7%)	<0.05[f]

[a] estimated from figure

[b] t-test using pooled error term from ANCOVA/ANOVA (SAS Type III analysis)

[c] Mantel–Haenszel test blocking for centre

[d] Mantel–Haenszel test

[e] t-test using pooled error term from ANOVA (SAS Type III)

[f] Fisher's exact test

Methodological issues

Randomisation and allocation: Randomisation procedure not described. Rivastigmine and placebo tablets were identical and the number taken was the same at each dose in all groups.

Data analysis: ADAS-cog - two-way treatment by centre ANOVA and ANCOVA (SAS type III analysis) on changes from baseline for each time point (12, 18 and 26w), using the baseline score as covariate.

ADAS-cog - categorical analysis to determine the proportion of patinets showing at least a 4 point score at 26w, with Mantel-Haenszel blocking for centre.

CIBIC-Plus improvers - categorical analysis to determine proportion showing imporvements versus those showing no change or worsening, with Mantel-Haenszel blocking for centre.

CIBIC-Plus - 2 way ANOVA (SAS type III analysis).

PDS and ADAS-CogA - ANCOVA on changesd from baseline to week 26, and post hoc Cohen's D effect sizes calculated at each visit for the ADAS-Cog and CIBIC-Plus by dividing mean differences by pooled standard deviations.

Comparisons with placebo were two tailed with the critical significance level set at $p<0.05$. In order to control for multiplicity in the analyses of efficacy data, the primary comparison was specified as rivastigmine administered BID against placebo. If this test was statistically significant at the 0.05 level, then the rivastigmine administered TID against placebo was tested at the 0.05 level subsequently. As both primary efficacy variables were required to be significant, no further correction of the size of the tests for the multiplicity of variables was required.

Power calculation: The study sample size was determined on the basis of an estimated 3.0 point difference between rivastigmine administered BID and placebo on the ADAS-cog, an estimated 0.4 point difference between BID and placebo on the CIBIC-Plus and an increased proportion of responders with CIBIC-Plus ratings of .4 of 20% within the BID rivastigmine group (35% rivastigmine vs 15% placebo). Sample sizes of 192 per group were

required. For practical reasons the sample size was chosen as 200 (intention to treat (ITT) population). An individual power

of 90% guaranteed protection of the global power in view of the requirement that both ADAS-cog and CIBIC-Plus analyses

should be significant at the 0.0499 level.

Conflicts of interest: HF has received honoraria for consulting, advisory boards and for participation in CME programs sponsored by Novartis. He has also received grant-in-aid funding for research from Novartis. RL is an employee of Novartis. The study was commissioned by Novartis Pharma AG in Switzerland.

Quality appraisal

1. **Was the assignment to the treatment groups really random?** UNKNOWN
2. **Was the treatment allocation concealed?** UNKNOWN
3. **Were the groups similar at baseline in terms of prognostic factors?** REPORTED - YES
4. **Were the eligibility criteria specified?** UNKNOWN
5. **Were outcome assessors blinded to the treatment allocation?** UNKNOWN
6. **Was the care provider blinded?** ADEQUATE
7. **Was the patient blinded?** ADEQUATE
8. **Were the point estimates and measure of variability presented for the primary outcome measure?** ADEQUATE
9. **Did the analyses include an intention-to-treat analysis?** ADEQUATE
10. **Were withdrawals and dropouts completely described?** ADEQUATE

Design	Participants	Arms	OUTCOMES
Mazza et al. (2006){1081 /id} **Study design:** Parallel double-blind RCT **Country:** Italy? **No. of centres:** 1 **Funding:** Not reported **Length of follow-up (wk):** 24	**Number randomised:** 76 **MMSE min:** 13 **MMSE max:** 25 **Inclusion criteria:** AD (DSM-IV criteria) Brief Cognitive Rating scale mean score 3-5 Hachinski Iscaemic Score <4 Adequate level of premorbid intelligence (IG>80, global assessment) **Exclusion criteria:** Dementia of other aetiology Severe organic diseases (tumours, severe infectious diseases, brain trauma, epilepsy, cerebrovascular malformations, alcohol or drug abuse) Pseudodementia or a histiory of schizophrenic or affective psychoses (Geriatric Depression Scale, 15-item version, total score <9) Vasoactive drugs, nootropics and long-term treatment with other drugs were proscribed during the study, with the exception of low doses of benzodiazepines and neuroleptics in the treatment of behavioural disturbances. **Therapy common to all participants:** Single-blind placebo 4-week run-in period (in order to exclude placebo responders) **Sample attrition / dropout:** 60 of 76 randomised patients completed the study (a further 41 were excluded during the run-in period; reasons not reported).	**Arm No:** 1 **Name:** Donepezil **N:** 25 **Drug:** Donepezil **Starting daily dose (mg):** 5 **Dosage details:** 5mg daily **Arm No:** 2 **Name:** Placebo **N:** 26 **Drug:** Placebo **Starting daily dose (mg):** - **Dosage details:** Not reported	**Cognitive** ▪ Mini Mental State Examination ▪ Syndrom Kurztest (psychometric test battery for assessment of memory and attention, consisting of nine 1-minute sub-tests that are partly speed-oriented and partly span-oriented, total score range from 1 (very good) to 27 (very poor)) ▪ Clinical Global Impression: item 2 (cognitive) (global change in observable cognitive functioning, transitional scale ranging from 1 (very much improved) to 7 (very much deteriorated))

Notes
-

Baseline characteristics

		Donepezil			Placebo			
		N	K	MEAN	N	K	MEAN	*P*
ITT population								
Demographics:								
Age	C	25		64.5 (SD 6)	26		69.8 (SD 3)	<0.001[a]
Sex (n male)	D	25	13	(52.0%)	26	10	(38.5%)	0.490[b]
Cognitive:								
Mini Mental State Examination – 0wk	C	25		18.6 (SD 3.47)	26		18.8 (SD 3.63)	
Syndrom Kurztest – 0wk	C	25		15.2 (SD 3.48)	26		15.9 (SD 3.86)	
Clinical Global Impression: item 2 (cognitive) – 0wk	C	25		4.5 (SD 0.76)	26		5.05 (SD 0.99)	

[a] student's t-test (calculated by reviewer)

[b] chi-square test (Yates's correction) (calculated by reviewer)

Results

		Donepezil			Placebo			
		N	K	MEAN	N	K	MEAN	P
ITT population								
Cognitive:								
Mini Mental State Examination – 24wk	C	25		19.8 (SD 3.16)	26		18.6 (SD 3.66)	NS[a]
Mini Mental State Examination – 24wk	MC	25		1.2 (SD 12.2)	26		-0.25 (SD 5)[b]	0.06[a]
Syndrom Kurztest – 24wk	C	25		11.8 (SD 2.9)	26		16.9 (SD 3.9)	0.01[a]
Syndrom Kurztest – 24wk	MC	25		-3.3 (SD -2.55)	26		0.9 (SD 1.3)	<0.001[a]
Clinical Global Impression: item 2 (cognitive) – 24wk	C	25		3.6 (SD 0.94)	26		5.2 (SD 0.95)	0.01[a]
Clinical Global Impression: item 2 (cognitive) – 24wk	MC	25		-0.9 (SD 1.02)	26		0.15 (SD 0.338)	<0.001[a]
Disposition of participants:								
Discontinued treatment due to AEs – 24wk	D	25	4	(16.0%)	26	0	(0.0%)	
Discontinued treatment before end of trial – 24wk	D	25	4	(16.0%)	26	6[c]	(23.1%)	

[a] ANOVA, covarying age, gender, and severity of cognitive impairment at baseline

[b] reported 95%CI is asymmetric, suggesting calculation error

[c] "loss of efficacy was the first cause for withdrawal"

Methodological issues

Randomisation and allocation: Randomisation computer-generated (whether unreadable before allocation is not stated). Appearance of pills and placebo not reported.

Data analysis: MMSE, SKT, CGI (item 2) - t-test for paired samples was used to compare each group from baseline to 24 weeks of treatment. ANOVA to detect difference between groups (Age, gender, and severity of cognitive impairment at baseline were factors of ANOVA model).

Power calculation: Not reported

Conflicts of interest: Not reported

Quality appraisal

1. **Was the assignment to the treatment groups really random?** PARTIAL
2. **Was the treatment allocation concealed?** INADEQUATE
3. **Were the groups similar at baseline in terms of prognostic factors?** REPORTED - YES
4. **Were the eligibility criteria specified?** INADEQUATE
5. **Were outcome assessors blinded to the treatment allocation?** PARTIAL
6. **Was the care provider blinded?** PARTIAL
7. **Was the patient blinded?** PARTIAL
8. **Were the point estimates and measure of variability presented for the primary outcome measure?** ADEQUATE
9. **Did the analyses include an intention-to-treat analysis?** PARTIAL
10. **Were withdrawals and dropouts completely described?** PARTIAL

Design	Participants	Arms	OUTCOMES
Moraes et al. (2008){1158 /id} **Study design:** Parallel double-blind RCT **Country:** Brazil **No. of centres:** 1 **Funding:** FAPESP (Fundacao	**Number randomised:** 23 **MMSE min:** 6 **MMSE max:** 27 **Inclusion criteria:** AD (ADRDA criteria) Rating of 1-2 (mild to	**Arm No:** 1 **Name:** Donepezil **N:** 11 **Drug:** Donepezil **Starting daily dose (mg):** 5 **Dosage details:** Single dose	▪ ADAS-cog (multiple cognitive functions including word evocation, verbal fluency, understanding of simple commands, constructive praxis, ideational praxis, temporospatial orientation, word recognition,

de Amparoa Pesquisa do Estado de Sao Paulo) AFIP (Associacao Fundo de Incentivo a Psicofarmacolgia) **Length of follow-up (wk):** 12	moderate) on Brazilian version of Clinical Dementia Rating **Exclusion criteria:** Rating of >=3 on Brazilian version of Clinical Dementia Rating Other causes of dementia Other current severe medical or psychiatric disease Psychoactive drugs in the month prior to entering the study **Therapy common to all participants:** 2 nights of polysomnographic recording (for purposes of habituation) **Sample attrition / dropout:** Not reported	of 5mg (administered at bedtime) in the first month, increased to single dose of 10mg in second month **Arm No:** 2 **Name:** Placebo **N:** 12 **Drug:** Placebo **Starting daily dose (mg):** - **Dosage details:** Single dose administered at bedtime	verbal fluency, vocabulary, and understanding. Scores range from 0 to 70, with higher scores indicating more cognitive deterioration)
Notes -			

Baseline characteristics

		Donepezil			Placebo			
		N	K	MEAN	N	K	MEAN	*P*
OC population								
Demographics:								
Age	C	11		76.8 (SD 6.2)	12		72.6 (SD 11)	0.27[a]
Sex (n male)	D	11	3	(27.3%)	12	5	(41.7%)	0.49[a]
BMI (kg/m2)	C	11		26.3 (SD 4.8)	12		26.6 (SD 4.1)	0.85[a]
Cognitive:								
ADAS-cog – 0wk	C	11		34.5 (SD 15.8)	12		29.3 (SD 17.3)	
Mini Mental State Examination	C	11		19 (SD 3.6)	12		17.2 (SD 7.8)	0.50[a]
Global severity:								
Clinical Dementia Rating	C	11		1.3 (SD 0.5)	12		1.3 (SD 0.5)	0.76[a]

[a] ANOVA

Results

		Donepezil			Placebo			
		N	K	MEAN	N	K	MEAN	*P*
OC population								
Cognitive:								
ADAS-cog – 13wk	C	11		29.7 (SD 15.7)	12		31.8 (SD 18.5)	<0.05[a]

[a] ANOVA

Mild and transitory side effects involving nausea and headache occurred in three patients receiving donepezil.

Methodological issues

Randomisation and allocation: Randomisation performed using computer-generated random number list (0-1) with uniform distribution, with patients consecutively allocated to the two treatment groups (<=0.5 to group A, >0.5 to group B). Donepezil and placebo pills were 'packed in the same fashion', but precise appearance of pills not reported.

Data analysis: One-way analysis of variance (ANOVA) was used to compare all variables for donepezil and placebo groups during the baseline recording night. Polysomnographic and cognitive data at baseline and after 3 months of treatment were analyzed using two-way

ANOVA for repeated measures with treatment group and treatment time as the main factors and time/treatment interaction

effect followed by Bonferroni test, with p <=0.01 comparing data

Power calculation: Not reported

Conflicts of interest: Authors state no conflicts of interest to disclose

Quality appraisal

1. **Was the assignment to the treatment groups really random?** INADEQUATE
2. **Was the treatment allocation concealed?** INADEQUATE
3. **Were the groups similar at baseline in terms of prognostic factors?** REPORTED - YES
4. **Were the eligibility criteria specified?** UNKNOWN
5. **Were outcome assessors blinded to the treatment allocation?** PARTIAL
6. **Was the care provider blinded?** ADEQUATE
7. **Was the patient blinded?** ADEQUATE
8. **Were the point estimates and measure of variability presented for the primary outcome measure?** ADEQUATE
9. **Did the analyses include an intention-to-treat analysis?** UNKNOWN
10. **Were withdrawals and dropouts completely described?** INADEQUATE

Design	Participants	Arms	OUTCOMES
Mowla et al. (2007){1174 /id} **Study design:** Parallel double-blind RCT **Country:** Not reported. Lead author based in Iran **No. of centres:** Not reported **Funding:** Shiraz University of Medical Sciences **Length of follow-up (wk):** 12 **Notes** **Notes:** 12-week mean MMSE/WMS/ADL/HAM scores in the fluoxetine plus rivastigmine arm were much lower than in the other arms - potential error?	**Number randomised:** 122 **MMSE min:** 10 **MMSE max:** 24 **Inclusion criteria:** AD (DSM-IV criteria) Brief Cognitive Rating Score mean 3-5 Hachinski Iscahemic Score <4 Adequate level of premorbid intelligence (IG >80, global assessment) **Exclusion criteria:** Dementia of other aetiology Severe organic disease (tumours, severe infectious disease, brain trauma, epilepsy, cerebrovascular malformations, alcohol or drug abuse) Other psychiatric disorders (Hamilton Depression Scale, 17-item version, total score <10) **Therapy common to all participants:** Single-blind placebo 6-week run-in period to exclude placebo responders **Sample attrition / dropout:** 98 of 122 completed study. Drop-outs: Rivastigmine arm n=7; Fluoxetine plus rivastigmine n=9; placebo n=8. Major cause of withdrawal in fluoxetine plus rivastigmine arm was adverse events, in placebo arm it was loss of efficacy.	**Arm No:** 1 **Name:** Rivastigmine **N:** 41 **Drug:** Rivastigmine **Starting daily dose (mg):** 3 **Dosage details:** Titrated from initial dose of 1.5mg twice a day, doubled every 2wk until maximum dose of 6mg twice a day reached (or dose which patient could tolerate) **Notes:** no details of placebo fluoxetine administration **Arm No:** 2 **Name:** Rivastigmine+Fluoxetine **N:** 41 **Drug:** Rivastigmine **Starting daily dose (mg):** 3 **Dosage details:** Titrated from initial dose of 1.5mg twice a day, doubled every 2wk until maximum dose of 6mg twice a day reached (or dose which patient could tolerate) **Notes:** Fluoxetine 20mg/d **Arm No:** 3 **Name:** Placebo **N:** 40 **Drug:** Placebo **Starting daily dose (mg):** -	**Cognitive** ▪ Mini Mental State Examination ▪ Wechsler Memory Scale III (immediate and delayed logical memory, digit span forward and backward, and family pictures I and II from Persian standardised WMS-III) ▪ Clinical Global Impression: item 2 (cognitive) (global change in observable cognitive functioning, scale from 1 (very much improved) to 7 (very much deteriorated)) **Functional** ▪ ADL (Lawton and Brody scale, 8 items in Instrumental ADL and 6 items in Basic ADL, subtest scores aggregated to give a total functional assessment (ADL) score (scale in subtests from 1 (being completely capable of doing the activity) to 5 (being thoroughly unable to perform the activity)) **Behavioural** ▪ Hamilton Depression Scale (not reported)

		Dosage details: -	

Baseline characteristics

	All study participants		
	N	**K**	**MEAN**
Demographics:			
Age	122		69.2
Sex (n male)	122	65[a]	(53.3%)

[a] approximated to nearest integer (percentages only presented in text); poor rounding suggests true denominator may be less than full sample size

		Rivastigmine			Placebo			
		N	**K**	**MEAN**	**N**	**K**	**MEAN**	***P***
Cognitive:								
Mini Mental State Examination – 0wk	C	41		16.3 (SD 4.1)	40		16.5 (SD 3.6)	0.816[a]
Wechsler Memory Scale III – 0wk	C	41		7.7 (SD 2.2)	40		8.3 (SD 2)	0.203[a]
Functional:								
ADL – 0wk	C	41		26.5 (SD 7.7)	40		26.8 (SD 7.5)	0.860[a]
Behavioural:								
Hamilton Depression Scale – 0wk	C	41		8.06 (SD 1.7)	40		7.33 (SD 1.39)	0.038[a]

[a] student's t-test (calculated by reviewer)

		Rivastigmine+Fluoxetine			Placebo			
		N	**K**	**MEAN**	**N**	**K**	**MEAN**	***P***
Cognitive:								
Mini Mental State Examination – 0wk	C	41		15.6 (SD 0.73)	40		16.5 (SD 3.6)	0.121[a]
Wechsler Memory Scale III – 0wk	C	41		8 (SD 0.32)	40		8.3 (SD 2)	0.346[a]
Functional:								
ADL – 0wk	C	41		27.4 (SD 1.3)	40		26.8 (SD 7.5)	0.615[a]
Behavioural:								
Hamilton Depression Scale – 0wk	C	41		8.17 (SD 0.32)	40		7.33 (SD 1.39)	<0.001[a]

[a] student's t-test (calculated by reviewer)

Results

		Rivastigmine			Placebo			
		N	**K**	**MEAN**	**N**	**K**	**MEAN**	***P***
ITT population								
Disposition of participants:								
Discontinued treatment due to AEs – 12wk	D	41	3	(7.3%)	40	0[a]	(0.0%)	
Discontinued treatment before end of trial – 12wk	D	41	7	(17.1%)	40	8	(20.0%)	
OC population								
Cognitive:								
Mini Mental State Examination – 12wk	MC	41		1.1 (SD 1.4)	40		-0.5 (SD 0.5)	<0.001[b]
Mini Mental State Examination – 12wk	C	34		17.4 (SD 3.7)	32		16 (SD 3.7)	0.129[c]
Mini Mental State Examination – 12wk	MC	34		1.1 (SD 1.4)	32		-0.5 (SD 0.5)	<0.001[b]
Wechsler Memory Scale III – 12wk	MC	41		0.97 (SD 1.7)	40		-0.66 (SD 1.1)	<0.001[b]
Wechsler Memory Scale III – 12wk	C	34		8.7 (SD 2.2)	32		7.5 (SD 1.4)	0.011[c]
Wechsler Memory Scale III – 12wk	MC	34		0.97 (SD 1.7)	32		-0.66 (SD 1.1)	<0.001[b]

Clinical Global Impression: item 2 (cognitive) – 12wk	C	34	3.1 (SD 0.96)	32	3.7 (SD 0.67)	0.005[c]
Functional:						
ADL – 12wk	MC	41	1.2 (SD 2.6)	40	-0.68 (SD 1.3)	0.58[d]
ADL – 12wk	C	34	25.3 (SD 6.6)	32	27.1 (SD 6.9)	0.283[c]
ADL – 12wk	MC	34	1.2 (SD 2.6)	32	-0.68 (SD 1.3)	0.58[d]
Behavioural:						
Hamilton Depression Scale – 12wk	C	34	6.26 (SD 2.9)	32	8.33 (SD 1.12)	<0.001[c]

[a] none explicitly reported, whereas numbers are given for other arms, suggesting there were none in this arm

[b] post-hoc Tukey test

[c] student's t-test (two-tailed) (calculated by reviewer)

[d] post-hoc Tukey test; NB t-test p<0.001

		Rivastigmine+Fluoxetine			Placebo			
		N	K	MEAN	N	K	MEAN	*P*
ITT population								
Disposition of participants:								
Discontinued treatment due to AEs – 12wk	D	41	5	(12.2%)	40	0[a]	(0.0%)	
Discontinued treatment before end of trial – 12wk	D	41	9	(22.0%)	40	8	(20.0%)	
OC population								
Cognitive:								
Mini Mental State Examination – 12wk	MC	41		1.6 (SD 2.7)	40		-0.5 (SD 0.5)	0.002[b]
Mini Mental State Examination – 12wk	C	32		17.2 (SD 0.63)	32		16 (SD 3.7)	
Mini Mental State Examination – 12wk	MC	32		1.6 (SD 2.7)	32		-0.5 (SD 0.5)	0.002[b]
Wechsler Memory Scale III – 12wk	MC	41		0.96 (SD 2.1)	40		-0.66 (SD 1.1)	<0.001[b]
Wechsler Memory Scale III – 12wk	C	32		8.9 (SD 0.54)	32		7.5 (SD 1.4)	
Wechsler Memory Scale III – 12wk	MC	32		0.96 (SD 2.1)	32		-0.66 (SD 1.1)	<0.001[b]
Clinical Global Impression: item 2 (cognitive) – 12wk	C	32		2.5 (SD 1.2)	32		3.7 (SD 0.67)	
Functional:								
ADL – 12wk	MC	41		3.2 (SD 3.2)	40		-0.68 (SD 1.3)	0.001[b]
ADL – 12wk	C	32		24.2 (SD 0.95)	32		27.1 (SD 6.9)	
ADL – 12wk	MC	32		3.2 (SD 3.2)	32		-0.68 (SD 1.3)	0.001[b]
Behavioural:								
Hamilton Depression Scale – 12wk	C	32		6.55 (SD 0.32)	32		8.33 (SD 1.12)	

[a] none explicitly reported, whereas numbers are given for other arms, suggesting there were none in this arm

[b] post-hoc Tukey test

The main adverse effects in 2 active treatment groups were gastrointestinal disturbance and headache. No further details of safety.

Methodological issues

Randomisation and allocation: Computer-generated (on-site) randomisation - whether researchers were able to view randomisation sequence prior to allocation is not reported. Same number of pills for all trial arms, but appearance of these pills not reported (simply described as 'similar')

Data analysis: MMSE/WMS/ADL/HAM: t test for paired samples (within-group comparisons)

MMSE/WMS/ADL/CGI-2: ANOVA followed by Tukey post hoc comparison when significant effects present

Power calculation: Not reported

Conflicts of interest: Not reported

Quality appraisal

1. **Was the assignment to the treatment groups really random?** PARTIAL
2. **Was the treatment allocation concealed?** ADEQUATE
3. **Were the groups similar at baseline in terms of prognostic factors?** REPORTED - YES
4. **Were the eligibility criteria specified?** UNKNOWN
5. **Were outcome assessors blinded to the treatment allocation?** PARTIAL
6. **Was the care provider blinded?** PARTIAL

7.	**Was the patient blinded?** PARTIAL
8.	**Were the point estimates and measure of variability presented for the primary outcome measure?** ADEQUATE
9.	**Did the analyses include an intention-to-treat analysis?** INADEQUATE
10.	**Were withdrawals and dropouts completely described?** ADEQUATE

Design	Participants	Arms	OUTCOMES
Ancoli-Israel et al. (2005){1199 /id} **Study design:** Parallel double-blind RCT **Country:** Not reported. All study authors based in USA **No. of centres:** Not reported **Funding:** Janssen Medical Affairs **Length of follow-up (wk):** 8	**Number randomised:** 63 **MMSE min:** 10 **MMSE max:** 24 **Inclusion criteria:** Mild to moderate AD (criteria not reported) MMSE 10-24 >=60y of age Resident with a responsible caregiver who agreed to participate and monitor sleep and answer questionnaires **Exclusion criteria:** Other neurodegenerative disease contributing to dementia (including mulit-infarct dementia or clinically active cerebrovascular disease) Other medical conditions causing cognitive impairment Clinically significant co-existing medical conditions (psychiatric, cardiovascular, or oactive peptic ulcer disease; urinary outflow obstruction; hepatic, renal, pulmonary, metabolic or endocrine disturbances) Use of a muscarinic-1 agonist or AChEI within 30d prior to involvement **Therapy common to all participants:** 2-week, single-blind, placebo run-in **Sample attrition / dropout:** 54 of 63 completed study; discontinued due to adverse event (n=3 in galantamine arm; n=4 in donepezil arm); discontinued due to severe adverse event possibly related to trial drug (hepatic failure, n=1 in donepezil arm); death (judged to be unrelated to trial drug, n=1)	**Arm No:** 1 **Name:** Donepezil **N:** 32 **Drug:** Donepezil **Starting daily dose (mg):** 5 **Dosage details:** Dose titrated from 5mg once a day at night for the first 4wk up to 10mg once a day at night for remainder of study **Arm No:** 2 **Name:** Galantamine **N:** 31 **Drug:** Galantamine **Starting daily dose (mg):** 8 **Dosage details:** Dose titrated from 4mg twice a day for the first 4wk up to 8mg twice a day for remainder of study	**Global severity** ▪ CIBIC-plus (Clinician's assessment of patient's general functioning, cognition, behaviour, and performance of daily living activities) **Adverse events**

Notes

-

Baseline characteristics

	Donepezil			Galantamine			
	N	K	MEAN	N	K	MEAN	*P*

Demographics:								
Age	C	32		77.8 (SD 6.2)	31		76.5 (SD 7.7)	0.463[a]
Sex (n male)	D	32	14	(43.8%)	31	10	(32.3%)	0.497[b]
Education (at least high school)	D	32	26	(81.3%)	31	22	(71.0%)	0.508[b]
Race (n white)	D	32	26	(81.3%)	31	25	(80.6%)	0.795[b]
Race (n black)	D	32	2	(6.3%)	31	3	(9.7%)	0.970[b]
Race (n hispanic)	D	32	1	(3.1%)	31	2	(6.5%)	0.978[b]
Race (n Asian)	D	32	1	(3.1%)	31	1	(3.2%)	0.487[b]
Race (n other)	D	32	2	(6.3%)	31	0	(0.0%)	0.573[b]
Caregiver characteristics:								
Age	C	32		69.4 (SD 11.4)	31		67.7 (SD 15.9)	0.627[a]
Sex (n male)	D	32	15	(46.9%)	31	15	(48.4%)	0.895[b]
Race (n white)	D	32	26	(81.3%)	31	25	(80.6%)	0.795[b]
Race (n black)	D	32	2	(6.3%)	31	3	(9.7%)	0.970[b]
Race (n Hispanic)	D	32	1	(3.1%)	31	2	(6.5%)	0.978[b]
Race (n Asian)	D	32	1	(3.1%)	31	1	(3.2%)	0.487[b]
Race (n other)	D	32	2	(6.3%)	31	0	(0.0%)	0.573[b]
Education: at least high school	D	32	26	(81.3%)	31	24	(77.4%)	0.949[b]
Relationship to participant: spouse	D	32	24	(75.0%)	31	22	(71.0%)	0.939[b]
Relationship to participant: child	D	32	7	(21.9%)	31	5	(16.1%)	0.795[b]
Relationship to participant: relative/friend	D	32	0	(0.0%)	31	3	(9.7%)	0.287[b]
Relationship to participant: other	D	32	1	(3.1%)	31	1	(3.2%)	0.487[b]
Cognitive:								
Mini Mental State Examination	C	32		19.4 [rng 13–24]	31		19.3 [rng 11–24]	NS[c]

[a] student's t-test (calculated by reviewer)

[b] chi-square test (Yates's correction) (calculated by reviewer)

[c] test not specified

Results

		Donepezil			Galantamine			
		N	K	MEAN	N	K	MEAN	*P*
Global severity:								
CIBIC-plus score – 8wk	C	29		3.97 (SD 1.02)	27		3.59 (SD 0.636)	0.106[a]
CIBIC-plus: markedly improved – 8wk	D	29	0	(0.0%)	27	0	(0.0%)	0.330[b]
CIBIC-plus: moderately improved – 8wk	D	29	3	(10.3%)	27	2	(7.4%)	0.933[b]
CIBIC-plus: minimally improved – 8wk	D	29	4	(13.8%)	27	7	(25.9%)	0.421[b]
CIBIC-plus: no change – 8wk	D	29	18	(62.1%)	27	18	(66.7%)	0.936[b]
CIBIC-plus: minimally worse – 8wk	D	29	3	(10.3%)	27	0	(0.0%)	0.334[b]
CIBIC-plus: moderately worse – 8wk	D	29	3	(10.3%)	27	0	(0.0%)	0.334[b]
CIBIC-plus: markedly worse – 8wk	D	29	0	(0.0%)	27	0	(0.0%)	0.330[b]
Adverse events:								
Nausea – 8wk	D	32	1	(3.1%)	31	3	(9.7%)	0.583[b]
Diarrhoea – 8wk	D	32	5	(15.6%)	31	1	(3.2%)	0.212[b]
Injury – 8wk	D	32	2	(6.3%)	31	2	(6.5%)	0.628[b]
Headache – 8wk	D	32	3	(9.4%)	31	2	(6.5%)	0.970[b]
Constipation – 8wk	D	32	3	(9.4%)	31	0	(0.0%)	0.317[b]
Pain – 8wk[c]	D	32	3	(9.4%)	31	2	(6.5%)	0.970[b]
Bronchitis – 8wk	D	32	0	(0.0%)	31	3	(9.7%)	0.287[b]
Disposition of participants:								
Discontinued treatment due to AEs – -1wk	D	32	4	(12.5%)	31	3	(9.7%)	0.964[b]
Discontinued treatment before end of trial – -1wk	D	32	4	(12.5%)	31	5	(16.1%)	0.959[b]

[a] student's t-test (two-tailed) (calculated by reviewer)

[b] chi-square test (Yates's correction) (calculated by reviewer)

[c] no description of specific pain indicated

this study is primarily interested in sleep outcomes; data not extracted

Methodological issues

Randomisation and allocation: Randomisation procedure not described

Data analysis: Percent sleep (MC from baseline (SE))

Actigraphy measured (mean (SE))

PSQI (mean (SE) and Pearson correlation coefficient)

CIBIC-Plus, descriptive statistics only (%)

Power calculation: None

Conflicts of interest: Lead author declares no financial disclosure; co-authors are employees of funder (Janssen Medical Affairs)

Quality appraisal

1. **Was the assignment to the treatment groups really random?** UNKNOWN
2. **Was the treatment allocation concealed?** UNKNOWN
3. **Were the groups similar at baseline in terms of prognostic factors?** REPORTED - YES
4. **Were the eligibility criteria specified?** UNKNOWN
5. **Were outcome assessors blinded to the treatment allocation?** PARTIAL
6. **Was the care provider blinded?** PARTIAL
7. **Was the patient blinded?** PARTIAL
8. **Were the point estimates and measure of variability presented for the primary outcome measure?** ADEQUATE
9. **Did the analyses include an intention-to-treat analysis?** PARTIAL
10. **Were withdrawals and dropouts completely described?** ADEQUATE

Design	Participants	Arms	OUTCOMES
Nordberg et al. (2009){1212 /id} **Study design:** - **Country:** Not reported **No. of centres:** Not reported **Funding:** Novartis Pharmaceuticals; Swedish Research Council; KI foundations, L-H Osterman and Stohne's Foundations supported two co-authors (AN, TDS). Alpha-Plus provided editorial assistance with the production of the manuscript. **Length of follow-up (wk):** 13 **Notes** -	**Number randomised:** 63 **MMSE min:** 10 **MMSE max:** 20 **Inclusion criteria:** AD (DSM-IV criteria) and probable or possible AD (NINCDS-ADRDA criteria) Age 50-85yr MMSE 10-20 Provided the dose had been stabilised for the past month, treatment with psychotropics was permitted **Exclusion criteria:** Prior exposure to rivastigmine, donepezil or galantamine Advance, severe or unstable disease of any type that might interfere with study evaluation or put the patient at special risk Imaging findings consistent with a condition other than AD that would explain the patient's dementia Current treatment with coumarin derivatives Blood clotting abnormalities or inadequate platelet function **Therapy common to all**	**Arm No:** 1 **Name:** Donepezil **N:** 20 **Drug:** Donepezil **Starting daily dose (mg):** 5 **Dosage details:** starting dose 5mg qd; after >=4wk, if tolerated, up-titrated to 10mg qd; no subsequent up-titrations **Arm No:** 2 **Name:** Galantamine **N:** 21 **Drug:** Galantamine **Starting daily dose (mg):** 8 **Dosage details:** starting dose 4mg bd; after >=4wk, if tolerated, up-titrated to 8mg bd; subsequent up-titrations could be made after >=4wk at each dose, based upon the patient's well-being and tolerability, to a maximum of 12mg bd **Arm No:** 3 **Name:** Rivastigmine	▪ **Adverse events only**

	participants: None **Sample attrition / dropout:** 53 of 63 completed study. 10 withdrew after allocation; adverse events (n=8), withdrew consent (n=1), lost to follow-up (n=1)	**N:** 22 **Drug:** Rivastigmine **Starting daily dose (mg):** 3 **Dosage details:** starting dose 1.5mg bd; after >=4wk, if tolerated, up-titrated to 3mg bid; subsequent up-titrations could be made after >=4wk at each dose, based upon the patient's well-being and tolerability, to a maximum of 6mg bid	

Baseline characteristics

		Donepezil			Galantamine			
		N	K	MEAN	N	K	MEAN	*P*
Demographics:								
Age	C	20		74 (SD 8)	21		73.7 (SD 6.5)	0.896[a]
Sex (n male)	D	20	9	(45.0%)	21	5	(23.8%)	0.271[b]
Weight (kg)	C	20		65.2 (SD 8)	21		65.7 (SD 11.5)	0.873[a]
Race (n white)	D	20	20	(100.0%)	21	21	(100.0%)	0.323[b]
Race (n other)	D	20	0	(0.0%)	21	0	(0.0%)	0.323[b]
Disease characteristics:								
Duration of dementia (mo)	C	20		32.4 (SD 19.2)	21		39.6 (SD 25.2)	0.312[a]
Family history of AD	D	20	7	(35.0%)	21	9	(42.9%)	0.845[b]
Cognitive:								
Mini Mental State Examination	C	20		20 (SD 3.5)	21		19.2 (SD 3.1)	0.443[a]

[a] student's t-test (calculated by reviewer)

[b] chi-square test (Yates's correction) (calculated by reviewer)

		Donepezil			Rivastigmine			
		N	K	MEAN	N	K	MEAN	*P*
Demographics:								
Age	C	20		74 (SD 8)	22		76.8 (SD 8.9)	0.292[a]
Sex (n male)	D	20	9	(45.0%)	22	5	(22.7%)	0.230[b]
Weight (kg)	C	20		65.2 (SD 8)	22		65.1 (SD 9.7)	0.971[a]
Race (n white)	D	20	20	(100.0%)	22	21	(95.5%)	0.947[b]
Race (n other)	D	20	0	(0.0%)	22	1	(4.5%)	0.947[b]
Disease characteristics:								
Duration of dementia (mo)	C	20		32.4 (SD 19.2)	22		34.8 (SD 25.2)	0.732[a]
Family history of AD	D	20	7	(35.0%)	22	9	(40.9%)	0.940[b]
Cognitive:								
Mini Mental State Examination	C	20		20 (SD 3.5)	22		18.8 (SD 3.8)	0.295[a]

[a] student's t-test (calculated by reviewer)

[b] chi-square test (Yates's correction) (calculated by reviewer)

		Galantamine			Rivastigmine			
		N	K	MEAN	N	K	MEAN	*P*
Demographics:								
Age	C	21		73.7 (SD 6.5)	22		76.8 (SD 8.9)	0.201[a]
Sex (n male)	D	21	5	(23.8%)	22	5	(22.7%)	0.782[b]
Weight (kg)	C	21		65.7 (SD 11.5)	22		65.1 (SD 9.7)	0.854[a]
Race (n white)	D	21	21	(100.0%)	22	21	(95.5%)	0.974[b]
Race (n other)	D	21	0	(0.0%)	22	1	(4.5%)	0.974[b]

Disease characteristics:								
Duration of dementia (mo)	C	21		39.6 (SD 25.2)	22		34.8 (SD 25.2)	0.536[a]
Family history of AD	D	21	9	(42.9%)	22	9	(40.9%)	0.857[b]
Cognitive:								
Mini Mental State Examination	C	21		19.2 (SD 3.1)	22		18.8 (SD 3.8)	0.708[a]

[a] student's t-test (calculated by reviewer)

[b] chi-square test (Yates's correction) (calculated by reviewer)

Results

		Donepezil			Galantamine			
		N	K	MEAN	N	K	MEAN	*P*
Safety population								
Adverse events:								
Nausea – 13wk	D	20	2	(10.0%)	21	6	(28.6%)	0.269[a]
Diarrhoea – 13wk	D	20	0	(0.0%)	21	6	(28.6%)	0.046[a]
Vomiting – 13wk	D	20	0	(0.0%)	21	3	(14.3%)	0.317[a]
Abdominal pain – 13wk	D	20	2	(10.0%)	21	0	(0.0%)	0.522[a]
Dizziness – 13wk	D	20	1	(5.0%)	21	3	(14.3%)	0.635[a]
Headache – 13wk	D	20	2	(10.0%)	21	2	(9.5%)	0.635[a]
Upper respiratory tract infection – 13wk	D	20	1	(5.0%)	21	0	(0.0%)	0.973[a]
Weight loss – 13wk	D	20	1	(5.0%)	21	1	(4.8%)	0.490[a]
Insomnia – 13wk	D	20	2	(10.0%)	21	2	(9.5%)	0.635[a]
Influenza – 13wk	D	20	0	(0.0%)	21	2	(9.5%)	0.578[a]
Muscle spasms – 13wk	D	20	3	(15.0%)	21	1	(4.8%)	0.563[a]
Disposition of participants:								
Discontinued treatment due to AEs – -1wk	D	20	1	(5.0%)	21	4	(19.0%)	0.370[a]
Discontinued treatment before end of trial – -1wk	D	20	1	(5.0%)	21	5	(23.8%)	0.207[a]

[a] chi-square test (Yates's correction) (calculated by reviewer)

		Donepezil			Rivastigmine			
		N	K	MEAN	N	K	MEAN	*P*
Safety population								
Adverse events:								
Nausea – 13wk	D	20	2	(10.0%)	22	10	(45.5%)	0.028[a]
Diarrhoea – 13wk	D	20	0	(0.0%)	22	2	(9.1%)	0.605[a]
Vomiting – 13wk	D	20	0	(0.0%)	22	4	(18.2%)	0.187[a]
Abdominal pain – 13wk	D	20	2	(10.0%)	22	0	(0.0%)	0.496[a]
Dizziness – 13wk	D	20	1	(5.0%)	22	3	(13.6%)	0.670[a]
Headache – 13wk	D	20	2	(10.0%)	22	3	(13.6%)	0.910[a]
Upper respiratory tract infection – 13wk	D	20	1	(5.0%)	22	2	(9.1%)	0.932[a]
Weight loss – 13wk	D	20	1	(5.0%)	22	2	(9.1%)	0.932[a]
Insomnia – 13wk	D	20	2	(10.0%)	22	1	(4.5%)	0.932[a]
Influenza – 13wk	D	20	0	(0.0%)	22	1	(4.5%)	0.947[a]
Muscle spasms – 13wk	D	20	3	(15.0%)	22	0	(0.0%)	0.252[a]
Disposition of participants:								
Discontinued treatment due to AEs – -1wk	D	20	1	(5.0%)	22	3	(13.6%)	0.670[a]
Discontinued treatment before end of trial – -1wk	D	20	1	(5.0%)	22	4	(18.2%)	0.401[a]

[a] chi-square test (Yates's correction) (calculated by reviewer)

		Galantamine			Rivastigmine			
		N	K	MEAN	N	K	MEAN	*P*

Safety population								
Adverse events:								
Nausea – 13wk	D	21	6	(28.6%)	22	10	(45.5%)	0.407[a]
Diarrhoea – 13wk	D	21	6	(28.6%)	22	2	(9.1%)	0.212[a]
Vomiting – 13wk	D	21	3	(14.3%)	22	4	(18.2%)	0.946[a]
Abdominal pain – 13wk	D	21	0	(0.0%)	22	0	(0.0%)	0.323[a]
Dizziness – 13wk	D	21	3	(14.3%)	22	3	(13.6%)	0.705[a]
Headache – 13wk	D	21	2	(9.5%)	22	3	(13.6%)	0.956[a]
Upper respiratory tract infection – 13wk	D	21	0	(0.0%)	22	2	(9.1%)	0.577[a]
Weight loss – 13wk	D	21	1	(4.8%)	22	2	(9.1%)	0.967[a]
Insomnia – 13wk	D	21	2	(9.5%)	22	1	(4.5%)	0.967[a]
Influenza – 13wk	D	21	2	(9.5%)	22	1	(4.5%)	0.967[a]
Muscle spasms – 13wk	D	21	1	(4.8%)	22	0	(0.0%)	0.974[a]
Disposition of participants:								
Discontinued treatment due to AEs – -1wk	D	21	4	(19.0%)	22	3	(13.6%)	0.946[a]
Discontinued treatment before end of trial – -1wk	D	21	5	(23.8%)	22	4	(18.2%)	0.937[a]

[a] chi-square test (Yates's correction) (calculated by reviewer)

Methodological issues

Randomisation and allocation: Randomisation procedure not described. Open-label trial (although laboratory personnel who processed CSF samples were blinded).

Data analysis: Changes from baseline compared between treatment groups using ANCOVA with baseline and treatment as factors. Correction factor for multiplicity applied for primary outcome, but not for secondary outcomes (intended to be hypothesis-generating only). Al statistical tests were conducted against a two-sided alternative hypothesis, employing a significance level of 0.05.

Primary efficacy analyses based on the completer population. Secondary analyses based on ITT population (all randomised patients who received at least one dose of study medication and provided at least one post-baseline efficacy measurement)

Power calculation: Assuming a mean treatment difference of 0.3 U/L (primary outcome variable), SD 0.28 and two-sided significance level of 0.025, z-test showed approximately 20 patients per treatment group were required to achieve a power of 0.85 for detecting a significant pairwise treatment difference.

Conflicts of interest: Three co-authors (AN, TD-S, MM) were responsible for the enzyme analysis and received research sponsorship from Novartis. One co-author's (HS) institute received research sponsorship from Novartis for this study. Two co-authors (GE, RL) are fulltime employees of Novartis.

Quality appraisal

1. **Was the assignment to the treatment groups really random?** UNKNOWN
2. **Was the treatment allocation concealed?** UNKNOWN
3. **Were the groups similar at baseline in terms of prognostic factors?** REPORTED - YES
   Although note fewer women in donepezil group
4. **Were the eligibility criteria specified?** UNKNOWN
5. **Were outcome assessors blinded to the treatment allocation?** INADEQUATE
   Open label trial, monitoring personnel were not blinded (although laboratory personnel who processed CSF samples were blinded)
6. **Was the care provider blinded?** INADEQUATE
   Open label trial
7. **Was the patient blinded?** INADEQUATE
   Open label trial
8. **Were the point estimates and measure of variability presented for the primary outcome measure?** ADEQUATE
9. **Did the analyses include an intention-to-treat analysis?** INADEQUATE
10. **Were withdrawals and dropouts completely described?** ADEQUATE

Design	Participants	Arms	OUTCOMES
Peng et al. (2005){1267 /id} **Study design:** Parallel	**Number randomised:** 90	**Arm No:** 1	**Cognitive**

double-blind RCT **Country:** China **No. of centres:** 15 hospitals in Beijing, Shanghai, and Guangzhou **Funding:** Not reported **Length of follow-up (wk):** 12 **Notes** -	**MMSE min:** 10 **MMSE max:** 24 **Inclusion criteria:** AD (NINCDS-ADRDA and DSM-IVR criteria) >=55y old In female patients, menopause >=2y MMSE 10-24 Sufficinet vision and hearing to complete assessments **Exclusion criteria:** Other disease that may lead to dementia Severe heart or kidney dysfunction, active peptic ulcer, or active epilepsy Allergy to cholinergic drugs **Therapy common to all participants:** None **Sample attrition / dropout:** 89 of 90 completed the study. 1 dropped out due to adverse event (dizziness); not stated from which arm.	**Name:** Donepezil **N:** 46 **Drug:** Donepezil **Starting daily dose (mg):** 5 **Dosage details:** Same dose administered throughout duration of study **Arm No:** 2 **Name:** Placebo **N:** 43 **Drug:** Placebo **Starting daily dose (mg):** - **Dosage details:** -	▪ Mini Mental State Examination (cognitive functions (direction, memory, calculation, language)) **Functional** ▪ ADL (described as 'testing daily living abilities') **Global severity** ▪ Clinical Dementia Rating (not defined)

Baseline characteristics

		Donepezil			Placebo			
		N	K	MEAN	N	K	MEAN	*P*
OC population								
Demographics:								
Age	C	46		72.6 (SD 6.8)	43		71.8 (SD 8.2)	0.617[a]
Sex (n male)	D	46	21	(45.7%)	43	19	(44.2%)	0.941[b]
Cognitive:								
Mini Mental State Examination – 0wk	C	46		17.8 (SD 2.3)	43		18.2 (SD 2.7)	0.453[a]
Functional:								
ADL – 0wk	C	46		47.2 (SD 7.9)	43		47.2 (SD 7.9)	1.000[a]
Global severity:								
Clinical Dementia Rating – 0wk	C	46		1.9 (SD 0.3)	43		2 (SD 0.2)	0.070[a]

[a] student's t-test (calculated by reviewer)

[b] chi-square test (Yates's correction) (calculated by reviewer)

Results

		Donepezil			Placebo			
		N	K	MEAN	N	K	MEAN	*P*
OC population								
Cognitive:								
Mini Mental State Examination – 12wk	C	46		22.1 (SD 2)	43		18.7 (SD 2.4)	<0.01[a]
Functional:								
ADL – 12wk	C	46		40.5 (SD 7.6)	43		49.5 (SD 6.3)	<0.01[a]

Global severity: Clinical Dementia Rating – 12wk	C	46	1.2 (SD 0.2)	43	2 (SD 0.2)	<0.05[a]

[a] t-test

Safety data not presented for randomised study only (conflated with data from observational study). Among the 145 cases in the RCT and the observational study who took donepezil, 7 (4.8%) experienced dizziness, nausea, inappetence, mild diarrhoea, constipation, fatigue, agitation. Four of these seven cases stopped taking medicine while the other 3 experienced mild side effects that not affect medication. Among cases in placebo group of the randomised trial, 2 cases (4. 7%) experienced dizziness and stopped medication for this reason.

Methodological issues

Randomisation and allocation: Randomisation procedure not described. Placebo described as having the same colour, shape, flavour and size as donezepil

Data analysis: MMSE/CDR/ADL - t test

Power calculation: Not reported

Conflicts of interest: Not reported

Quality appraisal

1. **Was the assignment to the treatment groups really random?** UNKNOWN
2. **Was the treatment allocation concealed?** UNKNOWN
3. **Were the groups similar at baseline in terms of prognostic factors?** REPORTED - YES
4. **Were the eligibility criteria specified?** UNKNOWN
5. **Were outcome assessors blinded to the treatment allocation?** UNKNOWN
6. **Was the care provider blinded?** ADEQUATE
7. **Was the patient blinded?** ADEQUATE
8. **Were the point estimates and measure of variability presented for the primary outcome measure?** ADEQUATE
9. **Did the analyses include an intention-to-treat analysis?** INADEQUATE
10. **Were withdrawals and dropouts completely described?** ADEQUATE

Design	Participants	Arms	OUTCOMES
Porsteinsson et al. (2008){1307 /id} **Study design:** Parallel double-blind RCT **Country:** USA **No. of centres:** 38 **Funding:** Forest Laboratories, Inc. (New York, NY) provided all financial and material support for research and analyses - and assisted the Memantine Study Group in the development of the trial design, implementation, data collection, post-hoc analyses, and manuscript development. **Length of follow-up (wk):** 24 **Notes** -	**Number randomised:** 433 **MMSE min:** 10 **MMSE max:** 22 **Inclusion criteria:** Probable AD (NINCDS-ADRDA criteria) Age >=50y MRI or CT scan results consistent with AD diagnosis and acquired within 1y of study MMSE 10-22 at screening and baseline Treatment with cholinesterase inhibitors for >=6mo, and a stable dosing regimen for >=3mo (donezepil 5 or 10mg/ day; rivastigmine 6, 9 or 12 mg/day; galantamine 16 or 24mg/day) A knowledgable and reliable caregiver to acompany the participant to all study visits and supervise administraton of	**Arm No:** 1 **Name:** Memantine + ChEI **N:** 217 **Drug:** Memantine+ChEI **Starting daily dose (mg):** 5 **Dosage details:** Titrated from an initial dosage of 5mg/dy in 5mg weekly increments to a maximum dose of 20mg/dy (administered as four 5mg tablet once a day at bedtime) **Notes:** Tablets dispensed in blister packs to allow assessment of compliance (inventory of returned blister packs): 97.2% of participants received at least 75% of the memantine doses **Arm No:** 2 **Name:** Placebo + ChEI **N:** 216	**Cognitive** ▪ ADAS-cog (not defined) ▪ Mini Mental State Examination (not defined) **Functional** ▪ ADCS-ADL (not defined) **Behavioural** ▪ NPI (not defined) **Global severity** ▪ CIBIC-plus score (not defined) **Adverse events**

	study frug Ability to ambulate Vision and hearing sufficient to permit compliance with assessments Montgomery-Asberg Depression Rating Scale (MADRS) score <22 Medically stable Post-menopausal for >=2yr, or surgically sterile (female participants) **Exclusion criteria:** Clinically significant and active pulmonary, gastrointestinal, renal, hepatic, endocrine, or cardiovascular disease Clinically significant B12 or folate deficiency Evidence (including CT/MRI) of other psychiatric or neurological disorders Dementia complicated by organic disease or AD with delusions or delirium Undergoing treatment for an oncology diagnosis, or completion of treatment within 6mo of screening Modified Hachinski Ischaemia Scale score >4 Poorly controlled hypertension Substance abuse Participation in an investigational drug study or use of an investigational drug within 30dy (or 5 half-lives, whichever is longer) of screening Depot neuroleptic use within 6mo of screening Positive urine drug test Likely institutionalisation during trial Previous memantine treatment or participation in an investgational study of memantine Likely cessation of cholinesterase inhibitors during the trial **Therapy common to all participants:** all participants continued to take cholinesterase inhibitor (donepezil, galantamine, or rivastigmine) 1 to 2 week single-blind placebo lead-in phase completed before	**Drug:** Placebo+ChEI **Starting daily dose (mg):** - **Dosage details:** - **Notes:** Tablets dispensed in blister packs to allow assessment of compliance (inventory of returned blister packs): 97.2% of participants received at least 75% of the placebo doses	

	randomisation to assess compliance **Sample attrition / dropout:** 385 of 433 completed study. Drop-outs in memantine arm: adverse events n=13, withdrew consent n=4, protocol violation n=5, insufficient therapeutic response n=1; drop-outs in placebo arm: adverse events n=17, withdrew consent n=4, protocol violation n=1, insufficient therapeutic response n=1, other n=2. No differences between groups.		

Baseline characteristics

		Memantine + ChEI			Placebo + ChEI			
		N	K	MEAN	N	K	MEAN	*P*
Demographics:								
Age	C	217		74.9 (SD 7.64)	216		76 (SD 8.43)	0.156[a]
Sex (n male)	D	217	100	(46.1%)	216	107	(49.5%)	0.533[b]
Weight (kg)	C	217		70 (SD 14.9)	216		72.2 (SD 14.7)	0.123[a]
Disease characteristics:								
Hachinski Ischaemia Score	C	217		0.6 (SD 0.76)	216		0.6 (SD 0.68)	1.000[a]
Cognitive:								
Mini Mental State Examination – 0wk	C	217		16.7 (SD 3.67)	216		17 (SD 3.64)	0.394[a]
Behavioural:								
Montgomery-Asberg Depression Rating Scale	C	217		5.7 (SD 4.65)	216		5.3 (SD 4.1)	0.343[a]
LOCF analysis								
Cognitive:								
ADAS-cogA	C	212		27.9 (SD 11)	212		26.8 (SD 9.88)	0.279[a]
Mini Mental State Examination – 0wk	C	213		16.7 (SD 3.68)	213		17 (SD 3.63)	0.397[a]
Functional:								
ADCS-ADL – 0wk	C	214		54.7 (SD 14.4)	213		54.8 (SD 13.1)	0.940[a]
Behavioural:								
NPI – 0wk	C	214		11.8 (SD 13.1)	213		12.3 (SD 13.3)	0.696[a]

[a] student's t-test (calculated by reviewer)

[b] chi-square test (Yates's correction) (calculated by reviewer)

Results

		Memantine + ChEI			Placebo + ChEI			
		N	K	MEAN	N	K	MEAN	*P*
ITT population								
Disposition of participants:								
Discontinued treatment due to AEs – 24wk	D	217	13	(6.0%)	216	17	(7.9%)	
Discontinued treatment before end of trial – 24wk	D	217	26	(12.0%)	216	25	(11.6%)	
Study medication:								
Dose (mg/d) – 24wk	C	217		19.5 (SD 1.2)	216		19.6 (SD 1)	
LOCF analysis								
Cognitive:								
ADAS-cog – 24wk	C	214		28.5 (SD 12.8)	213		28 (SD 11.9)	0.184[a]
Mini Mental State Examination – 24wk	C	210		16.5 (SD 5.38)	198		16.4 (SD 5.08)	0.123[a]
Functional:								
ADCS-ADL – 24wk	C	214		51.8 (SD 15.9)	213		52 (SD 15.7)	0.816[a]

Behavioural:						
NPI – 24wk	MC	212	0.7 (SD 12)	209	0.4 (SD 12.3)	
NPI – 24wk	C	212	12.9 (SD 14.5)	209	12.6 (SD 14.6)	0.743[a]
Global severity:						
CIBIC-plus score – 24wk	C	214	4.38 (SD 1)	213	4.42 (SD 0.96)	0.843[b]
OC population						
Cognitive:						
ADAS-cog – 24wk	C	192	28.2 (SD 12.8)	188	27.6 (SD 11.7)	0.186[a]
Mini Mental State Examination – 24wk	C	193	16.6 (SD 5.41)	188	16.4 (SD 5.08)	0.190[a]
Functional:						
ADCS-ADL – 24wk	C	193	51.8 (SD 16)	189	53.6 (SD 14.6)	0.741[a]
Behavioural:						
NPI – 12wk[c]	MC	193	0.8 (SD 10.8)	189	0.3 (SD 10.6)	NS[a]
NPI – 24wk	C	193	12.3 (SD 13.7)	189	11.9 (SD 13.5)	0.985[a]
NPI – 24wk	MC	193	0 (SD 11.8)	189	0 (SD 11.7)	NS[a]
Global severity:						
CIBIC-plus score – 24wk	C	192	4.36 (SD 1.01)	189	4.4 (SD 0.96)	0.650[b]
Safety population						
Adverse events:						
Any serious AE – 24wk	D	217	27 (12.4%)	216	30 (13.9%)	0.762[d]
Diarrhoea – 24wk	D	217	12 (5.5%)	216	14 (6.5%)	0.830[d]
Agitation – 24wk	D	217	17 (7.8%)	216	17 (7.9%)	0.869[d]
Depression – 24wk	D	217	14 (6.5%)	216	15 (6.9%)	0.990[d]
Injury – 24wk	D	217	20 (9.2%)	216	16 (7.4%)	0.612[d]
Dizziness – 24wk	D	217	16 (7.4%)	216	16 (7.4%)	0.865[d]
Upper respiratory tract infection – 24wk	D	217	12 (5.5%)	216	6 (2.8%)	0.233[d]
Fall – 24wk	D	217	22 (10.1%)	216	15 (6.9%)	0.309[d]
Influenza-like symptoms – 24wk	D	217	15 (6.9%)	216	12 (5.6%)	0.700[d]
Abnormal gait – 24wk	D	217	14 (6.5%)	216	9 (4.2%)	0.398[d]
Confusion – 24wk	D	217	12 (5.5%)	216	9 (4.2%)	0.662[d]
Fatigue – 24wk	D	217	11 (5.1%)	216	7 (3.2%)	0.476[d]
Hypertension – 24wk	D	217	11 (5.1%)	216	6 (2.8%)	0.327[d]

[a] ANCOVA (treatment group and centre as main effects; baseline score as covariate)

[b] Cochran-Mantel-Haenszel statistic using modified Ridit scores (Van Elteren test) controlling for study centre

[c] sample size not stated; assumed same as 24-wk OC population, which will underestimate true sample size and overestimate precision

[d] chi-square test (Yates's correction) (calculated by reviewer)

ADAS-cog, CIBIC-plus, ADCS-ADL, and NPI available from graphs at 4, 8, 12, 18wk

Methodological issues

Randomisation and allocation: Randomised in permuted blocks of 4 in accordance with randomisation list generated and retained by Forest Research Institute, Department of Statistical Programming. Participants were sequentially assigned randomisation numbers at the baseline visit. No individual participant randomisation code was revealed during the trial. Memantine and placebo tablets described as being identical in appearance.

Data analysis: Primary efficacy analyses (ADAS-cog and CIBIC-Plus) based on the ITT population with LOCF for missing data imputation with only post-baseline data carried forward.

Secondary efficacy analyses (ADCS-ASL, NPI, MMSE) used the observed cases approach.

ADAS-cog (inlcuding post-hoc analyses of items and subscales), ADCS-ADL, NPI, and MMSE: 2-way ANCOVA with treatment group and centre as main effects and baseline as covariate (least square means) for differences between memantine and placebo groups on change from baseline.

CIBIC-Plus: Cochran-Mantel-Haenszel (CMH) statistic using modified Ridit scores (Van Elteren test) controlling for study centre was used to compare distributions between groups.

Power calculation: Assuming an effect size (defined as difference of mean scores between treatment groups on ADAS-Cog at endpoint (LOCF), relative to pooled standard deviation) of 0.325, at least 400 participants were needed to provide 90% power at an alpha level of 0.05 (2-sided), based on a 2-sided t test. The total patient population, consisting of all participants randomised into the study (n=433) was identical to the safety population , which consusted of randomised participants who received at least 1 dose of double-blind study medication. The ITT population (n=427) comprised participants in the safety population who completed at least 1 post-baseline ADAS-cog or CIBIC-Plus assessment.

Conflicts of interest: One co-author's (JO) affilliation is Novartis, Inc.

Quality appraisal

1. **Was the assignment to the treatment groups really random?** ADEQUATE
2. **Was the treatment allocation concealed?** ADEQUATE
3. **Were the groups similar at baseline in terms of prognostic factors?** REPORTED - YES
4. **Were the eligibility criteria specified?** INADEQUATE
5. **Were outcome assessors blinded to the treatment allocation?** UNKNOWN
6. **Was the care provider blinded?** ADEQUATE
7. **Was the patient blinded?** ADEQUATE
8. **Were the point estimates and measure of variability presented for the primary outcome measure?** ADEQUATE
9. **Did the analyses include an intention-to-treat analysis?** ADEQUATE
10. **Were withdrawals and dropouts completely described?** ADEQUATE

Design	Participants	Arms	OUTCOMES
Rockwood et al. (2006){1391 /id} **Study design:** Parallel double-blind RCT **Country:** Canada **No. of centres:** 10 **Funding:** Janssen-Ortho Canada (80%) and the Canadian Institutes of Health Research (20%) (grant no. DCT-49981). The sponsor provided all medications and matching placebos, conducted on-site monitoring and gathered and electronically coded the case report forms. All data are held by the principal investigator (Kenneth Rockwood), who initiated and supervised all analyses. Janssen-Ortho received the paper 45 days before submission to verify protocol details. At the authors' request, Janssen-Ortho statisticians answered questions about the use of the mixed effects model but had no other input in the analyses. **Length of follow-up (wk):** 16 **Notes** **Notes:** Five patients (2 in galantamine group, 3 in placebo group) had MMSE scores that were outside the 10-25 range stipulated in the inclusion criteria; 1 had an MMSE score <10, the other 4 had MMSE scores >25. Seven patients (4 in galantamine group, 3 in placebo group) had ADAS-Cog scores that were outside the >17 range stipulated in the inclusion criteria; in each case	**Number randomised:** 130 **MMSE min:** 10 **MMSE max:** 25 **Inclusion criteria:** Probable Alzheimer's disease (NINCDS-ADRDA criteria) MMSE score 10–25 inclusive ADAS-cof score >=18 Daily contact with a responsible caregiver **Exclusion criteria:** Resident in nursing home Disabling communication difficulties (problems in language, speech, vision or hearing) Other active medical issues or competing causes of dementia Patients who had taken anti-dementia medications within 30 days before screening for study enrolment Hypersensitivity to cholinomimetic agents or bromide Participation in other galantamine trials **Therapy common to all participants:** None reported **Sample attrition / dropout:** 109 of 130 completed study. 21 withdrew after allocation: adverse event n=7; noncompliance n=6; insufficient response n=4; lost to follow-up n=1; withdrew consent n=2; died n=1. More patients in the galantamine group (n=5_ withdrew due to adverse events than in the placebo group (n=2), otherwise no difference between groups.	**Arm No:** 1 **Name:** Galantamine **N:** 64 **Drug:** Galantamine **Starting daily dose (mg):** 8 **Dosage details:** Initial dose of 8mg/dy (4mg twice daily) for 4 wk, followed by 16mg/dy for another 4 wk. At the end of week 8, dose could be increased to 24mg/dy depending on tolerability. At week 12, patients were re-evaluated; the dose could then be reduced to 16mg/dy if necessary, after which time it could not be changed. **Arm No:** 2 **Name:** Placebo **N:** 66 **Drug:** Placebo **Starting daily dose (mg):** - **Dosage details:** - **Notes:** Sham titration schedule	**Cognitive** ▪ ADAS-cog (assessed memory, language, and praxis, scores ranging from 0 (no impairment) to 70 (severe impairment)) **Functional** ▪ Goal Attainment Scaling (individualized outcome measure in which goals are set and then followed over the course of a trial. The goals are personalized (i.e., people set goals according to their own needs). What is standardized is the extent of their attainment, which can be either "no change," or "much better" (or "much worse") than expected. Two independent GAS assessments were completed: one by physicians, after interviewing patients and caregivers and completing all study procedures, and the other by patients and caregivers, in a separate interview facilitated by an experienced, independent health professional (usually a research nurse) who was blinded to all other outcomes and adverse events except for the CIBIC-plus, which the health professional also scored. GAS raters completed a 4-hour training session. Blinded qualitative raters from the coordinating study site coded every video-recorded interview and made domain assignments; this step provided quality assurance for how goals were set but did not influence scoring.) **Global severity** ▪ CIBIC-plus score (score

the score was below the lower limit, which indicated milder impairment			range from 1 (very much improved) to 4 (no change) to 7 (very much worse)) ▪ **Adverse events**

Baseline characteristics

		Galantamine			Placebo			
		N	K	MEAN	N	K	MEAN	*P*
Demographics:								
Age	C	64		77 (SD 8)	66		78 (SD 8)	0.477[a]
Sex (n male)	D	64	23	(35.9%)	66	25	(37.9%)	0.962[b]
Education (yrs)	C	64		11 (SD 3)	66		11 (SD 3)	1.000[a]
Cognitive:				24.2 (SD			27.9 (SD	
ADAS-cog – 0wk	C	64		6.4)	66		8.4)	0.006[a]
				20.8 (SD			19.9 (SD	
Mini Mental State Examination	C	64		3.3)	66		4.2)	0.178[a]
Mini Mental State Examination: 10-19	D	64	17	(26.6%)	66	26	(39.4%)	0.171[b]
Mini Mental State Examination: 20-25	D	64	47	(73.4%)	66	40	(60.6%)	0.171[b]
Functional:				76.4 (SD			70.6 (SD	
Disability Assessment for Dementia	C	64		19.7)	66		21.4)	0.111[a]
Caregiver burden scale	C	64		29 (SD 10)	66		29 (SD 10)	1.000[a]
Global severity:				3.4 (SD			3.7 (SD	
CIBIC-plus score – 0wk[c]	C	64		0.7)	66		0.9)	0.036[a]
Data extracted from secondary publication reporting subgroup with verbal repetition goals{1396 /id}								
Demographics:				77.3 (SD			79.1 (SD	
Age	C	24		6.1)	33		7.2)	0.325[a]
Sex (n male)	D	24	10	(41.7%)	33	12	(36.4%)	0.896[b]
				10.4 (SD				
Education (yrs)	C	24		2.8)	33		11.9 (SD 3)	0.061[a]
Cognitive:				23.8 (SD				
ADAS-cog – 0wk	C	24		5.9)	33		27.2 (SD 8)	0.084[a]
				21.8 (SD			19.9 (SD	
Mini Mental State Examination	C	24		2.5)	33		4.5)	0.067[a]
Mini Mental State Examination: 10-19	D	24	4	(16.7%)	33	12	(36.4%)	0.182[b]
Mini Mental State Examination: 20-25	D	24	20	(83.3%)	33	21	(63.6%)	0.182[b]
Functional:				72.1 (SD			70.1 (SD	
Disability Assessment for Dementia	C	24		18.7)	33		21.6)	0.717[a]
				30.9 (SD				
Caregiver burden scale	C	24		10.4)	33		31 (SD 9.4)	0.970[a]
Global severity:				3.3 (SD			3.7 (SD	
CIBIC-plus score – 0wk[c]	C	24		0.8)	33		0.9)	0.088[a]

[a] student's t-test (calculated by reviewer)

[b] chi-square test (Yates's correction) (calculated by reviewer)

[c] not clear what this quantity represents, since CIBIC-plus should be anchored at 4 at baseline (and methods state this)

Results

		Galantamine			Placebo			
		N	K	MEAN	N	K	MEAN	*P*
ITT population								
Disposition of participants:								
Discontinued treatment due to AEs – 16wk	D	64	5	(7.8%)	66	2	(3.0%)	
Discontinued treatment before end of trial – 16wk	D	64	11	(17.2%)	66	10	(15.2%)	
LOCF analysis								
Cognitive:				-1.85 (SD			-0.25 (SD	
ADAS-cog – 8wk	MC	62		4.18)	65		4.97)	

ADAS-cog – 16wk	MC	62	-1.6 (SD 5.38)	65	0.325 (SD 5.49)	
Functional:						
Goal Attainment Scaling (clinician-rated) – 8wk	C	61	52.5 (SD 9.12)	66	52.2 (SD 6.97)	
Goal Attainment Scaling (clinician-rated) – 16wk	C	61	54.8 (SD 9.36)	66	50.9 (SD 9.74)	0.02[a]
Goal Attainment Scaling (patient-caregiver-rated) – 8wk	C	61	54.6 (SD 7.97)	66	52.5 (SD 8.57)	
Goal Attainment Scaling (patient-caregiver-rated) – 16wk	C	61	54.2 (SD 10.8)	66	52.3 (SD 9.12)	0.27[a]
Global severity:						
CIBIC-plus score – 8wk	C	61	3.64 (SD 0.797)	65	4.17 (SD 0.905)	
CIBIC-plus score – 16wk	C	61	3.67 (SD 0.996)	65	4.12 (SD 0.987)	0.03[b]
Safety population						
Adverse events:						
Any AE – 0wk	D	64	54 (84.4%)	66	41 (62.1%)	
Anorexia – 0wk	D	64	7 (10.9%)	66	1 (1.5%)	
Nausea – 0wk	D	64	15 (23.4%)	66	4 (6.1%)	
Vomiting – 0wk	D	64	11 (17.2%)	66	2 (3.0%)	
Upper respiratory tract infection – 0wk	D	64	8 (12.5%)	66	2 (3.0%)	
Data extracted from secondary publication reporting subgroup with verbal repetition goals{1396 /id}						
Functional:						
GAS - verbal repetition: improved – 16wk	D	20	14 (70.0%)	30	8 (26.7%)	<0.01[c]
GAS - verbal repetition: no change – 16wk	D	20	4 (20.0%)	30	12 (40.0%)	
GAS - verbal repetition: worsened – 16wk	D	20	2 (10.0%)	30	10 (33.3%)	

[a] ANOVA

[b] test not stated; presumed to be ANOVA

[c] mixed effects model, with dementia severity and treatment assignment as fixed effects, and the patient as the random effect

Methodological issues

Randomisation and allocation: Randomization was determined immediately before medication was administered by research nurse phoning into a contracted, interactive voice-response system for an assignment number. Nurse was blind to the number's meaning in terms of treatment assignment. Randomisation was in blocks of 2, by site, to decrease the chance of incomplete blocks (the GAS instrument was new to investigators at the study sites and that some sites might have had to withdraw if investigators did not know how to complete it)

Data analysis: GAS (clinician-rated and patient-caregiver-rated); ADAS-Cog; CIBIC-Plus; DAD; CBS - Effect sizes estimated as standardized response means (SRMs), derived as the mean difference between groups divided by the pooled standard deviation of their change.

GAS; CIBIC-Plus Secondary analysis we using a mixed-effects model (to allow the effects of dropout to be assessed and adjust for dementia severity at baseline)

All of the patients who were randomly assigned were included in analyses of safety, demographic and baseline characteristics. The intention-to-treat analysis included all randomly assigned patients who took at least 1 dose (treatment drug or placebo) during the placebo-controlled phase and who provided any follow-up GAS. Missing data were imputed based on the last observation carried forward (excluding baseline data) during the placebo-controlled phase. The observed case analysis included only data from scheduled time points.

Power calculation: Authors state that on the basis that the GAS instrument can be more responsive than standard measures because it is personalized, this attribute had not been tested in a controlled trial in dementia. For the exploratory analysis, the sample size was estimated from the authors' limited experience with GAS in anti-dementia drug trials. Assuming a moderate effect size of about 0.524 and a 15% dropout at 4 months, it was determined that 152 subjects would be required to detect differences at the 5% significance

level (2-tailed) with 80% power. Authors recognized that this might not result in statistically significant results for the secondary outcomes, which were used to compare with the primary outcomes and with results from other studies.

Conflicts of interest: Lead author has undertaken consultancies and received honoraria from Janssen Ortho, the study's co-sponsor, and from Pfizer, Novartis and Merck, and was also lead author of an earlier galantamine study. Lead author owns no stock in pharmaceutical companies. Lead author is part owner of DementiaGuide, which is developing a Web site to aid in goal setting for people with dementia. Co-authors: CM has received research grants from Janssen Ortho, Pfizer, Lundbeck and Novartis, but has received no personal payments; MG has received honoraria and travel grants from Janssen Ortho, Pfizer and Merck; SF and XS have no conflicts of interest to declare.

Quality appraisal

1.	**Was the assignment to the treatment groups really random?** ADEQUATE
2.	**Was the treatment allocation concealed?** ADEQUATE
3.	**Were the groups similar at baseline in terms of prognostic factors?** REPORTED - NO Placebo group had more patients with moderate dementia
4.	**Were the eligibility criteria specified?** INADEQUATE
5.	**Were outcome assessors blinded to the treatment allocation?** PARTIAL
6.	**Was the care provider blinded?** PARTIAL
7.	**Was the patient blinded?** PARTIAL
8.	**Were the point estimates and measure of variability presented for the primary outcome measure?** ADEQUATE
9.	**Did the analyses include an intention-to-treat analysis?** ADEQUATE
10.	**Were withdrawals and dropouts completely described?** ADEQUATE

Design	Participants	Arms	OUTCOMES
Van Dyck et al. (2007){1670 /id} **Study design:** Parallel double-blind RCT **Country:** USA **No. of centres:** 35 **Funding:** Forest Laboratories, Inc provided all financial and material support for the study, as well as statistical and editorial support for the manuscript. **Length of follow-up (wk):** 24 **Notes** -	**Number randomised:** 350 **MMSE min:** 5 **MMSE max:** 14 **Inclusion criteria:** Probable AD (NINCDS-ADRDA criteria) MMSE score 5-14 at screening and baseline Age >=50yr Brain imaging evaluation (CT or MRI performed within 12 months before study entry) consistent with probable AD A knowledgable and reliable caregiver to accompany the participant to all study visits and supervise administration of the study drug Ability to ambulate Sufficient vision and hearing to comply with assessments Medical stability Stable doses of the following medications were allowed: antihypertensives, anti-inflammatories, diuretics, laxatives, antidepressants, atypical antipsychotics, tocopherol **Exclusion criteria:** Significant and active pulmonary, gastrointestinal, renal, hepatic, endocrine, or cardiovascular disease Clinically significant B12 or folate deficiency Evidence of any psychiatric or neurologic disorder other than AD Hachinski Ischaemia Score >4 Delusions or delirium (DSM-IV criteria)	**Arm No:** 1 **Name:** Memantine **N:** 178 **Drug:** Memantine **Starting daily dose (mg):** 5 **Dosage details:** Initial dosage of 5mg/dy with titration in 5mg weekly increments to a final dosage of 20mg/dy (administered as two 5mg tablets twice a day). Dose adjustments were permitted between weeks 3 and 8 for participants with adverse events. Participants unable to tolerate 20mg/dy by the end of week 8 were discontinued from the study. **Notes:** Compliance monitored by inventory of returned individual blister packs, and protocol adherence by routine assessment of concomitant medication use. **Arm No:** 2 **Name:** Placebo **N:** 172 **Drug:** Placebo **Starting daily dose (mg):** - **Dosage details:** -	**Cognitive** ▪ Severe impairment battery (100-point, 40-item test to evaluate cognitive dysfunction (memory, language, social interaction, visuospatial ability, attention, praxis, construction) in patients with moderate to severe AD (higher score indicates better performance)) **Functional** ▪ ADCS-ADL (modified 54-point, assesses function in patients with moderate and severe dementia (higher scores reflect better functional ability)) ▪ ADCS-ADL-19 ▪ Functional Assessment Staging Tool (not defined) **Behavioural** ▪ NPI (not defined) ▪ Behavioral rating for Geriatric Patients: total (35-item rating scale, not defined) ▪ Behavioral rating for Geriatric Patients: care dependency (not defined) **Global severity** ▪ CIBIC-plus score (not defined) **Adverse events**

	Active malignancy History of subnstance abuse within 10yr Likelihood of nursing home placement within 6mo Previous memantine treatment Treatment with an investigational drug within 30dy (or 5 drug half-lives, whichever was longer) of screening Postmenopausal >2yr, or surgically sterile (female participants) **Therapy common to all participants:** 1 to 2wk single-blind placebo lead-in phase to assess compliance and minimise treatment response at baseline **Sample attrition / dropout:** 260 of 350 completed study. 90 withdrew after allocation: adverse events (n=45), consent withdrawn (n=26), protocol violation (n=8), insufficient therapeutic response (n=3), other (n=8). No differences between groups.		

Baseline characteristics

		Memantine			Placebo			
		N	K	MEAN	N	K	MEAN	*P*
Demographics:								
Age	C	178		78.1 (SD 8.2)	172		78.3 (SD 7.6)	0.813[a]
Sex (n male)	D	178	49	(27.5%)	172	51	(29.7%)	0.748[b]
Weight (kg)	C	176		64.4 (SD 13.5)	172		65.8 (SD 12.8)	0.322[a]
Race (n white)	D	178	142	(79.8%)	172	141	(82.0%)	0.698[b]
Cognitive:								
Mini Mental State Examination	C	178		10 (SD 2.8)	172		10.3 (SD 3.1)	0.342[a]
Severe impairment battery – 0wk	C	170		77.2 (SD 16.5)	165		75.6 (SD 19.7)	0.420[a]
Functional:								
ADCS-ADL – 0wk	C	171		33.1 (SD 11)	165		33.6 (SD 10.6)	0.672[a]
Functional Assessment Staging Tool – 0wk	C	171		1.4 (SD 2)	165		1.2 (SD 2)	0.360[a]
Behavioural:								
NPI – 0wk	C	171		20.3 (SD 15.7)	165		17.5 (SD 16.4)	0.111[a]
Behavioral rating for Geriatric Patients: total – 0wk	C	171		17.3 (SD 8.9)	165		16.7 (SD 8.8)	0.535[a]
Behavioral rating for Geriatric Patients: care dependency – 0wk	C	171		11.5 (SD 7)	165		11 (SD 6.7)	0.504[a]

[a] student's t-test (calculated by reviewer)

[b] chi-square test (Yates's correction) (calculated by reviewer)

Results

		Memantine			Placebo			
		N	K	MEAN	N	K	MEAN	P
ITT population								
Disposition of participants:								
Discontinued treatment due to AEs – 24wk	D	178	22	(12.4%)	172	23	(13.4%)	0.902[a]
Discontinued treatment before end of trial – 24wk	D	178	44	(24.7%)	172	46	(26.7%)	0.756[a]
LOCF analysis								
Cognitive:								
Severe impairment battery – 24wk	MC	170		-2 (SD 13)	165		-2.5 (SD 12.8)	0.616[b]
Functional:								
ADCS-ADL-19 – 24wk	MC	171		-2 (SD 7.85)	165		-2.7 (SD 7.71)	0.282[b]
Functional Assessment Staging Tool – 24wk	MC	151		0.3 (SD 1.23)	141		0.6 (SD 1.19)	0.093[b]
Behavioural:								
NPI – 24wk	MC	161		1 (SD 16.5)	154		1.1 (SD 17.4)	0.963[b]
Behavioral rating for Geriatric Patients: total – 24wk	MC	151		0.6 (SD 6.14)	141		1.5 (SD 7.12)	0.197[b]
Behavioral rating for Geriatric Patients: care dependency – 24wk	MC	151		0.5 (SD 4.92)	141		1.4 (SD 4.75)	0.076[b]
Global severity:								
CIBIC-plus score – 24wk	C	171		4.3 (SD 1)	163		4.6 (SD 1)	0.182[c]
OC population								
Cognitive:								
Severe impairment battery – 4wk[d]	MC	167		0.875 (SD 7.43)	164		-0.3 (SD 6.4)	0.146[b]
Severe impairment battery – 8wk[d]	MC	158		2.08 (SD 7.86)	155		0.375 (SD 7.16)	0.064[b]
Severe impairment battery – 12wk[d]	MC	146		1.65 (SD 9.06)	150		-0.825 (SD 8.27)	0.008[b]
Severe impairment battery – 18wk[d]	MC	140		0 (SD 8.28)	139		-2.12 (SD 9.14)	0.065[b]
Severe impairment battery – 24wk	MC	131		-1.8 (SD 12.6)	126		-2.4 (SD 13.5)	0.617[b]
Functional:								
ADCS-ADL-19 – 4wk[d]	MC	168		0.312 (SD 4.37)	164		0.512 (SD 4)	0.801[b]
ADCS-ADL-19 – 8wk[d]	MC	159		-0.0875 (SD 5.2)	156		-0.188 (SD 4.84)	0.665[b]
ADCS-ADL-19 – 12wk[d]	MC	147		0 (SD 5.46)	150		-0.488 (SD 5.05)	0.155[b]
ADCS-ADL-19 – 18wk[d]	MC	142		-0.688 (SD 7.3)	140		-1.38 (SD 5.62)	0.357[b]
ADCS-ADL-19 – 24wk	MC	133		-1.3 (SD 6.92)	127		-2.3 (SD 6.76)	0.188[b]
Functional Assessment Staging Tool – 24wk	MC	133		0.3 (SD 1.15)	127		0.6 (SD 1.13)	0.074[b]
Behavioural:								
NPI – 24wk	MC	133		0.5 (SD 15)	127		1 (SD 15.8)	0.782[b]
Behavioral rating for Geriatric Patients: total – 24wk	MC	133		0.4 (SD 6.92)	127		1.1 (SD 6.76)	0.312[b]
Behavioral rating for Geriatric Patients: care dependency – 24wk	MC	133		0.4 (SD 4.61)	127		1.2 (SD 5.63)	0.138[b]
Global severity:								
CIBIC-plus score – 24wk	C	134		4.3 (SD 1.1)	127		4.6 (SD 1)	0.089[c]
Safety population								
Adverse events:								
Any AE – 24wk	D	178	131	(73.6%)	172	125	(72.7%)	0.941[a]
Any serious AE – 24wk	D	178	26	(14.6%)	172	29	(16.9%)	0.666[a]
Diarrhoea – 24wk	D	178	10	(5.6%)	172	8	(4.7%)	0.867[a]
Agitation – 24wk	D	178	16	(9.0%)	172	24	(14.0%)	0.197[a]
Anxiety – 24wk	D	178	10	(5.6%)	172	6	(3.5%)	0.485[a]
Depression – 24wk	D	178	9	(5.1%)	172	5	(2.9%)	0.451[a]
Injury – 24wk	D	178	10	(5.6%)	172	13	(7.6%)	0.605[a]
Dizziness – 24wk	D	178	12	(6.7%)	172	11	(6.4%)	0.932[a]
Headache – 24wk	D	178	3	(1.7%)	172	11	(6.4%)	0.048[a]
Urinary tract infection – 24wk	D	178	9	(5.1%)	172	9	(5.2%)	0.867[a]
Fall – 24wk	D	178	10	(5.6%)	172	17	(9.9%)	0.195[a]
Influenza-like symptoms – 24wk	D	178	10	(5.6%)	172	8	(4.7%)	0.867[a]
Confusion – 24wk	D	178	9	(5.1%)	172	8	(4.7%)	0.942[a]
Hypertension – 24wk	D	178	14	(7.9%)	172	4	(2.3%)	0.035[a]
Peripheral oedema – 24wk	D	178	12	(6.7%)	172	8	(4.7%)	0.541[a]
Constipation – 24wk	D	178	11	(6.2%)	172	8	(4.7%)	0.693[a]

Insomnia – 24wk	D	178	4	(2.2%)	172	9	(5.2%)	0.233[a]

[a] chi-square test (Yates's correction) (calculated by reviewer)

[b] ANCOVA (treatment group and centre as main effects; baseline score as covariate)

[c] Cochran-Mantel-Haenszel statistic using modified Ridit scores (Van Elteren test) controlling for study centre

[d] estimated from figure

Various post-hoc statistical analyses reported, some of which suggest a significant benefit for memantine

Methodological issues

Randomisation and allocation: Randomisation procedure not reported

Data analysis: SIB, BGP, ADCS-ADL, FAST, NPI, change from baseline compared between memantine and placebo groups: 2-way ANCOVA with treatment group and centre as main effects and baseline as covariate.

CIBIC-Plus: Cochran-Mantel-Haenszel test using modified Ridit score (Van Elteren test) controlling for study centre to compare distribution between groups.

Post-hoc analyses:

SIB, ADCS-ADL, NPI, CIBIC-Plus: ANCOVA analyses repeated adding previous ChEI use or age as covariates. For CIBIC-Plus, additional Cochran-Mantel-Haenszel tests were performed controlling either for prior ChEI use or age group (<=64yr, 65-74yr, 75-84yr, >=85yr) in addition to study centre.

SIB, ADCS-ADL: assumption of normality was violated at week 24 (when tested using Shapiro-Wilk test), therefore Wilcoxon Rank Sum test performed on the change from baseline scores at each timepoint using LOCF and OC approaches.

SIB, ADCS-ADL: re-analysed using mixed-effects model repeated measures (as LOCF may introduce biases, including favouring the treatment group with the higher dropout rate in a deteriorating illness) - change from baseline with treatment group, time from baseline, centre, and interaction of treatment group by time as fixed effects, and baseline score as covariate, with an unstructured covariance matrix to model the correlations of residuals over time.

Power calculation: Assuming an effect size of 0.35, at least 340 participants were needed to provide 90% power at an alpha-level of 0.05 (2-sided) on the basis of a 2 sample t test for change from baseline to week 24 in SIB and ADCS-ADL scores.

Conflicts of interest: Lead author (CD) and 2 co-authors (PT, BM) have received grant support and honoraria from Forest Laboratories, Inc. One co-author (PT) has given expert testimony related to memantine. One author (EM) is an employee of Forest Laboratories, Inc.

Quality appraisal

1. **Was the assignment to the treatment groups really random?** UNKNOWN
2. **Was the treatment allocation concealed?** UNKNOWN
3. **Were the groups similar at baseline in terms of prognostic factors?** REPORTED - YES
4. **Were the eligibility criteria specified?** UNKNOWN
5. **Were outcome assessors blinded to the treatment allocation?** UNKNOWN
6. **Was the care provider blinded?** PARTIAL
7. **Was the patient blinded?** PARTIAL
8. **Were the point estimates and measure of variability presented for the primary outcome measure?** ADEQUATE
9. **Did the analyses include an intention-to-treat analysis?** ADEQUATE
10. **Were withdrawals and dropouts completely described?** ADEQUATE

Design	Participants	Arms	OUTCOMES
Winblad et al. (2007){1775 /id} **Study design:** Parallel double-blind RCT **Country:** Chile, Czech Republic, Denmark, Finland, Germany, Guatemala, Israel, Italy, Korea, Mexico, Norway, Peru, Poland, Portugal, Russia, Slovak Republic,	**Number randomised:** 1195 **MMSE min:** 10 **MMSE max:** 20 **Inclusion criteria:** AD (DSM-IV criteria) and probable AD (NINCDS/ADRDA criteria) (brain scan (MRI or CT) used for establishing these criteria must have been done within	**Arm No:** 1 **Name:** Rivastigmine patch (10cm^2) **N:** 293 **Drug:** Rivastigmine **Starting daily dose (mg):** 4.75 **Dosage details:** 10cm2 patch	**Cognitive** ▪ ADAS-cog (to assess orientation, memory, language, visuospatial and praxis functions) ▪ Mini Mental State Examination (not defined) ▪ Ten-point clock-drawing test (for assessment of

Sweden, Taiwan, USA, Uruguay, Venezuela **No. of centres:** 100 **Funding:** Novartis Pharma AG, Basel, Switzerland **Length of follow-up (wk):** 24 **Notes** -	one year prior to randomization) Age 50-85yr MMSE 10-20 Living with someone in the community or, if living alone, in daily contact with a responsible caregiver **Exclusion criteria:** Advanced, severe, progressive, or unstable disease of any type that could interfere with study assessments or put the patient at special risk Any condition other than AD that could explain the dementia Use of any investigational drugs, new psychotropic or dopaminergic agents, cholinesterase inhibitors or anti-cholinergic agents during the 4 weeks prior to randomization **Therapy common to all participants:** None reported **Sample attrition / dropout:** 970 of 1195 patients completed study. Reasons for drop-out: adverse events, withdrawn consent, lost to follow-up, death, unsatisfactory therapeutic effect. No difference between groups.	group: titrated from initial 5cm2 dose (starting dose above calculated by review team as half the daily dose delivered by 10cm2 patch) up to 10cm2 patch in 5cm2 step at 4wk interval, followed by an 8wk maintenance phase. **Notes:** Dose adjustments (interruptions or down-titrations) were permitted to address perceived safety or tolerability issues. If the target dose was not achieved during the titration period the investigator could resume titration during the maintenance period. Patients were maintained at their highest well tolerated doses until the end of the study. The patch was applied by caregivers to clean, dry, hairless skin on the patient's upper back every morning and worn for 24 h, during which normal activities including bathing were allowed. To minimize possible skin irritation, patch placement on the upper back was alternated between the left and right sides, daily. **Arm No:** 2 **Name:** Rivastigmine patch (20cm^2) **N:** 303 **Drug:** Rivastigmine **Starting daily dose (mg):** 4.75 **Dosage details:** 20cm2 patch group: titrated from initial 5cm2 dose (starting dose above calculated by review team as half the daily dose delivered by 10cm2 patch) up to 20cm2 patch in 5cm2 steps at 4wk intervals, followed by an 8wk maintenance phase. **Notes:** Dose adjustments (interruptions or down-titrations) were permitted to address perceived safety or tolerability issues. If the target dose was not achieved during the titration period the investigator could resume titration during the maintenance period. Patients were maintained at their highest well tolerated doses until the end of the study. The patch was applied by caregivers to clean, dry,	visuospatial and executive functions) ▪ Trail-making test (for assessment of attention, visual tracking and motor processing speed) **Functional** ▪ ADCS-ADL (not defined) **Behavioural** ▪ NPI (for assessment of behaviour and psychiatric symptoms) ▪ NPI - caregiver distress (not defined) **Global severity** ▪ ADCS - Clinical Global Impression of Change: score (for assessment of orientation, memory, language, visuospatial and praxis functions) **Adverse events**

		hairless skin on the patient's upper back every morning and worn for 24 h, during which normal activities including bathing were allowed. To minimize possible skin irritation, patch placement on the upper back was alternated between the left and right sides, daily. **Arm No:** 3 **Name:** Rivastigmine capsules **N:** 297 **Drug:** Rivastigmine **Starting daily dose (mg):** 3 **Dosage details:** Tablet group: Initial dosage of 3mg/dy titrated upwards in steps of 3mg/dy up to a maximum of 12mg/dy **Notes:** Dose adjustments (interruptions or down-titrations) were permitted to address perceived safety or tolerability issues. If the target dose was not achieved during the titration period the investigator could resume titration during the maintenance period. Patients were maintained at their highest well tolerated doses until the end of the study. **Arm No:** 4 **Name:** Placebo **N:** 302 **Drug:** Placebo **Starting daily dose (mg):** - **Dosage details:** - **Notes:** The placebo patch was applied by caregivers to clean, dry, hairless skin on the patient's upper back every morning and worn for 24 h, during which normal activities including bathing were allowed. To minimize possible skin irritation, patch placement on the upper back was alternated between the left and right sides, daily.	

Baseline characteristics

	Rivastigmine patch (10cm^2)			Placebo			
	N	**K**	**MEAN**	**N**	**K**	**MEAN**	***P***

Demographics:								
Age	C	291		73.6 (SD 7.9)	302		73.9 (SD 7.3)	0.631[a]
Sex (n male)	D	291	93	(32.0%)	302	101	(33.4%)	0.766[b]
Education (yrs)	C	291		9.9 (SD 4.3)	302		9.9 (SD 4.3)	1.000[a]
Race (n white)	D	291	220	(75.6%)	302	227	(75.2%)	0.978[b]
Race (n black)	D	291	1	(0.3%)	302	2	(0.7%)	0.974[b]
Race (n Oriental)	D	291	25	(8.6%)	302	27	(8.9%)	0.996[b]
Race (n other)	D	291	45	(15.5%)	302	46	(15.2%)	0.972[b]
Disease characteristics:								
Duration of dementia (mo)	C	291		13.2 (SD 16.8)	302		13.2 (SD 16.8)	1.000[a]
Domestic circumstances:								
Living alone	D	291	43	(14.8%)	302	27	(8.9%)	0.038[b]
Living with caregiver or other	D	291	240	(82.5%)	302	264	(87.4%)	0.116[b]
Assisted living/group home	D	291	8	(2.7%)	302	11	(3.6%)	0.701[b]
Cognitive:								
Mini Mental State Examination – 0wk	C	291		16.6 (SD 3.1)	302		16.4 (SD 3)	0.425[a]
LOCF analysis								
Cognitive:								
ADAS-cog – 0wk	C	248		27 (SD 10.3)	281		28.6 (SD 9.9)	0.069[a]
Mini Mental State Examination – 0wk	C	250		16.7 (SD 3)	281		16.4 (SD 3)	0.251[a]
Ten-point clock-drawing test – 0wk	C	251		4.5 (SD 3.6)	269		4.3 (SD 3.6)	0.527[a]
Trail-making test – 0wk[c]	C	241		183 (SD 85.5)	258		178 (SD 85.6)	0.514[a]
Functional:								
ADCS-ADL – 0wk	C	247		50.1 (SD 16.3)	281		49.2 (SD 16)	0.523[a]
Behavioural:								
NPI – 0wk	C	248		13.9 (SD 14.1)	281		14.9 (SD 15.7)	0.444[a]
NPI - caregiver distress – 0wk	C	248		7.4 (SD 7.1)	281		7.8 (SD 7.7)	0.537[a]

[a] student's t-test (calculated by reviewer)

[b] chi-square test (Yates's correction) (calculated by reviewer)

[c] test A

		Rivastigmine patch (20cm^2)			**Placebo**			
		N	**K**	**MEAN**	**N**	**K**	**MEAN**	***P***
Demographics:								
Age	C	302		74.2 (SD 7.7)	302		73.9 (SD 7.3)	0.623[a]
Sex (n male)	D	302	103[b]	(34.1%)	302	101	(33.4%)	0.931[c]
Education (yrs)	C	302		9.9 (SD 4.4)	302		9.9 (SD 4.3)	1.000[a]
Race (n white)	D	302	227	(75.2%)	302	227	(75.2%)	0.925[c]
Race (n black)	D	302	3	(1.0%)	302	2	(0.7%)	1.000[c]
Race (n Oriental)	D	302	27	(8.9%)	302	27	(8.9%)	0.887[c]
Race (n other)	D	303	46	(15.2%)	302	46	(15.2%)	0.924[c]
Disease characteristics:								
Duration of dementia (mo)	C	302		13.2 (SD 16.8)	302		13.2 (SD 16.8)	1.000[a]
Domestic circumstances:								
Living alone	D	302	30	(9.9%)	302	27	(8.9%)	0.781[c]
Living with caregiver or other	D	302	265	(87.7%)	302	264	(87.4%)	1.000[c]
Assisted living/group home	D	302	8	(2.6%)	302	11	(3.6%)	0.641[c]
Cognitive:								
Mini Mental State Examination – 0wk	C	302		16.6 (SD 2.9)	302		16.4 (SD 3)	0.405[a]
LOCF analysis								
Cognitive:								
ADAS-cog – 0wk	C	262		27.4 (SD 9.7)	281		28.6 (SD 9.9)	0.155[a]
Mini Mental State Examination – 0wk	C	262		16.6 (SD 2.9)	281		16.4 (SD 3)	0.431[a]
Ten-point clock-drawing test – 0wk	C	245		4.7 (SD 3.8)	269		4.3 (SD 3.6)	0.221[a]
Trail-making test – 0wk[d]	C	238		176 (SD 84)	258		178 (SD 85.6)	0.813[a]
Functional:								
ADCS-ADL – 0wk	C	263		47.6 (SD 15.7)	281		49.2 (SD 16)	0.240[a]
Behavioural:								
NPI – 0wk	C	263		15.1 (SD 13.4)	281		14.9 (SD 15.7)	0.873[a]
NPI - caregiver distress – 0wk	C	263		8.4 (SD 7.6)	281		7.8 (SD 7.7)	0.361[a]

[a] student's t-test (calculated by reviewer)

[b] approximated to nearest integer (percentages only presented in text); poor rounding suggests true denominator may be less

than full sample size

[c] chi-square test (Yates's correction) (calculated by reviewer)

[d] test A

		Rivastigmine capsules			Placebo			
		N	K	MEAN	N	K	MEAN	P
Demographics:								
Age	C	294		72.8 (SD 8.2)	302		73.9 (SD 7.3)	0.084[a]
Sex (n male)	D	294	101	(34.4%)	302	101	(33.4%)	0.882[b]
Education (yrs)	C	294		9.9 (SD 4.4)	302		9.9 (SD 4.3)	1.000[a]
Race (n white)	D	294	219	(74.5%)	302	227	(75.2%)	0.924[b]
Race (n black)	D	294	5	(1.7%)	302	2	(0.7%)	0.426[b]
Race (n Oriental)	D	294	29	(9.9%)	302	27	(8.9%)	0.806[b]
Race (n other)	D	297	41	(13.8%)	302	46	(15.2%)	0.704[b]
Disease characteristics:								
Duration of dementia (mo)	C	294		13.2 (SD 16.8)	302		13.2 (SD 16.8)	1.000[a]
Domestic circumstances:								
Living alone	D	294	35	(11.9%)	302	27	(8.9%)	0.293[b]
Living with caregiver or other	D	294	255	(86.7%)	302	264	(87.4%)	0.900[b]
Assisted living/group home	D	294	4	(1.4%)	302	11	(3.6%)	0.129[b]
Cognitive:								
Mini Mental State Examination – 0wk	C	294		16.4 (SD 3.1)	302		16.4 (SD 3)	1.000[a]
LOCF analysis								
Cognitive:								
ADAS-cog – 0wk	C	253		27.9 (SD 9.4)	281		28.6 (SD 9.9)	0.404[a]
Mini Mental State Examination – 0wk	C	256		16.4 (SD 3)	281		16.4 (SD 3)	1.000[a]
Ten-point clock-drawing test – 0wk	C	246		4.4 (SD 3.6)	269		4.3 (SD 3.6)	0.753[a]
Trail-making test – 0wk[c]	C	240		177 (SD 86.2)	258		178 (SD 85.6)	0.886[a]
Functional:								
ADCS-ADL – 0wk	C	254		49.3 (SD 15.8)	281		49.2 (SD 16)	0.942[a]
Behavioural:								
NPI – 0wk	C	253		15.1 (SD 14.1)	281		14.9 (SD 15.7)	0.877[a]
NPI - caregiver distress – 0wk	C	253		8.2 (SD 7.6)	281		7.8 (SD 7.7)	0.547[a]

[a] student's t-test (calculated by reviewer)

[b] chi-square test (Yates's correction) (calculated by reviewer)

[c] test A

Results

		Rivastigmine patch (10cm^2)			Placebo			
		N	K	MEAN	N	K	MEAN	P
ITT population								
Disposition of participants:								
Discontinued treatment due to AEs – 24wk	D	293	28	(9.6%)	302	15	(5.0%)	
Discontinued treatment before end of trial – 24wk	D	293	64	(21.8%)	302	36	(11.9%)	
LOCF analysis								
Cognitive:								
ADAS-cog – 16wk[a]	MC	248		-0.825 (SD 6.3)	281		0 (SD 6.71)	0.09[b]
ADAS-cog – 24wk	MC	248		-0.6 (SD 6.4)	281		1 (SD 6.8)	0.005[b]
Mini Mental State Examination – 24wk	MC	250		1.1 (SD 3.3)	281		0 (SD 3.5)	0.002[c]
Ten-point clock-drawing test – 24wk	MC	251		0.1 (SD 3.1)	269		-0.1 (SD 3.2)	0.08[c]
Trail-making test – 24wk	MC	241		-12.3 (SD 55.1)	258		7.7 (SD 56.6)	<0.001[b]
Functional:								
ADCS-ADL – 16wk[a]	MC	247		-0.6 (SD 9.43)	281		-1.6 (SD 7.96)	NS[b]
ADCS-ADL – 24wk	MC	247		-0.1 (SD 9.1)	281		-2.3 (SD 9.4)	0.01[b]
Behavioural:								
NPI – 24wk	MC	248		-1.7 (SD 11.5)	281		-1.7 (SD 13.8)	0.74[b]
NPI - caregiver distress – 24wk	MC	248		-1 (SD 5.5)	281		-1.1 (SD 6.3)	0.37[b]

Global severity:								
ADCS - CGIC: score – 16wk[a]	C	248		3.9 (SD 1.14)	278		4.35 (SD 1.25)	NS[c]
ADCS - CGIC: score – 24wk	C	248		3.9 (SD 1.2)	278		4.2 (SD 1.3)	0.01[c]
ADCS - CGIC: markedly improved – 24wk	D	248	5	(2.0%)	278	2	(0.7%)	0.361[d]
ADCS - CGIC: moderately improved – 24wk	D	248	29	(11.7%)	278	26	(9.4%)	0.463[d]
ADCS - CGIC: minimally improved – 24wk	D	248	43	(17.3%)	278	50	(18.0%)	0.937[d]
ADCS - CGIC: unchanged – 24wk	D	248	105	(42.3%)	278	91	(32.7%)	0.029[d]
ADCS - CGIC: minimally worse – 24wk	D	248	41	(16.5%)	278	65	(23.4%)	0.065[d]
ADCS - CGIC: moderately worse – 24wk	D	248	22	(8.9%)	278	36	(12.9%)	0.177[d]
ADCS - CGIC: markedly worse – 24wk	D	248	3	(1.2%)	278	8	(2.9%)	0.303[d]
Safety population								
Adverse events:								
Any AE – 0wk	D	291	147	(50.5%)	302	139	(46.0%)	NS[e]
Nausea – 0wk	D	291	21	(7.2%)	302	15	(5.0%)	NS[e]
Diarrhoea – 0wk	D	291	18	(6.2%)	302	10	(3.3%)	NS[e]
Vomiting – 0wk	D	291	18	(6.2%)	302	10	(3.3%)	NS[e]
Dizziness – 0wk	D	291	7	(2.4%)	302	7	(2.3%)	NS[e]
Headache – 0wk	D	291	10	(3.4%)	302	5	(1.7%)	NS[e]
Weight loss – 0wk	D	291	8	(2.7%)	302	4	(1.3%)	NS[e]
Decreased appetite – 0wk	D	291	2	(0.7%)	302	3	(1.0%)	NS[e]
Asthenia – 0wk	D	291	5	(1.7%)	302	3	(1.0%)	NS[e]

[a] data extracted from figure

[b] two-way ANCOVA (explanatory variables: treatment, country, and baseline scores)

[c] Cochran-Mantel-Haenszel van Elteren test using modified ridit scores stratified by country

[d] chi-square test (Yates's correction) (calculated by reviewer)

[e] test not specified

		Rivastigmine patch (20cm^2)			**Placebo**			
		N	**K**	**MEAN**	**N**	**K**	**MEAN**	***P***
ITT population								
Disposition of participants:								
Discontinued treatment due to AEs – 24wk	D	303	26	(8.6%)	302	15	(5.0%)	
Discontinued treatment before end of trial – 24wk	D	303	62	(20.5%)	302	36	(11.9%)	
LOCF analysis								
Cognitive:								
ADAS-cog – 16wk[a]	MC	262		-1.39 (SD 6.47)	281		0 (SD 6.71)	<0.05[b]
ADAS-cog – 24wk	MC	262		-1.6 (SD 6.5)	281		1 (SD 6.8)	<0.001[b]
Mini Mental State Examination – 24wk	MC	262		0.9 (SD 3.4)	281		0 (SD 3.5)	<0.001[c]
Ten-point clock-drawing test – 24wk	MC	245		0.3 (SD 3.4)	269		-0.1 (SD 3.2)	0.08[c]
Trail-making test – 24wk	MC	238		-6.5 (SD 55.9)	258		7.7 (SD 56.6)	0.005[b]
Functional:							-1.6 (SD	
ADCS-ADL – 16wk[a]	MC	263		0.4 (SD 9.73)	281		7.96)	<0.05[b]
ADCS-ADL – 24wk	MC	263		0 (SD 11.6)	281		-2.3 (SD 9.4)	0.02[b]
Behavioural:							-1.7 (SD	
NPI – 24wk	MC	263		-2.3 (SD 13.3)	281		13.8)	0.69[b]
NPI - caregiver distress – 24wk	MC	263		-1.1 (SD 6.4)	281		-1.1 (SD 6.3)	0.98[b]
Global severity:								
ADCS - Clinical Global Impression of Change: score – 16wk[a]	C	260		3.93 (SD 1.17)	278		4.35 (SD 1.25)	NS[c]
ADCS - Clinical Global Impression of Change: score – 24wk	C	260		4 (SD 1.3)	278		4.2 (SD 1.3)	0.054[c]
ADCS - CGIC: markedly improved – 24wk	D	260	5	(1.9%)	278	2	(0.7%)	0.395[d]
ADCS - CGIC: moderately improved – 24wk	D	260	32	(12.3%)	278	26	(9.4%)	0.334[d]
ADCS - CGIC: minimally improved – 24wk	D	260	48	(18.5%)	278	50	(18.0%)	0.975[d]
ADCS - CGIC: unchanged – 24wk	D	260	94	(36.2%)	278	91	(32.7%)	0.457[d]
ADCS - CGIC: minimally worse – 24wk	D	260	50	(19.2%)	278	65	(23.4%)	0.285[d]
ADCS - CGIC: moderately worse – 24wk	D	260	27	(10.4%)	278	36	(12.9%)	0.429[d]
ADCS - CGIC: markedly worse – 24wk	D	260	4	(1.5%)	278	8	(2.9%)	0.448[d]

Safety population								
Adverse events:								
Any AE – 0wk	D	303	200	(66.0%)	302	139	(46.0%)	≤0.001[e]
Nausea – 0wk	D	303	64	(21.1%)	302	15	(5.0%)	≤0.001[e]
Diarrhoea – 0wk	D	303	31	(10.2%)	302	10	(3.3%)	≤0.001[e]
Vomiting – 0wk	D	303	57	(18.8%)	302	10	(3.3%)	≤0.001[e]
Dizziness – 0wk	D	303	21	(6.9%)	302	7	(2.3%)	≤0.05[e]
Headache – 0wk	D	303	13	(4.3%)	302	5	(1.7%)	NS[e]
Weight loss – 0wk	D	303	23	(7.6%)	302	4	(1.3%)	≤0.001[e]
Decreased appetite – 0wk	D	303	15	(5.0%)	302	3	(1.0%)	≤0.01[e]
Asthenia – 0wk	D	303	9	(3.0%)	302	3	(1.0%)	NS[e]

[a] data extracted from figure

[b] two-way ANCOVA (explanatory variables: treatment, country, and baseline scores)

[c] Cochran-Mantel-Haenszel van Elteren test using modified ridit scores stratified by country

[d] chi-square test (Yates's correction) (calculated by reviewer)

[e] test not specified

		Rivastigmine capsules			Placebo			
		N	**K**	**MEAN**	**N**	**K**	**MEAN**	***P***
ITT population								
Disposition of participants:								
Discontinued treatment due to AEs – 24wk	D	297	24	(8.1%)	302	15	(5.0%)	
Discontinued treatment before end of trial – 24wk	D	297	63	(21.2%)	302	36	(11.9%)	
LOCF analysis								
Cognitive:				-0.5 (SD				
ADAS-cog – 16wk[a]	MC	253		6.36)	281		0 (SD 6.71)	NS[b]
ADAS-cog – 24wk	MC	253		-0.6 (SD 6.2)	281		1 (SD 6.8)	0.003[b]
Mini Mental State Examination – 24wk	MC	256		0.8 (SD 3.2)	281		0 (SD 3.5)	0.002[c]
Ten-point clock-drawing test – 24wk	MC	246		0.2 (SD 2.9)	269		-0.1 (SD 3.2)	0.15[c]
Trail-making test – 24wk	MC	240		-9.8 (SD 66.1)	258		7.7 (SD 56.6)	<0.001[b]
Functional:				-0.4 (SD			-1.6 (SD	
ADCS-ADL – 16wk[a]	MC	254		7.97)	281		7.96)	NS[b]
ADCS-ADL – 24wk	MC	254		-0.5 (SD 9.5)	281		-2.3 (SD 9.4)	0.04[b]
Behavioural:				-2.2 (SD			-1.7 (SD	
NPI – 24wk	MC	253		11.9)	281		13.8)	0.51[b]
NPI - caregiver distress – 24wk	MC	253		-1.1 (SD 6.6)	281		-1.1 (SD 6.3)	0.12[b]
Global severity:								
ADCS - Clinical Global Impression of Change: score – 16wk[a]	C	253		4.25 (SD 1.11)	278		4.35 (SD 1.25)	NS[c]
ADCS - Clinical Global Impression of Change: score – 24wk	C	253		3.9 (SD 1.3)	278		4.2 (SD 1.3)	0.009[c]
ADCS - CGIC: markedly improved – 24wk	D	253	3	(1.2%)	278	2	(0.7%)	0.916[d]
ADCS - CGIC: moderately improved – 24wk	D	253	29	(11.5%)	278	26	(9.4%)	0.513[d]
ADCS - CGIC: minimally improved – 24wk	D	253	60	(23.7%)	278	50	(18.0%)	0.129[d]
ADCS - CGIC: unchanged – 24wk	D	253	96	(37.9%)	278	91	(32.7%)	0.244[d]
ADCS - CGIC: minimally worse – 24wk	D	253	30	(11.9%)	278	65	(23.4%)	<0.001[d]
ADCS - CGIC: moderately worse – 24wk	D	253	30	(11.9%)	278	36	(12.9%)	0.803[d]
ADCS - CGIC: markedly worse – 24wk	D	253	5	(2.0%)	278	8	(2.9%)	0.696[d]
Safety population								
Adverse events:								
Any AE – 0wk	D	294	186	(63.3%)	302	139	(46.0%)	≤0.001[e]
Nausea – 0wk	D	294	68	(23.1%)	302	15	(5.0%)	≤0.001[e]
Diarrhoea – 0wk	D	294	16	(5.4%)	302	10	(3.3%)	NS[e]
Vomiting – 0wk	D	294	50	(17.0%)	302	10	(3.3%)	≤0.001[e]
Dizziness – 0wk	D	294	22	(7.5%)	302	7	(2.3%)	≤0.01[e]
Headache – 0wk	D	294	18	(6.1%)	302	5	(1.7%)	≤0.01[e]
Weight loss – 0wk	D	294	16	(5.4%)	302	4	(1.3%)	≤0.01[e]
Decreased appetite – 0wk	D	294	12	(4.1%)	302	3	(1.0%)	≤0.05[e]
Asthenia – 0wk	D	294	17	(5.8%)	302	3	(1.0%)	≤0.001[e]

[a] data extracted from figure

[b] two-way ANCOVA (explanatory variables: treatment, country, and baseline scores)

[c] Cochran-Mantel-Haenszel van Elteren test using modified ridit scores stratified by country

[d] chi-square test (Yates's correction) (calculated by reviewer)

[e] test not specified

Methodological issues

Randomisation and allocation: Automated random assignment of treatment using an interactive voice-response system. Blocking was done on a study centre basis. All personnel directly involved in the conduct of the study remained unaware of the active treatment groups until all data had been

retrieved and finalized for analysis.

Appearance of tablets, patches and placebo not reported.

Data analysis: A hierarchical testing strategy was applied to adjust for multiplicity. Study objectives were assessed according to four hypotheses tested in sequence. If any of the four tests failed to show statistical significance, testing of subsequent hypotheses would be stopped in order to control the type 1 error. These hypotheses were that, based on changes from baseline at Week 24: (1) on the ADAS-Cog and ADCS-CGIC, the rivastigmine 20 cm2 patch would show superiority over placebo; (2) on the ADAS-Cog, the rivastigmine 20 cm2 patch would show non-inferiority to 12 mg/day rivastigmine capsules; (3) on the ADAS-Cog and ADCS-CGIC, the rivastigmine 10 cm2 patch would show superiority over placebo; (4) on the ADCSADL, the rivastigmine 20 cm2 patch would show superiority over placebo. The second hypothesis, which tested for non-inferiority, was a one-sided hypothesis. The remaining three hypotheses were two-sided hypotheses.

ADAS-Cog: Changes from baseline assessed by ANCOVA, with baseline values as covariates and treatment groups and countries as factors.

ADCS-CGIC: analysis was the treatment comparison based on a stratified Wilcoxon rank sum test using country as a blocking factor. Robustness analyses using a proportional odds model were prospectively planned.

ADCS-ADL, NPI-12, NPI distress, MMSE, Ten-point clock-drawing score, Trail-making Test A score: Changes from baseline analyzed using an ANCOVA model with treatment, country, and the corresponding baseline measurement as covariates, or a Cochran-

Mantel-Haenszel (CMH) test.

A prospective categorical analysis was conducted to determine percentages of patients

demonstrating clinically significant improvements on the ADAS-Cog (defined as >=4 point improvement over baseline at 24 weeks); a CMH test blocking for country was performed to compare treatment groups.

The main efficacy analysis was based on the ITT population using a Last Observation Carried Forward (LOCF) imputation. This ITT-LOCF population was pre-defined as all randomized patients who received at least one dose of study medication and had at least a pre- and post-baseline assessment for one of the primary efficacy variables on treatment (i.e. not more than 2 days after the last known date of study drug). Additional supportive analyses were included to confirm whether imputations and early discontinuations influenced the results. Among others, these included the ITT population without imputation (observed case, ITT-OC), the ITT-Retrieved Drop Out (ITT-RDO) population (all randomized patients who received at least one dose of study medication and had at least a pre- and post-baseline assessment for one of the primary efficacy variables, either under treatment or not), and a population that included all randomized patients.

Power calculation: In previous placebo-controlled trials of the rivastigmine capsule in AD patients, a treatment difference to placebo in the ADAS-Cog change from baseline of approximately 2.5 points was observed in the Intent-to-Treat (ITT) analysis. In the current trial, a non-inferiority margin was pre-defined as 1.25 points on the ADAS-Cog to preserve 50% of this effect, which was considered the smallest value that could represent a clinically meaningful difference. To determine the power of this study, the assumptions on delta (difference in means) and standard deviation (SD) for the change in ADAS-Cog and ADCS-CGIC from baseline were based on 24 week data from the rivastigmine capsule

studies that used the ADAS-Cog and CIBICplus. The ADCS-CGIC scale is comparable to the CIBIC-plus, which was used in previous rivastigmine capsule studies. To ensure that the study had adequate power, 1,040 evaluable patients were needed. In order to reach an overall power of 80% for all of the first three hypotheses (which is defined as the product of the individual powers), the sample size was 260 patients per treatment group.

Conflicts of interest: 3 co-authors (SZ, JN, RL) are employees of Novartis. Remaining authors were investigators (BW, NA, GG, MO, CS) and/or Study Publication Committee members (BW, JC, NA, GG, MO, SZ, JN, RL). BW, JC, NA, GG, MO and CS have provided consultation services to many pharmaceutical companies that develop dementia drugs, including Novartis. A writing committee prepared an initial draft of the manuscript, based on a report provided by Novartis, and all authors contributed to its finalization through interactive review.

Data were collected by investigators and co-investigators, entered into a central database using electronic data capture software, and analyzed by Novartis Pharma AG, which vouches for the data and the analysis.

Quality appraisal

1.	**Was the assignment to the treatment groups really random?** ADEQUATE
2.	**Was the treatment allocation concealed?** ADEQUATE
3.	**Were the groups similar at baseline in terms of prognostic factors?** REPORTED - YES
4.	**Were the eligibility criteria specified?** ADEQUATE
5.	**Were outcome assessors blinded to the treatment allocation?** ADEQUATE
6.	**Was the care provider blinded?** PARTIAL
7.	**Was the patient blinded?** PARTIAL
8.	**Were the point estimates and measure of variability presented for the primary outcome measure?** ADEQUATE
9.	**Did the analyses include an intention-to-treat analysis?** ADEQUATE
10.	**Were withdrawals and dropouts completely described?** ADEQUATE

Design	Participants	Arms	OUTCOMES
Winstein et al. (2007){1789 /id} **Study design:** Parallel double-blind RCT **Country:** USA **No. of centres:** 1 **Funding:** USC Alzheimer's Disease Research Centre, Alzheimer's Disease Research Centres of California, and Pfizer, Inc. **Length of follow-up (wk):** 4	**Number randomised:** 10 **MMSE min:** 11 **MMSE max:** 26 **Inclusion criteria:** Probable AD diagnosis (criteria not reported) Independent in ambulation Alert Able to follow simple instructions MMSE 11-26 **Exclusion criteria:** Delirium Familial tremor Parkinson's Disease Stroke Peripheral neuropathy Dementia due to other than probable AD Use of any concurrent pharmaceutical treatment for cognitive dysfunction **Therapy common to all participants:** None **Sample attrition / dropout:** 10 of 10 completed study	**Arm No:** 1 **Name:** Donepezil **N:** 5 **Drug:** Donepezil **Starting daily dose (mg):** 5 **Dosage details:** One tablet taken nightly **Arm No:** 2 **Name:** Placebo **N:** 5 **Drug:** Placebo **Starting daily dose (mg):** - **Dosage details:** -	▪ ADAS-cog (assessment of comprehension, spoken language, word finding, and praxis (score 0-70)) ▪ Serial Reaction Time Task (assessment of implicit (non-declarative) learning through comparing median response times to a coloured light stimulus)

Notes

-

Baseline characteristics

		Donepezil			Placebo			
		N	**K**	**MEAN**	**N**	**K**	**MEAN**	***P***
ITT population								
Demographics:								
Age	C	5		84.2 (SD 8.67)	5		88 (SD 7.62)	0.483[a]
Sex (n male)	D	5	2	(40.0%)	5	1	(20.0%)	1.000[b]
Cognitive:								
ADAS-cog – 0wk	C	5		24 (SD 3.08)	5		26 (SD 11.6)	0.720[a]
Mini Mental State Examination	C	5		19.2 (SD 3.35)	5		20.2 (SD 4.09)	0.683[a]

[a] student's t-test (calculated by reviewer)

[b] chi-square test (Yates's correction) (calculated by reviewer)

Results

		Donepezil			Placebo			
		N	K	MEAN	N	K	MEAN	*P*
ITT population								
Cognitive:								
ADAS-cog – 4wk	MC	5		-5 (SD 2)	5		0 (SD 4.85)	0.066[a]
Serial Reaction Time Task – 4wk	MC	5		3.32 (SD 8.39)	5		1.65 (SD 10.1)	0.782[a]

[a] student's t-test (calculated by reviewer)

baseline score not reported for Serial Reaction Time Task

Methodological issues

Randomisation and allocation: Randomisation procedure not described. Placebo described as identical in appearance to donepezil.

Data analysis: SRTT and ADAScog: multivariate between group test (Hotelling's Trace statistic)

Power calculation: Not reported

Conflicts of interest: None reported

Quality appraisal

1. **Was the assignment to the treatment groups really random?** UNKNOWN
2. **Was the treatment allocation concealed?** UNKNOWN
3. **Were the groups similar at baseline in terms of prognostic factors?** REPORTED - YES
4. **Were the eligibility criteria specified?** INADEQUATE
5. **Were outcome assessors blinded to the treatment allocation?** UNKNOWN
6. **Was the care provider blinded?** ADEQUATE
7. **Was the patient blinded?** ADEQUATE
8. **Were the point estimates and measure of variability presented for the primary outcome measure?** INADEQUATE
9. **Did the analyses include an intention-to-treat analysis?** PARTIAL
10. **Were withdrawals and dropouts completely described?** ADEQUATE

Appendix 4: Funnel plots from the synthesis with existing evidence

Donepezil v. placebo

FIGURE 1 *Cognitive outcomes (SMD) at 24–26wk – donepezil (all dosages) v. placebo: funnel plot*

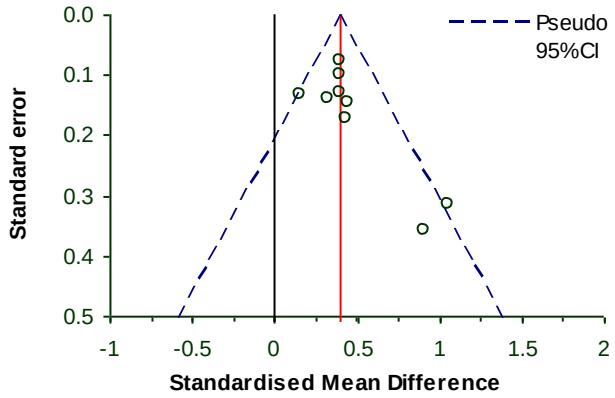


FIGURE 2 *Functional outcomes (SMD) at 24wk – donepezil (all dosages) v. placebo: funnel plot*

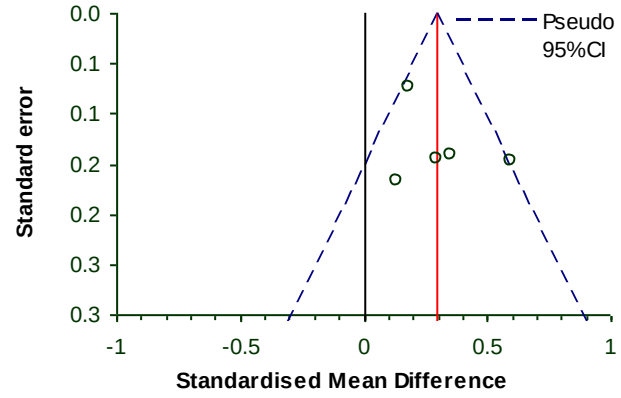
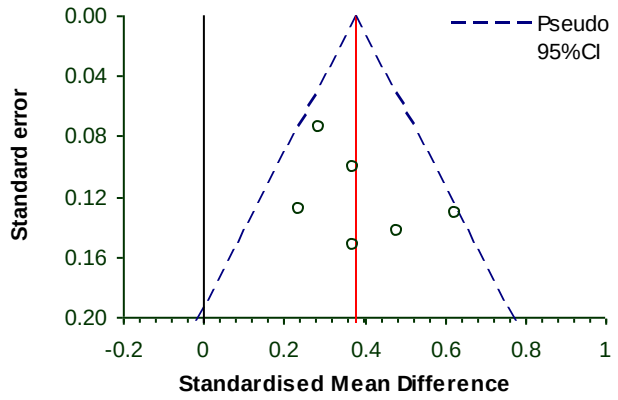


FIGURE 3 *Global outcomes (SMD) at 24wk – donepezil (all dosages) v. placebo: funnel plot*



Appendix 5: Combined dose and dose-specific meta-analyses

Donepezil

Donepezil 5mg/d

FIGURE 4 *Random-effects meta-analysis: ADAS-cog at 12wk (mean change from baseline) – donepezil (5mg/d) v. placebo*

	Donepezil			Placebo				
	N	mean	SD	N	mean	SD	WMD (95%CI)	Wght
LOCF analysis								
Rogers et al. (1998)[4]	156	-2.10	5.37	150	0.40	5.27	-2.500 (-3.692, -1.308)	26.1
subtotal							**-2.500 (-3.692, -1.308)**	**26.1**
							p<0.001	
OC population								
Burns et al. (1999)[5]	271	-1.60	4.94	274	0.40	4.97	2.000 (1.168, 2.832)	53.6
Homma et al. (2000)[6]	126	-3.03	5.33	113	-0.85	5.32	2.175 (0.823, 3.527)	20.3
subtotal (Q=0.05 [p on 1 d.f.=0.829]; I^2=0.0%; τ^2=0.000)							**2.048 (1.340, 2.756)**	**73.9**
							p<0.001	
Overall pooled estimate							**2.166 (1.557, 2.775)**	
(Q=0.45 [p on 2 d.f.=0.797]; I^2=0.0%; τ^2=0.000)							*p*<0.001	
Inter stratum heterogeneity: p=0.523								
Small-study effects: Egger's *p*=0.508								

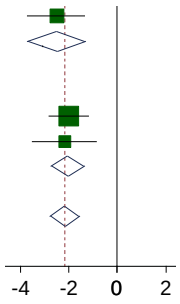


FIGURE 5 *Random-effects meta-analysis: ADAS-cog at 24wk (mean change from baseline) – donepezil (5mg/d) v. placebo*

	Donepezil			Placebo				
	N	mean	SD	N	mean	SD	WMD (95%CI)	Wght
LOCF analysis								
Rogers et al. (1998)[7]	152	-0.67	6.29	153	1.82	6.06	-2.490 (-3.876, -1.104)	21.3
Burns et al. (1999)[5]	271	0.20	6.58	274	1.70	4.97	-1.500 (-2.480, -0.520)	36.6
Homma et al. (2000)[6]	126	-2.43	5.05	113	0.11	0.52	-2.540 (-3.427, -1.653)	42.1
subtotal (*Q*=2.66 [*p* on 2 d.f.=0.264]; I^2=24.9%; τ^2=0.097)							**-2.148 (-2.847, -1.450)**	**100.0**
							p<0.001	
Overall pooled estimate							**-2.148 (-2.847, -1.450)**	
(*Q*=2.66 [*p* on 2 d.f.=0.264]; I^2=24.9%; τ^2=0.097)							*p*<0.001	
Small-study effects: Egger's *p*=0.935								

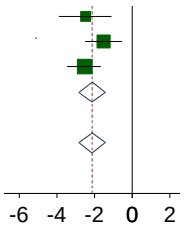


FIGURE 6 *Random-effects meta-analysis: MMSE at 24wk (mean change from baseline) – donepezil (5mg/d) v. placebo*

	Donepezil			Placebo				
	N	mean	SD	N	mean	SD	WMD (95%CI)	Wght
ITT population								
Mazza et al. (2006)[8]	25	1.20	12.25	26	-0.25	5.00	1.450 (-3.720, 6.620)	2.3
subtotal							**1.450 (-3.720, 6.620)**	**2.3**
							p=0.583	
LOCF analysis								
Rogers et al. (1998)[7]	153	0.24	3.59	154	-0.97	3.47	1.210 (0.420, 2.000)	97.7
subtotal							**1.210 (0.420, 2.000)**	**97.7**
							p=0.003	
Overall pooled estimate							**1.215 (0.434, 1.996)**	
(Q=0.01 [p on 1 d.f.=0.928]; I^2=0.0%; τ^2=0.000)							*p*=0.002	
Inter-stratum heterogeneity: p=0.928								
Small-study effects: not calculable								

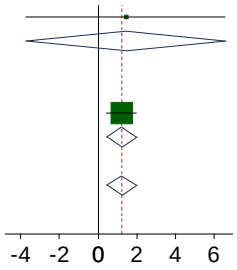


FIGURE 7 *Random-effects meta-analysis: CIBIC-plus at 12wk (mean change from baseline) – donepezil (5mg/d) v. placebo*

	Donepezil			Placebo				
	N	mean	SD	N	mean	SD	WMD (95%CI)	Wght
LOCF analysis								
Rogers et al. (1998)[4]	153	3.90	0.99	150	4.20	0.86	-0.300 (-0.508, -0.092)	38.9
subtotal							**-0.300 (-0.508, -0.092)**	**38.9**
							p=0.005	
OC population								
Burns et al. (1999)[5]	271	4.03	0.99	274	4.23	0.99	-0.200 (-0.366, -0.034)	61.1
subtotal							**-0.200 (-0.366, -0.034)**	**61.1**
							p=0.018	
Overall pooled estimate							**-0.239 (-0.369, -0.109)**	
(Q=0.54 [p on 1 d.f.=0.462]; I^2=0.0%; τ^2=0.000)							*p*<0.001	
Inter stratum heterogeneity: p=0.462								
Small-study effects: not calculable								

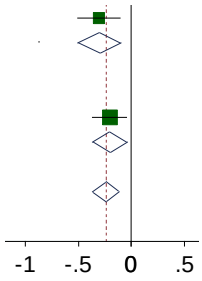


FIGURE 8 *Random-effects meta-analysis: CIBIC-plus at 24wk (mean change from baseline) – donepezil (5mg/d) v. placebo*

	Donepezil			Placebo				
	N	mean	SD	N	mean	SD	WMD (95%CI)	Wght
LOCF analysis								
Rogers et al. (1998)[7]	149	4.15	1.10	152	4.51	0.99	-0.360 (-0.596, -0.124)	33.2
Burns et al. (1999)[5]	271	4.23	0.99	274	4.52	0.99	-0.290 (-0.456, -0.124)	66.8
subtotal (Q=0.23 [p on 1 d.f.=0.635]; I^2=0.0%; τ^2=0.000)							**-0.313 (-0.449, -0.177)**	**100.0**
							p<0.001	
Overall pooled estimate							**-0.313 (-0.449, -0.177)**	
(Q=0.23 [p on 1 d.f.=0.635]; I 2=0.0%; τ2=0.000)							*p*<0.001	
Small-study effects: not calculable								

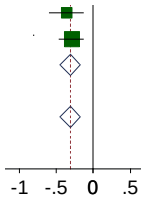


FIGURE 9 *Random-effects meta-analysis: Clinical dementia rating at 12wk (mean change from baseline) – donepezil (5mg/d) v. placebo*

	Donepezil			Placebo				
	N	mean	SD	N	mean	SD	WMD (95%CI)	Wght
LOCF analysis								
Rogers et al. (1998)[4]	156	-0.10	1.37	150	-0.14	1.35	0.040 (-0.265, 0.345)	28.8
subtotal							**0.040 (-0.265, 0.345)**	**28.8**
							p=0.797	
OC population								
Burns et al. (1999)[5]	271	-0.18	1.32	274	0.15	1.32	-0.330 (-0.552, -0.108)	37.8
Homma et al. (2000)[6]	116	-0.11	0.94	112	0.25	1.06	-0.363 (-0.623, -0.102)	33.4
subtotal (Q=0.03 [p on 1 d.f.=0.852]; I^2=0.0%; τ^2=0.000)							**-0.344 (-0.512, -0.175)**	**71.2**
							p<0.001	
Overall pooled estimate							**-0.234 (-0.464, -0.004)**	
(Q=4.69 [p on 2 d.f.=0.096]; I^2=57.4%; τ^2=0.024)							*p*=0.046	
Inter stratum heterogeneity: p=0.031								
Small-study effects: Egger's p=0.394								

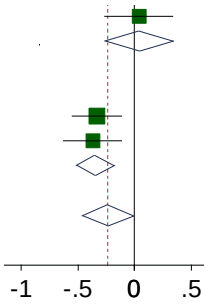
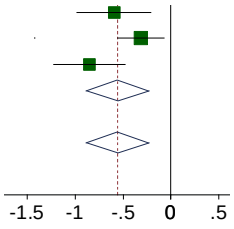


FIGURE 10 *Random-effects meta-analysis: Clinical dementia rating at 24wk (mean change from baseline) – donepezil (5mg/d) v. placebo*

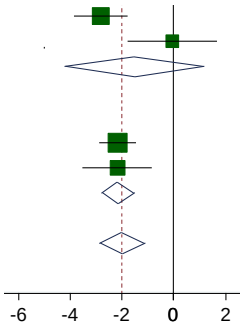
	Donepezil			Placebo				
	N	mean	SD	N	mean	SD	WMD (95%CI)	Wght
LOCF analysis								
Rogers et al. (1998)[7]	154	-0.01	1.74	153	0.58	1.73	-0.590 (-0.978, -0.202)	29.8
Burns et al. (1999)[5]	271	0.06	1.81	274	0.37	0.99	-0.310 (-0.556, -0.064)	39.7
Homma et al. (2000)[6]	116	-0.10	1.29	112	0.75	1.59	-0.850 (-1.226, -0.474)	30.5
subtotal (Q=5.82 [p on 2 d.f.=0.054]; I^2=65.7%; τ^2=0.055)							**-0.558 (-0.887, -0.230)**	**100.0**
							p<0.001	
Overall pooled estimate							**-0.558 (-0.887, -0.230)**	
(Q=5.82 [p on 2 d.f.=0.054]; I^2=65.7%; τ^2=0.055)							p<0.001	
Small-study effects: Egger's p=0.292								



Donepezil all doses combined

FIGURE 11 *Random-effects meta-analysis: ADAS-cog at 12wk (mean change from baseline) – donepezil (all dosages)* v. *placebo*

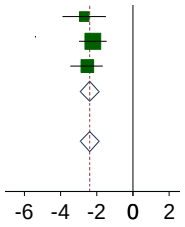
	Donepezil			Placebo				
	N	mean	SD	N	mean	SD	WMD (95%CI)	Wght
LOCF analysis								
Rogers et al. (1998)[4]	311[a]	-2.40	5.36	150	0.40	5.27	-2.799 (-3.831, -1.767)	27.6
Nunez et al. (2003)[9;10]	94	0.65	6.11	98	0.70	6.14	-0.050 (-1.782, 1.682)	16.3
subtotal (Q=7.14 [p on 1 d.f.=0.008]; I^2=86.0%; τ^2=3.249)							**-1.516 (-4.204, 1.172)**	**43.9**
							p=0.269	
OC population								
Burns et al. (1999)[5]	544[a]	-1.75	4.95	274	0.40	4.97	-2.151 (-2.871, -1.430)	34.4
Homma et al. (2000)[6]	126	-3.03	5.33	113	-0.85	5.32	-2.175 (-3.527, -0.823)	21.7
subtotal (Q=0.0 [p on 1 d.f.=0.975]; I^2=0.0%; τ^2=0.000)							**-2.156 (-2.792, -1.520)**	**56.1**
							p<0.001	
Overall pooled estimate							**-1.992 (-2.870, -1.114)**	
(Q=7.16 [p on 3 d.f.=0.067]; I^2=58.1%; τ^2=0.449)							p<0.001	
Inter stratum heterogeneity: p=0.890								
Small-study effects: Egger's p = 0.431								



[a] pooled 5mg/d and 10mg/d arms

FIGURE 12 *Random-effects meta-analysis: ADAS-cog at 24wk (mean change from baseline) – donepezil (all dosages)* v. *placebo*

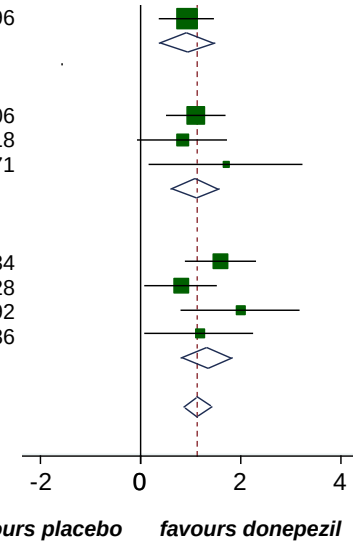
	Donepezil			Placebo				
	N	mean	SD	N	mean	SD	WMD (95%CI)	Wght
LOCF analysis								
Rogers *et al*.. (1998)[7]	302[a]	-0.86	6.27	153	1.82	6.06	-2.684 (-3.876, -1.491)	19.1
Burns et al. (1999)[5]	544[a]	-0.50	5.82	274	1.70	4.97	-2.203 (-2.968, -1.438)	46.4
Homma et al. (2000)[6]	126	-2.43	5.05	113	0.11	0.52	-2.540 (-3.427, -1.653)	34.5
subtotal (Q=0.57 [p on 2 d.f.=0.753]; I^2=0.0%; τ^2=0.000)							**-2.411 (-2.932, -1.890)**	**100.0**
							p<0.001	
Overall pooled estimate							**-2.411 (-2.932, -1.890)**	
(Q=0.57 [p on 2 d.f.=0.753]; I^2=0.0%; τ^2=0.000)							p<0.001	
Small-study effects: Egger's p=0.315								



[a] pooled 5mg/d and 10mg/d arms

FIGURE 13 *Random-effects meta-analysis: MMSE at 12wk (mean change from baseline) – donepezil (all dosages) v. placebo*

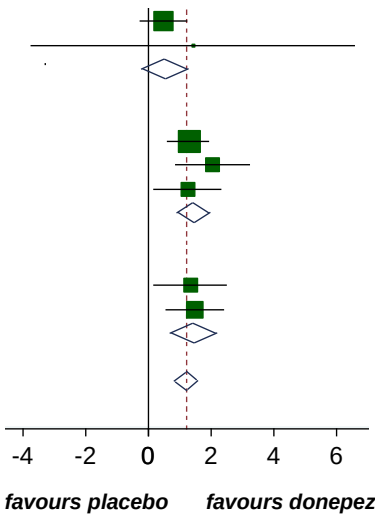
	Donepezil			Placebo				
	N	mean	SD	N	mean	SD	WMD (95%CI)	Wght
ITT population								
AD2000 (2004)[11]	245	0.93	3.24	263	0.00	2.96	0.930 (0.389, 1.471)	25.6
subtotal							**0.930 (0.389, 1.471)**	**25.6**
							p<0.001	
LOCF analysis								
Rogers et al. (1998)[4]	312[a]	1.15	3.06	150	0.04	3.06	1.110 (0.514, 1.706)	21.1
Nunez et al. (2003)[9;10]	93	1.41	3.18	99	0.58	3.18	0.830 (-0.071, 1.731)	9.2
Holmes et al. (2004)[12]	41	-0.10	3.84	55	-1.80	3.71	1.700 (0.169, 3.231)	3.2
subtotal (*Q*=0.93 [*p* on 2 d.f.=0.627]; I^2=0.0%; τ^2=0.000)							**1.089 (0.616, 1.562)**	**33.5**
							p<0.001	
OC population								
Mohs et al. (2001)[13]	171	1.45	3.43	178	-0.15	3.34	1.600 (0.889, 2.311)	14.8
Winblad et al. (2001)[14]	127	0.69	2.59	128	-0.11	3.28	0.800 (0.075, 1.525)	14.2
Gauthier et al. (2002)[15]	84	2.00	4.12	96	0.00	3.92	2.000 (0.820, 3.180)	5.4
Seltzer et al. (2004)[16]	79	1.58	3.33	51	0.40	2.86	1.175 (0.100, 2.250)	6.5
subtotal (*Q*=3.91 [*p* on 3 d.f.=0.271]; I^2=23.3%; τ^2=0.062)							**1.322 (0.822, 1.823)**	**40.9**
							p<0.001	
Overall pooled estimate							**1.138 (0.864, 1.411)**	
(*Q*=6.05 [*p* on 7 d.f.=0.533]; I^2=0.0%; τ^2=0.000)							*p*<0.001	
Inter-stratum heterogeneity: *p*=0.546								
Small-study effects: Egger's *p*=0.197								



[a] pooled 5mg/d and 10mg/d arms

FIGURE 14 *Random-effects meta-analysis: MMSE at 24wk (mean change from baseline) – donepezil (all dosages) v. placebo*

	Donepezil			Placebo				
	N	mean	SD	N	mean	SD	WMD (95%CI)	Wght
ITT population								
AD2000 (2004)[11]	211	0.50	-	229	0.00	-	0.500[a] (-0.250, 1.250)	24.0
Mazza et al. (2006)[8]	25	1.20	12.25	26	-0.25	5.00	1.450 (-3.720, 6.620)	0.5
subtotal (*Q*=0.13 [*p* on 1 d.f.=0.722]; I^2=0.0%; τ^2=0.000)							**0.520 (-0.223, 1.262)**	**24.5**
							p=0.170	
LOCF analysis								
Rogers et al. (1998)[7]	303[b]	0.31	3.57	154	-0.97	3.47	1.284 (0.604, 1.964)	29.1
Gauthier et al. (2002)[15]	91	1.50	4.29	100	-0.56	4.00	2.060 (0.880, 3.240)	9.7
Seltzer et al. (2004)[16]	91	1.35	3.34	55	0.10	3.15	1.250 (0.171, 2.329)	11.6
subtotal (*Q*=1.38 [*p* on 2 d.f.=0.502]; I^2=0.0%; τ^2=0.000)							**1.425 (0.908, 1.943)**	**50.4**
							p<0.001	
OC population								
Mohs et al. (2001)[13]	111	1.80	4.21	96	0.45	4.29	1.350 (0.188, 2.512)	10.0
Winblad et al. (2001)[14]	121	0.40	3.74	120	-1.09	3.72	1.490 (0.548, 2.432)	15.2
subtotal (*Q*=0.03 [*p* on 1 d.f.=0.854]; I^2=0.0%; τ^2=0.000)							**1.434 (0.703, 2.166)**	**25.2**
							p<0.001	
Overall pooled estimate							**1.206 (0.839, 1.573)**	
(*Q*=5.89 [*p* on 6 d.f.=0.436]; I^2=0.0%; τ^2=0.000)							*p*<0.001	
Inter-stratum heterogeneity: *p*=0.114								
Small-study effects: Egger's *p*=0.459								

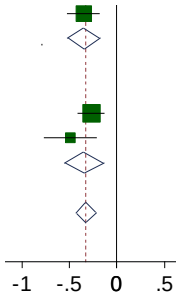


[a] WMD and error bars provided in publication; SE estimated on assumption that error-bars represent 95%CIs

[b] pooled 5mg/d and 10mg/d arms

FIGURE 15 *Random-effects meta-analysis: CIBIC-plus at 12wk (mean change from baseline) – donepezil (all dosages) v. placebo*

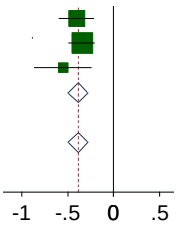
	Donepezil			Placebo				
	N	mean	SD	N	mean	SD	WMD (95%CI)	Wght
LOCF analysis								
Rogers et al. (1998)[4]	308[a]	3.85	0.99	150	4.20	0.86	-0.350 (-0.527, -0.174)	34.0
subtotal							**-0.350 (-0.527, -0.174)** p<0.001	**34.0**
OC population								
Burns et al. (1999)[5]	544[a]	3.96	0.91	274	4.23	0.99	-0.265 (-0.406, -0.125)	51.6
Gauthier et al. (2002)[15]	86	3.55	0.97	96	4.04	0.93	-0.490 (-0.768, -0.212)	14.3
subtotal (Q=2.01 [p on 1 d.f.=0.157]; I^2=50.2%; τ^2=0.013)							**-0.344 (-0.555, -0.134)** p=0.001	**66.0**
Overall pooled estimate (Q=2.13 [p on 2 d.f.=0.344]; I^2=6.3%; τ^2=0.001)							**-0.326 (-0.433, -0.220)** p<0.001	
Inter stratum heterogeneity: p=0.721								
Small-study effects: Egger's *p*=0.103								



[a] pooled 5mg/d and 10mg/d arms

FIGURE 16 *Random-effects meta-analysis: CIBIC-plus at 24wk (mean change from baseline) – donepezil (all dosages) v. placebo*

	Donepezil			Placebo				
	N	mean	SD	N	mean	SD	WMD (95%CI)	Wght
LOCF analysis								
Rogers et al. (1998)[7]	298[a]	4.11	0.98	152	4.51	0.99	-0.400 (-0.593, -0.207)	31.6
Burns et al. (1999)[5]	544[a]	4.18	0.99	274	4.52	0.99	-0.340 (-0.484, -0.196)	56.4
Gauthier et al. (2002)[15]	98	4.00	1.19	105	4.55	1.08	-0.545 (-0.858, -0.232)	12.0
subtotal (*Q*=1.4 [*p* on 2 d.f.=0.496]; I^2=0.0%; τ^2=0.000)							**-0.384 (-0.492, -0.275)** *p*<0.001	**100.0**
Overall pooled estimate (*Q*=1.4 [*p* on 2 d.f.=0.496]; I^2=0.0%; τ^2=0.000)							**-0.384 (-0.492, -0.275)** *p*<0.001	
Small-study effects: Egger's *p*=0.004								



[a] pooled 5mg/d and 10mg/d arms

Galantamine

Galantamine >24mg/d

FIGURE 17 *Random-effects meta-analysis: ADAS-cog at 12–16wk (mean change from baseline) – galantamine (maximum dose >24mg/d) v. placebo*

	Galantamine			Placebo				
	N	mean	SD	N	mean	SD	WMD (95%CI)	Wght
LOCF analysis								
Rockwood et al. (2001)[17]	239	-1.10	5.10	120	0.60	4.93	-1.700 (-2.794, -0.606)	36.2
Wilkinson & Murray (2001)[18]	51	-0.70	5.00	82	1.60	6.34	-2.300 (-4.240, -0.360)	12.2
subtotal (Q=0.28 [p on 1 d.f.=0.598]; I^2=0.0%; τ^2=0.000)							**-1.845 (-2.797, -0.892)**	**48.4**
							p<0.001	
OC population								
Raskind et al. (2000)[19]	117	-3.00	6.49	157	0.00	5.95	-3.000 (-4.500, -1.500)	20.1
Wilcock et al. (2000)[20]	152	-2.40	5.55	171	0.60	5.23	-3.000 (-4.180, -1.820)	31.5
subtotal (Q=0.0 [p on 1 d.f.=1.000]; I^2=0.0%; τ^2=0.000)							**-3.000 (-3.927, -2.073)**	**51.6**
							p<0.001	
Overall pooled estimate							**-2.444 (-3.132, -1.755)**	
(Q=3.18 [p on 3 d.f.=0.365]; I^2=5.6%; τ^2=0.029)							p<0.001	
Inter-stratum heterogeneity: p=0.089								
Small-study effects: Egger's p=0.721								

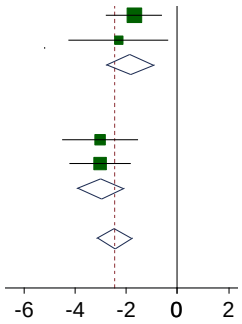


FIGURE 18 *Random-effects meta-analysis: ADAS-cog at 21–26wk (mean change from baseline) – galantamine (maximum dose >24mg/d) v. placebo*

	Galantamine			Placebo				
	N	mean	SD	N	mean	SD	WMD (95%CI)	Wght
LOCF analysis								
Raskind et al. (2000)[19]	197	-1.40	6.18	207	2.00	6.47	-3.400 (-4.634, -2.166)	47.1
Wilcock et al. (2000)[20]	217	-0.80	6.33	215	2.40	6.01	-3.200 (-4.364, -2.036)	52.9
subtotal (Q=0.05 [p on 1 d.f.=0.817]; I^2=0.0%; τ^2=0.000)							**-3.294 (-4.141, -2.447)**	**100.0**
							p<0.001	
Overall pooled estimate							**-3.294 (-4.141, -2.447)**	
(Q=0.05 [p on 1 d.f.=0.817]; I^2=0.0%; τ^2=0.000)							p<0.001	
Small-study effects: not calculable								

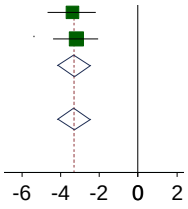
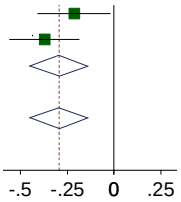


FIGURE 19 *Random-effects meta-analysis: CIBIC-plus at 26wk – galantamine (maximum dose >24mg/d) v. placebo*

	Galantamine			Placebo				
	N	mean	SD	N	mean	SD	WMD (95%CI)	Wght
LOCF analysis								
Raskind et al. (2000)[19]	171	4.17	0.90	196	4.38	0.99	-0.213 (-0.407, -0.019)	47.8
Wilcock et al. (2000)[20]	217	4.14	0.98	215	4.51	0.99	-0.372 (-0.557, -0.186)	52.2
subtotal (Q=1.34 [p on 1 d.f.=0.247]; I^2=25.5%; τ^2=0.003)							**-0.295 (-0.450, -0.140)**	**100.0**
							p<0.001	
Overall pooled estimate							**-0.295 (-0.450, -0.140)**	
(Q=1.34 [p on 1 d.f.=0.247]; I^2=25.5%; τ^2=0.003)							p<0.001	
Small-study effects: not calculable								

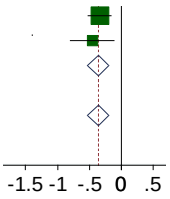


favours galantamine ***favours placebo***

Galantamine all doses

FIGURE 20 *Random-effects meta-analysis: CIBIC-plus at 13–16wk – galantamine (all dosages) v. placebo*

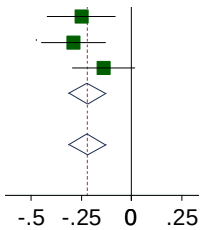
	Galantamine			Placebo				
	N	mean	SD	N	mean	SD	WMD (95%CI)	Wght
LOCF analysis								
Rockwood et al. (2001)[17]	240	3.92	0.80	123	4.26	0.90	-0.335 (-0.524, -0.146)	77.1
Rockwood et al. (2006)[21]	61	3.67	1.00	65	4.12	0.99	-0.450 (-0.797, -0.103)	22.9
subtotal (Q=0.33 [p on 1 d.f.=0.569]; I^2=0.0%; τ^2=0.000)							**-0.361 (-0.527, -0.196)**	**100.0**
							p<0.001	
Overall pooled estimate							**-0.361 (-0.527, -0.196)**	
(Q=0.33 [p on 1 d.f.=0.569]; I^2=0.0%; τ^2=0.000)							p<0.001	
Small-study effects: not calculable								



favours galantamine ***favours placebo***

FIGURE 21 *Random-effects meta-analysis: CIBIC-plus at 26wk – galantamine (all dosages) v. placebo*

	Galantamine			Placebo				
	N	mean	SD	N	mean	SD	WMD (95%CI)	Wght
LOCF analysis								
Raskind et al. (2000)[19]	357[a]	4.13	0.96	196	4.38	0.99	-0.248 (-0.419, -0.077)	30.0
Wilcock et al. (2000)[20]	437[a]	4.22	0.99	215	4.51	0.99	-0.288 (-0.450, -0.127)	33.7
Brodaty et al. (2005)[22]	593[b]	4.21	1.08	301	4.35	1.14	-0.138 (-0.294, 0.018)	36.3
subtotal (Q=1.86 [p on 2 d.f.=0.395]; I^2=0.0%; τ^2=0.000)							**-0.222 (-0.316, -0.128)**	**100.0**
							p<0.001	
Overall pooled estimate							**-0.222 (-0.316, -0.128)**	
(Q=1.86 [p on 2 d.f.=0.395]; I^2=0.0%; τ^2=0.000)							p<0.001	
Small-study effects: Egger's p=0.573								



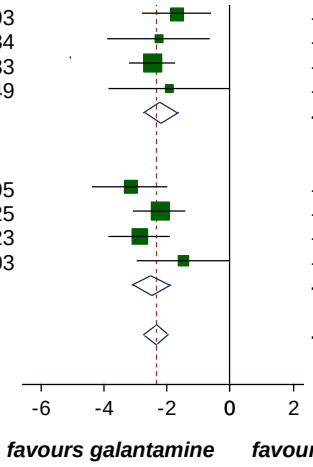
favours galantamine ***favours placebo***

[a] 24mg/d and 32mg/d arms pooled

[b] once-daily prolonged release formulation and twice-daily standard formulation pooled

FIGURE 22 *Random-effects meta-analysis: ADAS-cog at 12–16wk (mean change from baseline) – galantamine (all dosages) v. placebo*

	Galantamine			Placebo				
	N	mean	SD	N	mean	SD	WMD (95%CI)	Wght
LOCF analysis								
Rockwood et al. (2001)[17]	239	-1.10	5.10	120	0.60	4.93	-1.700 (-2.794, -0.606)	11.9
Wilkinson & Murray (2001)[18]	187[a]	-0.65	6.09	82	1.60	6.34	-2.246 (-3.872, -0.620)	5.4
Brodaty et al. (2005)[22]	586[b]	-2.25	5.22	296	0.20	5.33	-2.453 (-3.192, -1.713)	26.1
Rockwood et al. (2006)[21]	62	-1.60	5.38	65	0.33	5.49	-1.925 (-3.816, -0.034)	4.0
subtotal (Q=1.33 [p on 3 d.f.=0.721]; I^2=0.0%; τ^2=0.000)							**-2.195 (-2.744, -1.646)**	**47.4**
							p<0.001	
OC population								
Raskind et al. (2000)[19]	248[c]	-3.16	6.24	157	0.00	5.95	-3.158 (-4.371, -1.946)	9.7
Tariot et al. (2000)[23]	520[d]	-1.62	5.16	225	0.60	5.25	-2.225 (-3.042, -1.408)	21.4
Wilcock et al. (2000)[20]	308[e]	-2.25	5.28	171	0.60	5.23	-2.848 (-3.829, -1.867)	14.8
Bullock et al. (2004)[24]	148	-1.48	4.32	85	0.00	6.03	-1.475 (-2.933, -0.017)	6.7
subtotal (Q=3.94 [p on 3 d.f.=0.268]; I^2=23.9%; τ^2=0.094)							**-2.479 (-3.090, -1.867)**	**52.6**
							p<0.001	
Overall pooled estimate							**-2.344 (-2.721, -1.966)**	
(Q=5.81 [p on 7 d.f.=0.562]; I^2=0.0%; τ^2=0.000)							p<0.001	
Inter-stratum heterogeneity: p=0.465								
Small-study effects: Egger's p=0.513								



[a] 18mg/d, 24mg/d, and 36mg/d arms pooled

[b] once-daily prolonged release formulation and twice-daily standard formulation pooled

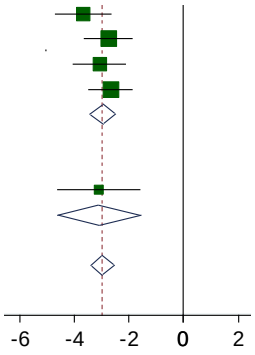
[c] 24mg/d and 36mg/d arms pooled

[d] 8mg/d, 16mg/d, and 24mg/d arms pooled

[e] 24mg/d and 32mg/d arms pooled

FIGURE 23 *Random-effects meta-analysis: ADAS-cog at 21–26wk (mean change from baseline) – galantamine (all dosages) v. placebo*

	Galantamine			Placebo				
	N	mean	SD	N	mean	SD	WMD (95%CI)	Wght
LOCF analysis								
Raskind et al. (2000)[19]	399[a]	-1.65	5.66	207	2.00	6.47	-3.653 (-4.696, -2.611)	17.6
Tariot et al. (2000)[23]	632[b]	-1.04	5.88	255	1.70	6.23	-2.741 (-3.633, -1.850)	24.1
Wilcock et al. (2000)[20]	437[c]	-0.65	5.99	215	2.40	6.01	-3.049 (-4.030, -2.068)	19.9
Brodaty et al. (2005)[22]	587[d]	-1.45	5.76	296	1.20	5.68	-2.651 (-3.449, -1.854)	30.1
subtotal (Q=2.54 [p on 3 d.f.=0.469]; I^2=0.0%; τ^2=0.000)							**-2.954 (-3.410, -2.497)**	**91.7**
							p<0.001	
OC population								
Bullock et al. (2004)[24]	147	-1.10	5.79	83	2.00	5.56	-3.100 (-4.620, -1.580)	8.3
subtotal							**-3.100 (-4.620, -1.580)**	**8.3**
							p<0.001	
Overall pooled estimate							**-2.966 (-3.403, -2.528)**	
(Q=2.57 [p on 4 d.f.=0.632]; I^2=0.0%; τ^2=0.000)							p<0.001	
Inter-stratum heterogeneity: p=0.857								
Small-study effects: Egger's p=0.366								



[a] 24mg/d and 36mg/d arms pooled

[b] 8mg/d, 16mg/d, and 24mg/d arms pooled

[c] 24mg/d and 32mg/d arms pooled

[d] once-daily prolonged release formulation and twice-daily standard formulation pooled

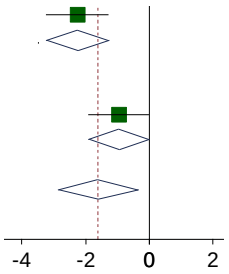
Rivastigmine

Rivastigmine ≤10mg/d

FIGURE 24 *Random-effects meta-analysis: ADAS-cog at 12–16wk (mean change from baseline) – rivastigmine (maximum dose ≤10mg/d) v. placebo*

	Rivastigmine			Placebo				
	N	mean	SD	N	mean	SD	WMD (95%CI)	Wght
ITT population								
Feldman & Lane (2007)[25]	455[a]	-1.35	6.36	220	0.90	5.93	-2.249 (-3.226, -1.271)	49.1
subtotal							**-2.249 (-3.226, -1.271)**	**49.1**
							p<0.001	
LOCF analysis								
Winblad et al. (2007)[26]	515[b]	-0.95	6.42	281	0.00	6.71	-0.953 (-1.913, 0.007)	50.9
subtotal							**-0.953 (-1.913, 0.007)**	**50.9**
							p=0.052	
Overall pooled estimate							**-1.597 (-2.867, -0.327)**	
							p=0.014	

(Q=3.44 [p on 1 d.f.=0.064]; I^2=70.9%; τ^2=0.595)
Inter-stratum heterogeneity: p=0.064
Small-study effects: not calculable



favours rivastigmine ***favours placebo***

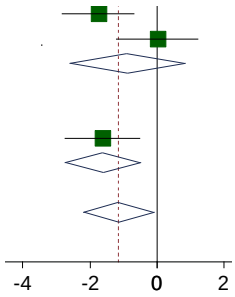
[a] bd and tid arms pooled

[b] 20cm^2 patch and 12mg/d capsules arms pooled

FIGURE 25 *Random-effects meta-analysis: ADAS-cog at 24–26wk (mean change from baseline) – rivastigmine (≤10mg/d) v. placebo*

	Rivastigmine			Placebo				
	N	mean	SD	N	mean	SD	WMD (95%CI)	Wght
ITT population								
Corey-Bloom et al. (1998)[27]	233	2.36	6.00	234	4.09	6.01	- (-2.819, -1.730 0.641)	34.7
Rosler et al. (1999){Rosler, 1999 2016 /id}	242	1.37	7.14	238	1.34	6.69	0.030 (-1.208, 1.268)	31.4
subtotal (Q=4.38 [p on 1 d.f.=0.036]; I^2=77.2%; τ^2=1.195)							**- (-2.600, 0.876 0.848)**	**66.1**
							p=0.320	
LOCF analysis								
Winblad et al. (2007)[26]	248	-0.60	6.40	281	1.00	6.80	- (-2.725, -1.600 0.475)	33.9
subtotal							**- (-2.725, -1.600 0.475)**	**33.9**
							p=0.005	
Overall pooled estimate							**- (-2.202, -1.133 0.065)**	
							p=0.038	

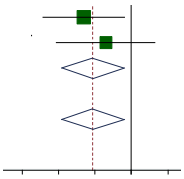
(Q=5.18 [p on 2 d.f.=0.075]; I^2=61.4%; τ^2=0.547)
Inter-stratum heterogeneity: p=0.369
Small-study effects: Egger's p=0.116



favours rivastigmine ***favours placebo***

FIGURE 26 *Random-effects meta-analysis: CIBIC-plus at 26wk – rivastigmine (4mg/d) v. placebo*

	Rivastigmine			Placebo				
	N	mean	SD	N	mean	SD	WMD (95%CI)	Wght
ITT population								
Corey-Bloom et al. (1998)[27]	233	4.23	1.25	234	4.49	1.25	- 0.260 (-0.486, -0.034)	59.1
Rosler et al. (1999){Rosler, 1999 2016 /id}	233	4.24	1.71	230	4.38	1.24	- 0.140 (-0.412, 0.132)	40.9
subtotal (Q=0.44 [p on 1 d.f.=0.506]; I^2=0.0%; τ^2=0.000)							**- 0.211 (-0.385, -0.037)** p=0.017	**100.0**
Overall pooled estimate							**- 0.211 (-0.385, -0.037)** p=0.017	
(Q=0.44 [p on 1 d.f.=0.506]; I^2=0.0%; τ^2=0.000)								
Small-study effects: not calculable								

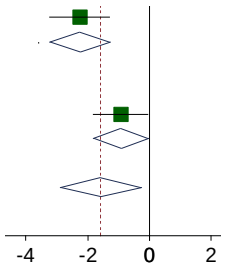


favours rivastigmine ***favours placebo***

Rivastigmine all doses

FIGURE 27 *Random-effects meta-analysis: ADAS-cog at 12–16wk (mean change from baseline) – rivastigmine (all dosages) v. placebo*

	Rivastigmine			Placebo				
	N	mean	SD	N	mean	SD	WMD (95%CI)	Wght
ITT population								
Feldman & Lane (2007)[25]	455[a]	-1.35	6.36	220	0.90	5.93	-2.249 (-3.226, -1.271)	46.2
subtotal							**-2.249 (-3.226, -1.271)** p<0.001	**46.2**
LOCF analysis								
Winblad et al. (2007)[26]	763[b]	-0.91	6.38	281	0.00	6.71	-0.911 (-1.817, -0.006)	53.8
subtotal							**-0.911 (-1.817, -0.006)** p=0.049	**53.8**
Overall pooled estimate							**-1.567 (-2.877, -0.256)** p=0.019	
(Q=3.87 [p on 1 d.f.=0.049]; I^2=74.2%; τ^2=0.663)								
Inter-stratum heterogeneity: p=0.049								
Small-study effects: not calculable								



favours rivastigmine ***favours placebo***

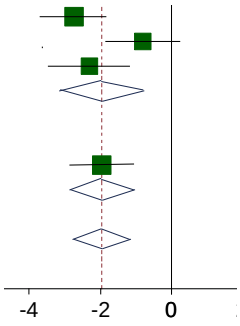
[a] bd and tid arms pooled

[b] 10cm^2 patch, 20cm^2 patch, and 12mg/d capsules arms pooled

FIGURE 28 *Random-effects meta-analysis: ADAS-cog at 24–26wk (mean change from baseline) – rivastigmine (all dosages) v. placebo*

	Rivastigmine			Placebo				
	N	mean	SD	N	mean	SD	WMD (95%CI)	Wght
ITT population								
Corey-Bloom et al. (1998)[27]	464[a]	1.34	5.98	234	4.09	6.01	- (-3.694, -2.751 1.808)	26.5
Rosler et al. (1999){Rosler, 1999 2016 /id}	484[a]	0.56	7.22	238	1.34	6.69	- (-1.851, 0.281) 0.785	24.1
Feldman & Lane (2007)[25]	455[b]	0.50	7.25	220	2.80	7.20	- (-3.460, -2.298 1.137)	22.4
subtotal (Q=7.68 [p on 2 d.f.=0.022]; I^2=73.9%; τ^2=0.820)							**- (-3.148, -1.956 0.763)** p=0.001	**72.9**
LOCF analysis								
Winblad et al. (2007)[26]	763[c]	-0.94	6.37	281	1.00	6.80	- (-2.858, -1.943 1.029)	27.1
subtotal							**- (-2.858, -1.943 1.029)** p<0.001	**27.1**
Overall pooled estimate							**- (-2.770, -1.957 1.145)** p<0.001	

(Q=7.69 [p on 3 d.f.=0.053]; I^2=61.0%; τ^2=0.418)
Inter-stratum heterogeneity: p=0.921
Small-study effects: Egger's p=0.711



[a] 4mg/d and 12mg/d arms pooled

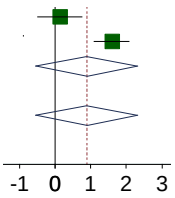
[b] bd and tid arms pooled

[c] 10cm^2 patch, 20cm^2 patch, and 12mg/d capsules arms pooled

FIGURE 29 *Random-effects meta-analysis: MMSE at 12–13wk (mean change from baseline) – rivastigmine (all dosages) v. placebo*

	Rivastigmine			Placebo				
	N	mean	SD	N	mean	SD	WMD (95%CI)	Wght
OC population								
Agid et al. (1998)[29]	214[a]	0.14	3.21	117	0.00	2.60	0.144 (-0.493, 0.782)	49.0
Mowla et al. (2007)[30]	34	1.10	1.40	32	-0.50	0.50	1.600 (1.099, 2.101)	51.0
subtotal (Q=12.37 [p on 1 d.f.<0.001]; I^2=91.9%; τ^2=0.974)							**0.886 (-0.540, 2.312)** p=0.223	**100.0**
Overall pooled estimate							**0.886 (-0.540, 2.312)** p=0.223	

(Q=12.37 [p on 1 d.f.<0.001]; I^2=91.9%; τ^2=0.974)
Small-study effects: not calculable

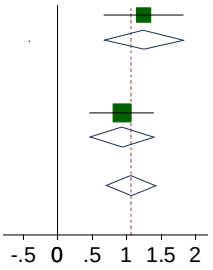


[a] 4mg/d and 6mg/d arms pooled

FIGURE 30 *Random-effects meta-analysis: MMSE at 24–26wk (mean change from baseline) – rivastigmine (all dosages) v. placebo*

	Rivastigmine			Placebo				
	N	mean	SD	N	mean	SD	WMD (95%CI)	Wght
ITT population								
Feldman & Lane (2007)[25]	454[a]	-0.15	3.60	220	-1.40	3.60	1.250 (0.670, 1.830)	39.8
subtotal							**1.250 (0.670, 1.830)**	**39.8**
							p<0.001	
LOCF analysis								
Winblad et al. (2007)[26]	768[b]	0.93	3.30	281	0.00	3.50	0.932 (0.461, 1.403)	60.2
subtotal							**0.932 (0.461, 1.403)**	**60.2**
							p<0.001	
Overall pooled estimate							**1.058 (0.693, 1.424)**	
							p<0.001	

(*Q*=0.7 [*p* on 1 d.f.=0.404]; I^2=0.0%; τ^2=0.000)
Inter-stratum heterogeneity: *p*=0.404
Small-study effects: not calculable



favours placebo ***favours rivastigmine***

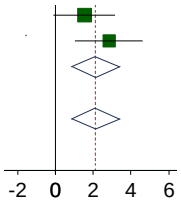
[a] bd and tid arms pooled

[b] 10cm^2 patch, 20cm^2 patch, and 12mg/d capsules arms pooled

FIGURE 31 *Random-effects meta-analysis: PDS at 24–26wk (mean change from baseline) – rivastigmine (all dosages) v. placebo*

	Rivastigmine			Placebo				
	N	mean	SD	N	mean	SD	WMD (95%CI)	Wght
ITT population								
Corey-Bloom et al. (1998)[27]	464[a]	-3.36	10.34	234	-4.90	10.30	1.537 (-0.084, 3.158)	54.7
Feldman & Lane (2007)[25]	452[b]	-2.05	11.20	221	-4.90	11.20	2.848 (1.046, 4.649)	45.3
subtotal (Q=1.12 [p on 1 d.f.=0.289]; I^2=11.0%; τ^2=0.094)							**2.131 (0.852, 3.409)**	**100.0**
							p=0.001	
Overall pooled estimate							**2.131 (0.852, 3.409)**	
(Q=1.12 [p on 1 d.f.=0.289]; I^2=11.0%; τ^2=0.094)							*p*=0.001	

Small-study effects: not calculable



favours placebo ***favours rivastigmine***

[a] 4mg/d and 12mg/d arms pooled

[b] bd and tid arms pooled

FIGURE 32 *Random-effects meta-analysis: CIBIC-plus at 26wk – rivastigmine (all dosages) v. placebo*

	Rivastigmine			Placebo				
	N	mean	SD	N	mean	SD	WMD (95%CI)	Wght
ITT population								
Corey-Bloom et al. (1998)[27]	464[a]	4.22	1.24	234	4.49	1.25	- 0.275 (-0.471, -0.079)	36.4
Rosler et al. (1999){Rosler, 1999 2016 /id}	452[a]	4.08	1.62	230	4.38	1.24	- 0.300 (-0.519, -0.081)	31.0
Feldman & Lane (2007)[25]	444[b]	4.00	1.30	216	4.50	1.30	- 0.500 (-0.711, -0.289)	32.6
subtotal (Q=2.69 [p on 2 d.f.=0.260]; I^2=25.7%; τ^2=0.004)							**- 0.356 (-0.496, -0.216)** p<0.001	**100.0**
Overall pooled estimate							**- 0.356 (-0.496, -0.216)** p<0.001	
(Q=2.69 [p on 2 d.f.=0.260]; I^2=25.7%; τ^2=0.004)								
Small-study effects: Egger's p=0.771								

-.8 -.6 -.4 -.2 0 .2

favours rivastigmine ***favours placebo***

[a] 4mg/d and 12mg/d arms pooled

[b] bd and tid arms pooled

FIGURE 33 *Random-effects meta-analysis: CIBIC-plus at 26wk – rivastigmine (12mg/d) v. placebo*

	Rivastigmine			Placebo				
	N	mean	SD	N	mean	SD	WMD (95%CI)	Wght
ITT population								
Corey-Bloom et al. (1998)[27]	231	4.20	1.24	234	4.49	1.25	- 0.290 (-0.516, -0.064)	34.2
Rosler et al. (1999){Rosler, 1999 2016 /id}	219	3.91	1.51	230	4.38	1.24	- 0.470 (-0.726, -0.214)	26.7
Feldman & Lane (2007)[25]	444[a]	4.00	1.30	216	4.50	1.30	- 0.500 (-0.711, -0.289)	39.2
subtotal (Q=1.96 [p on 2 d.f.=0.374]; I^2=0.0%; τ^2=0.000)							**- 0.420 (-0.553, -0.288)** p<0.001	**100.0**
Overall pooled estimate							**- 0.420 (-0.553, -0.288)** p<0.001	
(Q=1.96 [p on 2 d.f.=0.374]; I^2=0.0%; τ^2=0.000)								
Small-study effects: Egger's p=0.974								

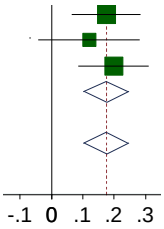
-.8 -.6 -.4 -.2 0 .2

favours rivastigmine ***favours placebo***

[a] bd and tid arms pooled

FIGURE 34 *Random-effects meta-analysis: GDS at 26wk (mean change from baseline) – rivastigmine (all dosages) v. placebo*

	Rivastigmine			Placebo				
	N	mean	SD	N	mean	SD	WMD (95%CI)	Wght
ITT population								
Corey-Bloom et al. (1998)[27]	464[a]	-0.15	0.70	234	-0.32	0.70	0.175 (0.065, 0.285)	41.2
Rosler et al. (1999){Rosler, 1999 2016 /id}	484[a]	-0.14	0.90	238	-0.26	1.10	0.120 (-0.042, 0.282)	19.2
Feldman & Lane (2007)[25]	456[b]	-0.10	0.70	222	-0.30	0.70	0.200 (0.087, 0.312)	39.7
subtotal (Q=0.63 [p on 2 d.f.=0.730]; I^2=0.0%; τ^2=0.000)							**0.174 (0.103, 0.245)**	**100.0**
							p<0.001	
Overall pooled estimate							**0.174 (0.103, 0.245)**	
(Q=0.63 [p on 2 d.f.=0.730]; I^2=0.0%; τ^2=0.000)							p<0.001	
Small-study effects: Egger's p=0.283								



[a] 4mg/d and 12mg/d arms pooled

[b] bd and tid arms pooled

Appendix 6: Data sets used in meta-analysis of pooled multiple outcome measures

Donepezil

TABLE 1 *Data included in random-effects meta-analysis of cognitive outcomes (multiple measures pooled using SMD) at 24–26wk: donepezil (all dosages) v. placebo*

Study	Outcome	Type	+/-	Donepezil			Placebo			SMD	(95%CI)
				N	mean	SD	N	mean	SD		
ITT population											
Mazza et al. (2006)[8]	MMSE	MC	+	25	1.20	12.25	26	-0.25	5.00	1.059	(0.445, 1.673)
	Syndrom Kurztest	MC	-	25	-3.30	2.55	26	0.90	1.30		
	CGI: item 2	MC	-	25	-0.90	1.02	26	0.15	0.34		
LOCF analysis											
Rogers et al. (1998)[7]	MMSE	MC	+	303[a]	0.31	3.57	154	-0.97	3.47	0.398	(0.202, 0.594)
	ADAS-cog	MC	-	302[a]	-0.86	6.27	153	1.82	6.06		
Burns et al. (1999)[5]	ADAS-cog	MC	-	544[a]	-0.50	5.82	274	1.70	4.97	0.397	(0.250, 0.543)
Homma et al. (2000)[6]	MFIS	MC	+	116	-0.72	5.71	112	1.84	7.30	0.150	(-0.112, 0.412)
	ADAS-cog	MC	-	126	-2.43	5.05	113	0.11	0.52		
Gauthier et al. (2002)[15]	SIB	MC	+	98	1.58	11.14	104	-2.85	11.22	0.445	(0.161, 0.728)
	MMSE	MC	+	91	1.50	4.29	100	-0.56	4.00		
Seltzer et al. (2004)[16]	MMSE	MC	+	91	1.35	3.34	55	0.10	3.15	0.427	(0.089, 0.766)
	ADAS-cog/13	MC	-	91	-1.65	4.77	55	0.58	4.64		
OC population											
Mohs et al. (2001)[13]	MMSE	MC	+	111	1.80	4.21	96	0.45	4.29	0.318	(0.043, 0.593)
Winblad et al. (2001)[14]	MMSE	MC	+	121	0.40	3.74	120	-1.09	3.72	0.399	(0.144, 0.654)
Moraes et al. (2006)[31]	ADAS-cog	A	-	17	28.30	12.30	18	42.80	18.70	0.911	(0.212, 1.609)

[a] pooled 5mg/d and 10mg/d arms

TABLE 2 *Data included in random-effects meta-analysis of functional outcomes (multiple measures pooled using SMD) at 24wk: donepezil (all dosages) v. placebo*

Study	Outcome	+/-	Galantamine			Placebo			SMD	(95%CI)
			N	mean[a]	SD	N	mean[a]	SD		
LOCF analysis										
Burns et al. (1999)[5]	IDDD - complex tasks	-	544[b]	69.90[c]	6.60	274	71.10[c]	6.62	0.182	(0.036, 0.327)
Homma et al. (2000)[6]	CMCS	-	103	1.03	6.70	99	3.45	7.06	0.352	(0.074, 0.630)
Gauthier et al. (2002)[15]	DAD	+	92	0.00	15.35	101	-9.25	15.58	0.598	(0.309, 0.887)
OC population										
Mohs et al. (2001)[13]	ADFACS	-	97	-0.30	4.19	94	0.90	4.00	0.293	(0.008, 0.578)
Winblad et al. (2001)[14]	Caregiver time (m/d)	-	69	-11.40	161.98	74	10.80	163.44	0.136	(-0.192, 0.465)

[a] mean change from baseline, except where noted

[b] pooled 5mg/d and 10mg/d arms

[c] absolute value

TABLE 3 *Data included in random-effects meta-analysis of global outcomes (multiple measures pooled using SMD) at 24wk: donepezil (all dosages) v. placebo*

Study	Outcome	+/-	Donepezil			Placebo			SMD	(95%CI)
			N	mean[a]	SD	N	mean[a]	SD		
LOCF analysis										
Rogers et al. (1998)[7]	CDR-SB	-	305[b]	-0.01	1.73	153	0.58	1.73	0.375	(0.178, 0.571)
	CIBIC-plus	-	298[b]	4.11[c]	0.98	152	4.51[c]	0.99		
Burns et al. (1999)[5]	CDR-SB	-	544[b]	0.00	1.81	274	0.37	0.99	0.288	(0.142, 0.434)
	CIBIC-plus	-	544[b]	4.18[c]	0.99	274	4.52[c]	0.99		
Homma et al. (2000)[6]	ADCS – CGIC	-	133	3.58[c]	1.08	128	4.40[c]	1.39	0.626	(0.370, 0.883)
	CDR-SB	-	116	-0.10	1.29	112	0.75	1.59		
Gauthier et al. (2002)[15]	CIBIC-plus	-	98	4.00[c]	1.19	105	4.55[c]	1.08	0.482	(0.202, 0.761)
OC population										
Winblad et al. (2001)[14]	Gottfries-Bråne-Steen scale	-	122	1.70	13.25	121	5.00	15.40	0.236	(-0.017, 0.488)
	Global deterioration scale	-	122	0.01	0.66	121	0.17	0.66		
Gauthier et al. (2002)[15]	CIBIC-plus	-	83	3.95[c]	1.14	93	4.40[c]	1.25	0.375	(0.076, 0.673)

[a] mean change from baseline except where indicated

[b] pooled 5mg/d and 10mg/d arms

[c] absolute value (note, however, that CIBIC-plus is by definition a measure of change)

Galantamine

TABLE 4 *Data included in random-effects meta-analysis of functional outcomes (multiple measures pooled using SMD) at 21–26wk: galantamine (all dosages) v. placebo*

Study	Outcome	+/-	Galantamine			Placebo			SMD	(95%CI)
			N	mean[a]	SD	N	mean[a]	SD		
LOCF analysis										
Tariot et al. (2000)[23]	ADCS-ADL	+	637[b]	-1.52	9.47	262	-3.80	9.71	0.239	(0.094, 0.383)
Wilcock et al. (2000)[20]	DAD	+	426[c]	-2.85	15.26	210	-6.00	15.65	0.205	(0.039, 0.370)
Bullock et al. (2004)[24]	DAD	+	188	-1.00	15.77	97	-6.00	14.48	0.326	(0.079, 0.572)
Brodaty et al. (2005)[22]	ADCS-ADL	+	487[d]	-0.50	5.36	258	-2.70	8.99	0.322	(0.170, 0.474)

[a] mean change from baseline

[b] 8mg/d, 16mg/d, and 24mg/d arms pooled

[c] 24mg/d and 32mg/d arms pooled

[d] once daily prolonged release formulation and twice daily standard formulation pooled

Rivastigmine

TABLE 5 *Data included in random-effects meta-analysis of cognitive outcomes (multiple measures pooled using SMD) at 24–26wk: rivastigmine (all dosages) v. placebo*

Study	Outcome	+/-	Rivastigmine			Placebo			SMD	(95%CI)
			N	mean [a]	SD	N	mean [a]	SD		
ITT population										
Corey-Bloom et al. (1998)[27]	ADAS-cog	-	464 [b]	1.34	5.98	234	4.09	6.01	0.459	(0.300, 0.618)
Rosler et al. (1999){Rosler, 1999 2016 /id}	ADAS-cog	-	484 [b]	0.56	7.22	238	1.34	6.69	0.111	(-0.044, 0.267)
Feldman & Lane (2007)[25]	MMSE	+	454 [c]	-0.15	3.60	220	-1.40	3.60	0.328	(0.166, 0.490)
	ADAS-cog	-	455 [c]	0.50	7.25	220	2.80	7.20		
	ADAS-cogA	-	455 [c]	0.70	7.85	220	3.20	7.80		
LOCF analysis										
Winblad et al. (2007)[26]	Ten-point clock	+	742 [d]	0.20	3.14	269	-0.10	3.20	0.242	(0.103, 0.381)
	ADAS-cog	-	763 [d]	-0.94	6.37	281	1.00	6.80		
	MMSE	+	768 [d]	0.93	3.30	281	0.00	3.50		
	Trail-making test	-	719 [d]	-9.55	59.25	258	7.70	56.60		

[a] mean change from baseline

[b] 4mg/d and 12mg/d arms pooled

[c] bd and tid arms pooled

[d] $10cm^2$ patch, $20cm^2$ patch, and 12mg/d capsules arms pooled

TABLE 6 *Data included in random-effects meta-analysis of functional outcomes (multiple measures pooled using SMD) at 24–26wk: rivastigmine (all dosages) v. placebo*

Study	Outcome	+/-	Rivastigmine			Placebo			SMD	(95%CI)
			N	mean[a]	SD	N	mean[a]	SD		
ITT population										
Corey-Bloom et al. (1998)[27]	PDS	+	464[b]	-3.36	10.34	234	-4.90	10.30	0.149	(-0.008, 0.306)
Feldman & Lane (2007)[25]	PDS	+	452[c]	-2.05	11.20	221	-4.90	11.20	0.254	(0.093, 0.416)
LOCF analysis										
Winblad et al. (2007)[26]	ADCS-ADL	+	764[d]	-0.20	10.15	281	-2.30	9.40	0.211	(0.074, 0.348)

[a] mean change from baseline

[b] 4mg/d and 12mg/d arms pooled

[c] bd and tid arms pooled

[d] $10cm^2$ patch, $20cm^2$ patch, and 12mg/d capsules arms pooled

TABLE 7 *Data included in random-effects meta-analysis of global outcomes (multiple measures pooled using SMD) at 24–26wk: rivastigmine (all dosages) v. placebo*

Study	Outcome	+/-	Rivastigmine			Placebo			SMD	(95%CI)
			N	mean [a]	SD	N	mean [a]	SD		
ITT population										
Corey-Bloom et al. (1998)[27]	GDS	+	464 [b]	-0.15	0.70	234	-0.32	0.70	0.235	(0.078, 0.393)
	CIBIC-plus score	-	464 [b]	4.22[c]	1.24	234	4.49[c]	1.25		
Rosler et al. (1999){Rosler, 1999 2016 /id}	GDS	+	484 [b]	-0.14	0.90	238	-0.26	1.10	0.161	(0.003, 0.318)
	CIBIC-plus score	-	452 [b]	4.08[c]	1.62	230	4.38[c]	1.24		
Feldman & Lane (2007)[25]	GDS	+	456 [d]	-0.10	0.70	222	-0.30	0.70	0.334	(0.171, 0.496)
	CIBIC-plus score	-	444 [d]	4.00[c]	1.30	216	4.50[c]	1.30		
LOCF analysis										
Winblad et al. (2007)[26]	ADCS-CGIC	-	761 [e]	3.93[c]	1.27	278	4.20[c]	1.30	0.208	(0.071, 0.346)

[a] mean change from baseline except where noted

[b] 4mg/d and 12mg/d arms pooled

[c] absolute value (note, however, that CIBIC plus is by definition a measure of change)

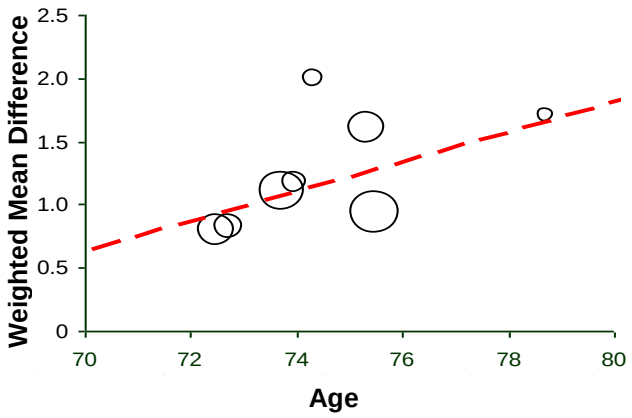
[d] bd and tid arms pooled

[e] 10cm2 patch, 20cm2 patch, and 12mg/d capsules arms pooled

Appendix 7: Meta-regression Figures

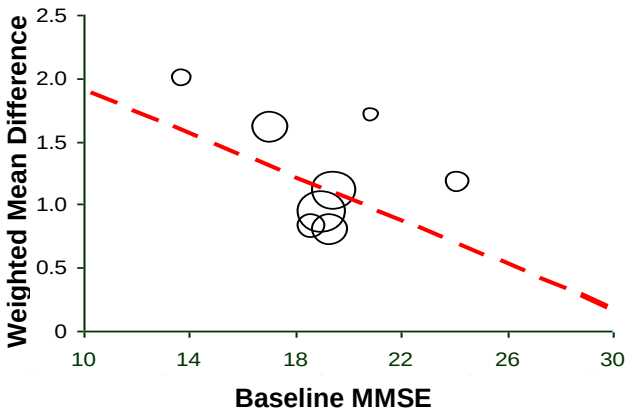
Donepezil v. Placebo – cognitive

FIGURE 35 *MMSE at 12wk (mean change from baseline) – donepezil (all dosages) v. placebo: association of treatment effect with average age of population*



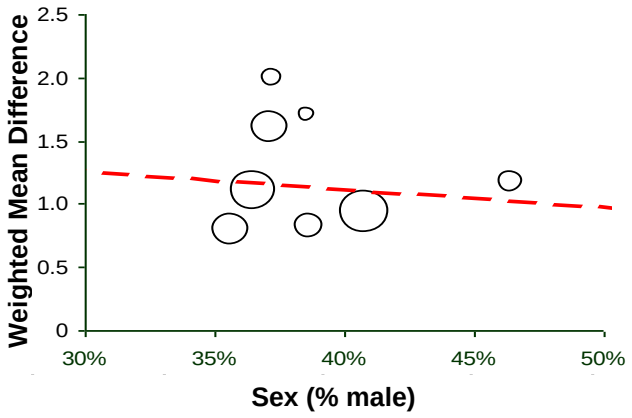
area of circles is proportional to weight of each study in random-effects meta-analysis; dashed line shows univariate metaregression estimate (α=-7.447; β=0.115; *p*=0.253)

FIGURE 36 *MMSE at 12wk (mean change from baseline) – donepezil (all dosages) v. placebo: association of treatment effect with average baseline MMSE score of population*



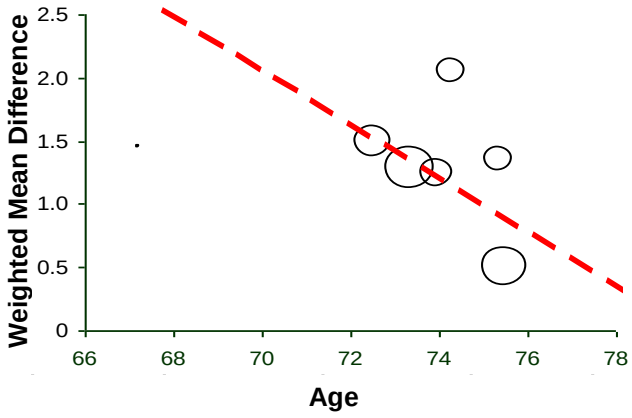
area of circles is proportional to weight of each study in random-effects meta-analysis; dashed line shows univariate metaregression estimate (α=2.743; β=-0.085; *p*=0.227)

FIGURE 37 *MMSE at 12wk (mean change from baseline) – donepezil (all dosages) v. placebo: association of treatment effect with sex of population*



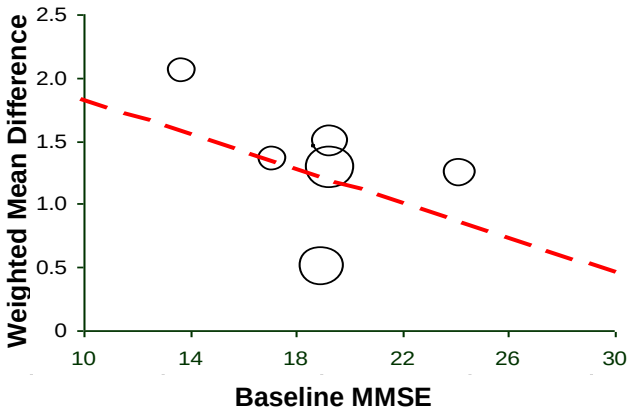
area of circles is proportional to weight of each study in random-effects meta-analysis; dashed line shows univariate metaregression estimate (α=1.701; β=-1.463; p=0.771)

FIGURE 38 *MMSE at 24wk (mean change from baseline) – donepezil (all dosages) v. placebo: association of treatment effect with average age of population*



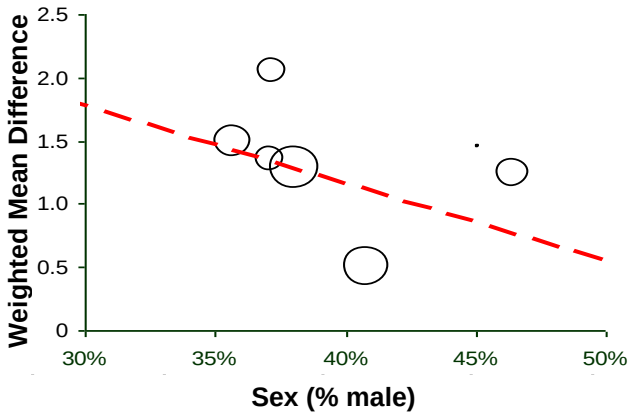
area of circles is proportional to weight of each study in random-effects meta-analysis; dashed line shows univariate metaregression estimate (α=19.302; β=-0.244; *p*=0.157)

FIGURE 39 *MMSE at 24wk (mean change from baseline) – donepezil (all dosages) v. placebo: association of treatment effect with average baseline MMSE score of population*



area of circles is proportional to weight of each study in random-effects meta-analysis; dashed line shows univariate metaregression estimate (α=2.489; β=-0.067; *p*=0.373)

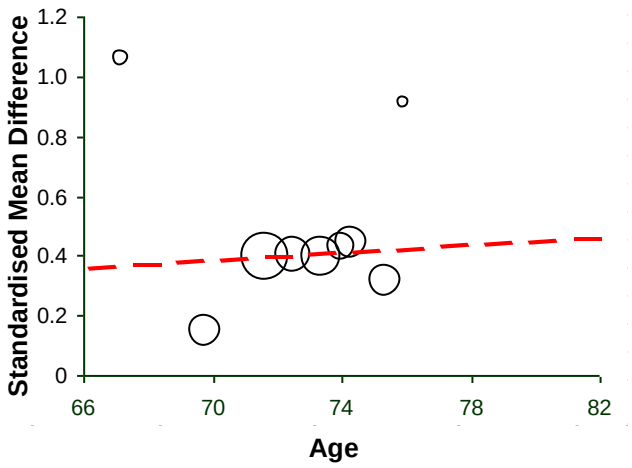
FIGURE 40 *MMSE at 12wk (mean change from baseline) – donepezil (all dosages) v. placebo: association of treatment effect with sex of population*



area of circles is proportional to weight of each study in random-effects meta-analysis; dashed line shows univariate metaregression estimate (α=3.582; β=-6.066; *p*=0.308)

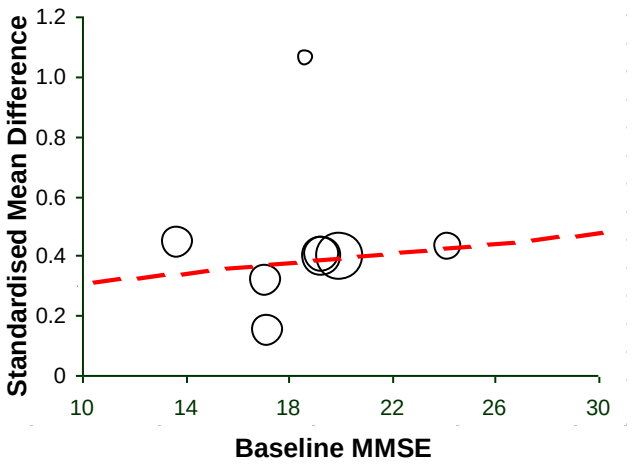
Pooled multiple outcomes

FIGURE 41 *Cognitive outcomes (SMD) at 24–26wk – donepezil (all dosages) v. placebo: association of standardised treatment effect with average age of population*



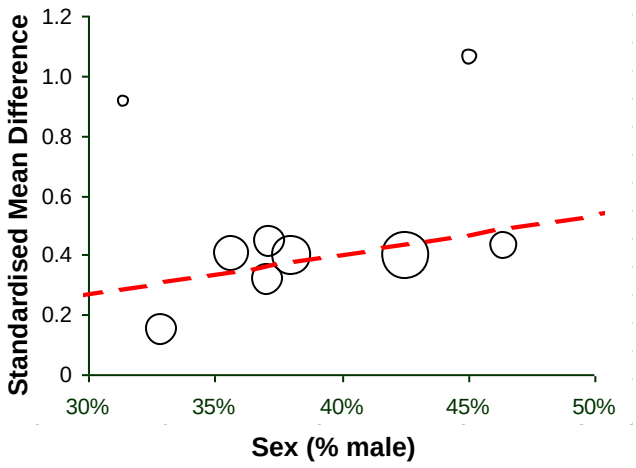
area of circles is proportional to weight of each study in random-effects meta-analysis; dashed line shows univariate metaregression estimate (α=-0.073; β=0.006; *p*=0.796)

FIGURE 42 *Cognitive outcomes (SMD) at 24–26wk – donepezil (all dosages) v. placebo: association of standardised treatment effect with average baseline MMSE score of population*



area of circles is proportional to weight of each study in random-effects meta-analysis; dashed line shows univariate metaregression estimate (α=0.229; β=0.008; *p*=0.668)

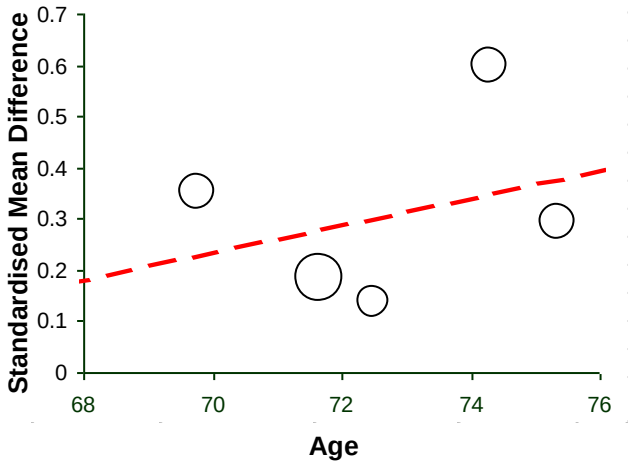
FIGURE 43 *Cognitive outcomes (SMD) at 24–26wk – donepezil (all dosages) v. placebo: association of standardised treatment effect with sex of population*



area of circles is proportional to weight of each study in random-effects meta-analysis; dashed line shows univariate metaregression estimate (α=-0.121; β=1.307; *p*=0.240)

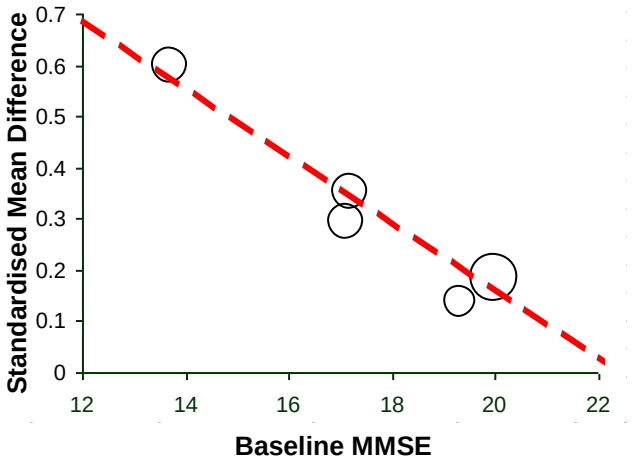
Donepezil v. Placebo – functional

FIGURE 44 *Functional outcomes at 24wk – donepezil (all dosages) v. placebo: association of standardised treatment effect with average age of population*



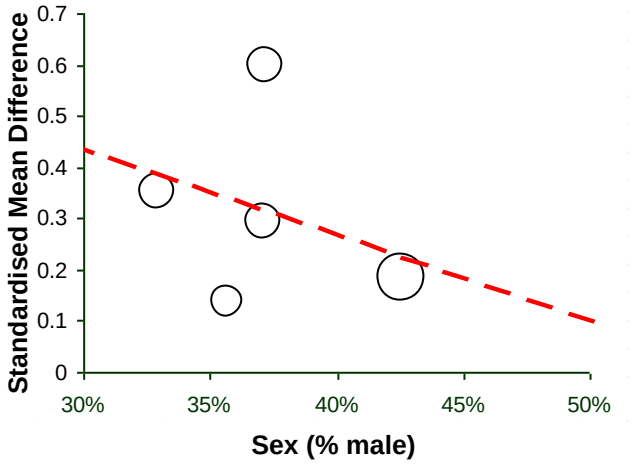
area of circles is proportional to weight of each study in random-effects meta-analysis; dashed line shows univariate metaregression estimate (α=-1.593; β=0.026; p=0.552)

FIGURE 45 *Functional outcomes at 24wk – donepezil (all dosages) v. placebo: association of standardised treatment effect with average baseline MMSE score of population*



area of circles is proportional to weight of each study in random-effects meta-analysis; dashed line shows univariate metaregression estimate (α=1.456; β=-0.065; p=0.009)

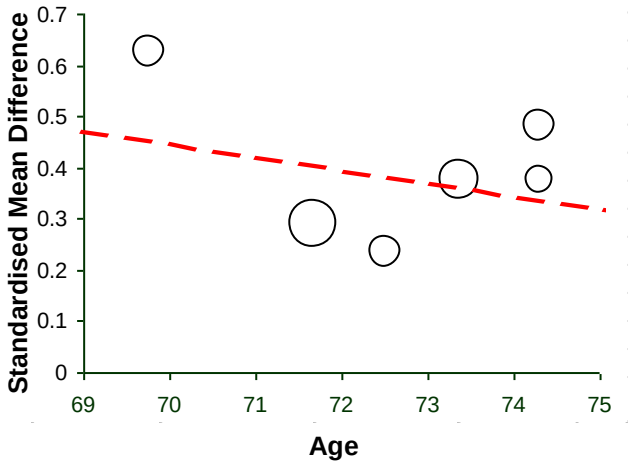
FIGURE 46 *Functional outcomes at 24wk – donepezil (all dosages) v. placebo: association of standardised treatment effect with sex of population*



area of circles is proportional to weight of each study in random-effects meta-analysis; dashed line shows univariate metaregression estimate (α=0.932; β=-1.673; *p*=0.435)

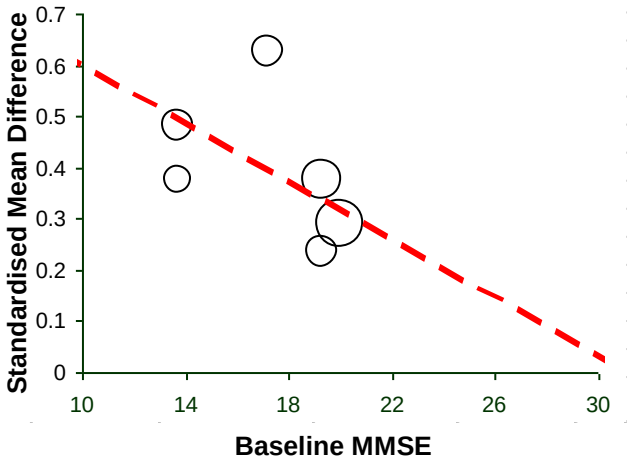
Donepezil v. Placebo – global

FIGURE 47 *Global outcomes (SMD) at 24wk – donepezil (all dosages) v. placebo: association of standardised treatment effect with average age of population*



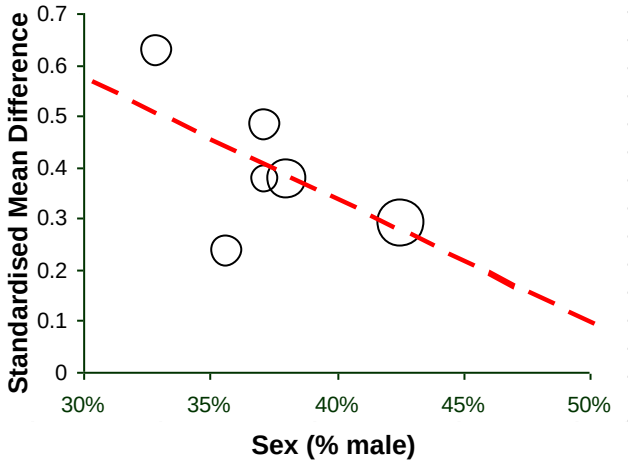
area of circles is proportional to weight of each study in random-effects meta-analysis; dashed line shows univariate metaregression estimate (α=2.191; β=-0.025; *p*=0.536)

FIGURE 48 *Global outcomes (SMD) at 24wk – donepezil (all dosages) v. placebo: association of standardised treatment effect with average baseline MMSE score of population*



area of circles is proportional to weight of each study in random-effects meta-analysis; dashed line shows univariate metaregression estimate (α=0.876; β=-0.028; *p*=0.147)

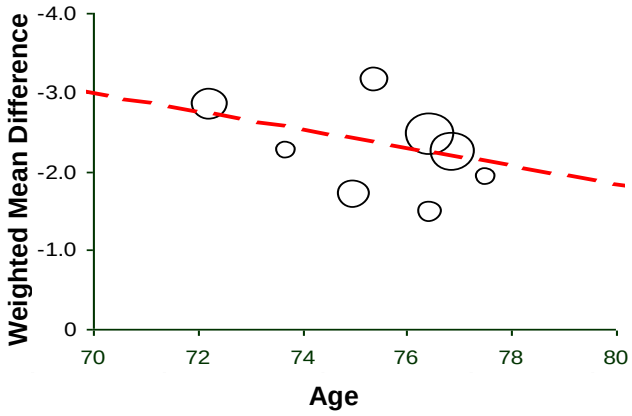
FIGURE 49 *Global outcomes (SMD) at 24wk – donepezil (all dosages) v. placebo: association of standardised treatment effect with sex of population*



area of circles is proportional to weight of each study in random-effects meta-analysis; dashed line shows univariate metaregression estimate (α=1.277; β=-2.357; *p*=0.082)

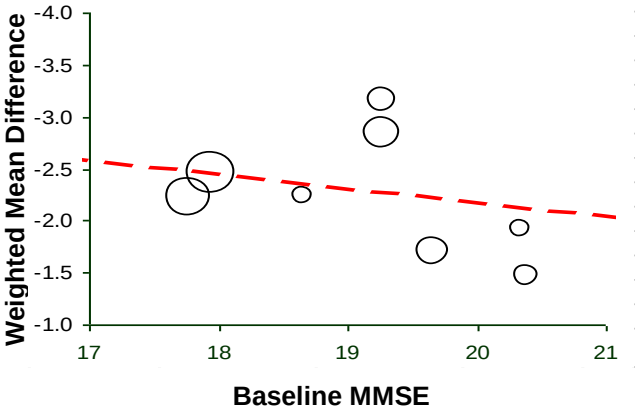
Galantamine v. placebo-cognitive

FIGURE 50 *ADAS-cog at 12-16wk (mean change from baseline) – galantamine (all dosages) v. placebo: association of treatment effect with average age of population*



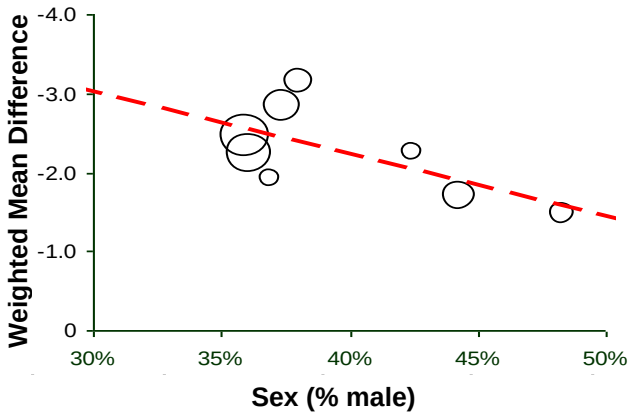
area of circles is proportional to weight of each study in random-effects meta-analysis; dashed line shows univariate metaregression estimate (α=-10.938; β=0.114; *p*=0.335)

FIGURE 51 *ADAS-cog at 12.16wk (mean change from baseline) – galantamine (all dosages) v. placebo: association of treatment effect with average baseline MMSE score of population*



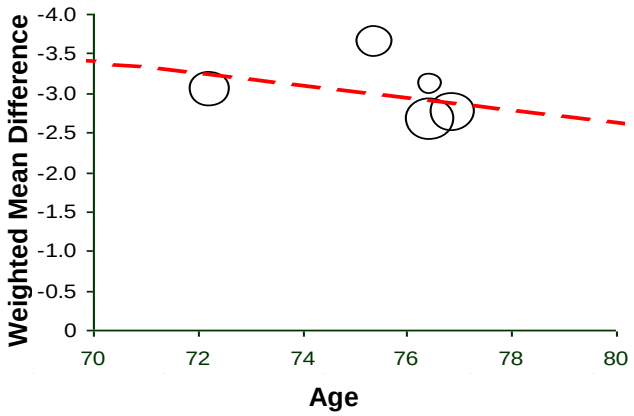
area of circles is proportional to weight of each study in random-effects meta-analysis; dashed line shows univariate metaregression estimate (α=-4.851; β=0.134; *p*=0.529)

FIGURE 52 *ADAS-cog at 12-16wk (mean change from baseline) – galantamine (all dosages) v. placebo: association of treatment effect with sex of population*



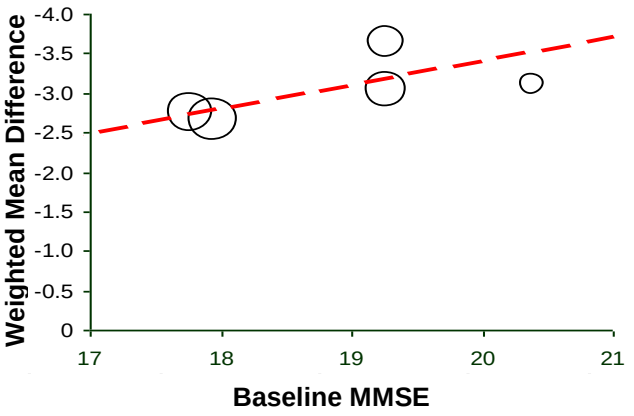
area of circles is proportional to weight of each study in random-effects meta-analysis; dashed line shows univariate metaregression estimate (α=-5.372; β=7.845; *p*=0.120)

FIGURE 53 *ADAS-cog at 21–26wk (mean change from baseline) – galantamine (all dosages) v. placebo: association of treatment effect with average age of population*



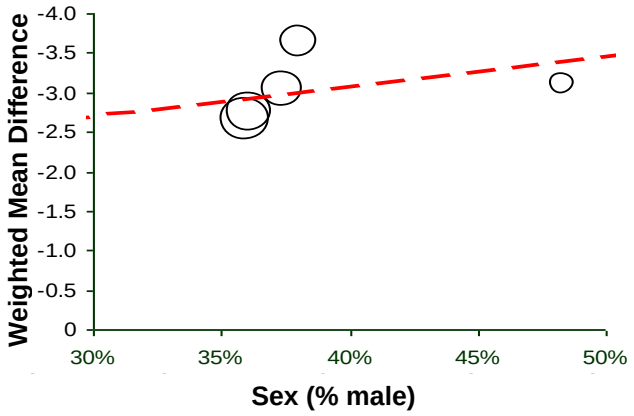
area of circles is proportional to weight of each study in random-effects meta-analysis; dashed line shows univariate metaregression estimate (α=-8.677; β=0.076; *p*=0.561)

FIGURE 54 *ADAS-cog at 21–26wk (mean change from baseline) – galantamine (all dosages) v. placebo: association of treatment effect with average baseline MMSE score of population*



area of circles is proportional to weight of each study in random-effects meta-analysis; dashed line shows univariate metaregression estimate (α=2.623; β=-0.300; *p*=0.251)

FIGURE 55 *ADAS-cog at 21–26wk (mean change from baseline) – galantamine (all dosages) v. placebo: association of treatment effect with sex of population*



area of circles is proportional to weight of each study in random-effects meta-analysis; dashed line shows univariate metaregression estimate (α=-1.562; β=-3.725; *p*=0.581)

Appendix 8: WinBUGS code for mixed treatment comparisons

```
model {
for (i in 1:N)  {
         var[i] <- (MDSE[i] * MDSE[i])
        prec[i] <- 1/var[i]
      MDdata[i] ~  dnorm(MDdist[i], prec[i])
      MDdist[i] ~  dnorm(MDmean[i], tau)
      MDmean[i] <- effect[Arm1Drug[i]] - effect[Arm2Drug[i]]
         dev[i] <- (MDdata[i]-MDdist[i]) * (MDdata[i]-MDdist[i]) / var[i]
       dummy[i] <- RefID[i]}

for (k in 2:NT) {
           effect[k] ~ dnorm(0, 0.000001)}

effect[1] <- 0
       sd ~  dunif(0,2)
      tau <- 1/pow(sd,2)
   resdev <- sum(dev[])

for (k in 1:NT) {
          rk[k] <- rank(effect[], k)
        best[k] <- equals(rk[k], (step(blnHiGood)*NT)+(step(-blnHiGood)*1))}

for (k in 2:NT) {
           p[k] <- abs(step(blnHiGood) - step(-effect[k]))}
}

# N = number of studies; NT = number of treatments
# trial data - MDdata and MDSE - read from rectangular vectors
# blnHiGood is a Boolean variable indicating whether, for the outcome in question,
higher numbers represent an improvement or a deterioration
# RefID is not used in the model, but is included to assist checking of data files
```

Appendix 9: Mixed treatment comparisons performed in specified measurement populations

Cognitive

ADAS-cog

TABLE 8 *Mixed treatment comparison – ADAS-cog at 12–16wk (mean change from baseline; LOCF data only): input data*

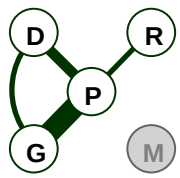
Evidence Network	Comparison	Study	WMD	(95%CI)
	Donepezil v. Placebo	Rogers et al. (1998)[4]	-2.799	(-3.831, -1.767)
		Nunez et al. (2003)[9,10]	-0.050	(-1.782, 1.682)
	Galantamine v. Placebo	Rockwood et al. (2001)[17]	-1.700	(-2.794, -0.606)
		Wilkinson & Murray (2001)[18]	-2.246	(-3.872, -0.620)
		Brodaty et al. (2005)[22]	-2.453	(-3.192, -1.713)
		Rockwood et al. (2006)[21]	-1.925	(-3.816, -0.034)
	Rivastigmine v. Placebo	Jones et al. (2004)[32]	-2.225	(-4.131, -0.319)
	Donepezil v. Galantamine	Winblad et al. (2007)[26]	-0.911	(-1.817, -0.006)

TABLE 9 *Mixed treatment comparison – ADAS-cog at 12–16wk (mean change from baseline; LOCF data only): results*

Technology	v. Placebo			Prob. most effective
	Effect	(95%CI)	Prob. more effective than placebo	
Placebo	-	-	-	0.000
Donepezil	-2.350	(-3.887, -0.684)	0.995	0.681
Galantamine	-1.840	(-2.951, -0.489)	0.995	0.212
Rivastigmine	-0.901	(-3.390, 1.573)	0.814	0.107
Memantine	-	-	-	-

TABLE 10 *Mixed treatment comparison – ADAS-cog at 12–26wk (mean change from baseline; classical ITT or LOCF data): input data*

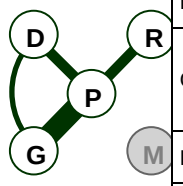
Evidence Network	Comparison	Study	WMD	(95%CI)
	Donepezil v. Placebo	Rogers et al. (1998)[4]	-2.799	(-3.831, -1.767)
		Nunez et al. (2003)[9,10]	-0.050	(-1.782, 1.682)
	Galantamine v. Placebo	Rockwood et al. (2001)[17]	-1.700	(-2.794, -0.606)
		Wilkinson & Murray (2001)[18]	-2.246	(-3.872, -0.620)
		Brodaty et al. (2005)[22]	-2.453	(-3.192, -1.713)
		Rockwood et al. (2006)[21]	-1.925	(-3.816, -0.034)
	Rivastigmine v. Placebo	Feldman & Lane (2007)[25]	-2.249	(-3.226, -1.271)
		Winblad et al. (2007)[26]	-0.911	(-1.817, -0.006)
	Donepezil v. Galantamine	Jones et al. (2004)[32]	-2.225	(-4.131, -0.319)

TABLE 11 *Mixed treatment comparison – ADAS-cog at 12–26wk (mean change from baseline; classical ITT or LOCF data): results*

Technology	v. placebo			Prob. most effective
	Effect	(95%CI)	Prob. more effective than placebo	
Placebo	-	-	-	0.000
Donepezil	-2.334	(-3.907, -0.714)	0.996	0.630
Galantamine	-1.833	(-2.980, -0.540)	0.996	0.190
Rivastigmine	-1.567	(-3.290, 0.133)	0.968	0.180
Memantine	-	-	-	-

TABLE 12 *Mixed treatment comparison – ADAS-cog at 12–16wk (mean change from baseline; OC populations only): input data*

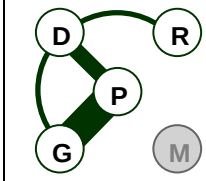
Evidence Network	Comparison	Study	WMD	(95%CI)
	Donepezil v. Placebo	Burns et al. (1999)[5]	-2.151	(-2.871, -1.430)
		Homma et al. (2000)[6]	-2.175	(-3.527, -0.823)
		Nunez et al. (2003)[9,10]	-0.570	(-2.497, 1.357)
	Galantamine v. Placebo	Raskind et al. (2000)[19]	-3.158	(-4.371, -1.946)
		Tariot et al. (2000)[23]	-2.225	(-3.042, -1.408)
		Wilcock et al. (2000)[20]	-2.848	(-3.829, -1.867)
		Rockwood et al. (2001)[17]	-1.900	(-3.037, -0.763)
		Bullock et al. (2004)[24]	-1.475	(-2.933, -0.017)
		Brodaty et al. (2005)[22]	-2.400	(-3.148, -1.652)
	Donepezil v. Rivastigmine	Wilkinson et al. (2002)[33]	0.150	(-1.561, 1.861)
	Donepezil v. Galantamine	Jones et al. (2004)[32]	-2.550	(-4.490, -0.610)

TABLE 13 *Mixed treatment comparison – ADAS-cog at 12–16wk (mean change from baseline; OC populations only): results*

Technology	v. Placebo			Prob. most effective
	Effect	(95%CI)	Prob. more effective than placebo	
Placebo	-	-	-	0.000
Donepezil	-2.287	(-3.306, -1.344)	1.000	0.251
Galantamine	-2.208	(-2.829, -1.425)	1.000	0.252
Rivastigmine	-2.433	(-4.851, -0.079)	0.978	0.497
Memantine	-	-	-	-

TABLE 14 *Mixed treatment comparison – ADAS-cog at 21–16wk (mean change from baseline; LOCF data only): input data*

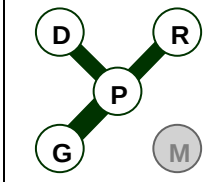
Evidence Network	Comparison	Study	WMD	(95%CI)
	Donepezil v. Placebo	Rogers et al. (1998)[7]	-2.684	(-3.876, -1.491)
		Burns et al. (1999)[5]	-2.203	(-2.968, -1.438)
		Homma et al. (2000)[6]	-2.540	(-3.427, -1.653)
	Galantamine v. Placebo	Raskind et al. (2000)[19]	-3.653	(-4.696, -2.611)
		Tariot et al. (2000)[23]	-2.741	(-3.633, -1.850)
		Wilcock et al. (2000)[20]	-3.049	(-4.030, -2.068)
		Brodaty et al. (2005)[22]	-2.651	(-3.449, -1.854)
	Rivastigmine v. Placebo	Rosler et al. (1999){Rosler, 1999 2016 /id}	-1.179	(-2.310, -0.048)
		Feldman & Lane (2007)[25]	-2.668	(-3.810, -1.527)
		Winblad et al. (2007)[26]	-1.943	(-2.858, -1.029)

TABLE 15 *Mixed treatment comparison – ADAS-cog at 21–16wk (mean change from baseline; LOCF data only): results*

Technology	v. Placebo			Prob. most effective
	Effect	(95%CI)	Prob. more effective than placebo	
Placebo	-	-	-	0.000
Donepezil	-2.430	(-3.134, -1.739)	1.000	0.106
Galantamine	-2.974	(-3.593, -2.371)	1.000	0.882
Rivastigmine	-1.929	(-2.678, -1.177)	1.000	0.012
Memantine	-	-	-	-

TABLE 16 *Mixed treatment comparison – ADAS-cog at 21–16wk (mean change from baseline; classical ITT + LOCF data): input data*

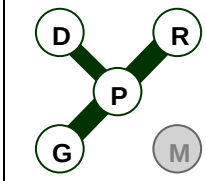
Evidence Network	Comparison	Study	WMD	(95%CI)
	Donepezil v. Placebo	Rogers et al. (1998)[7]	-2.684	(-3.876, -1.491)
		Burns et al. (1999)[5]	-2.203	(-2.968, -1.438)
		Homma et al. (2000)[6]	-2.540	(-3.427, -1.653)
	Galantamine v. Placebo	Raskind et al. (2000)[19]	-3.653	(-4.696, -2.611)
		Tariot et al. (2000)[23]	-2.741	(-3.633, -1.850)
		Wilcock et al. (2000)[20]	-3.049	(-4.030, -2.068)
		Brodaty et al. (2005)[22]	-2.651	(-3.449, -1.854)
	Rivastigmine v. Placebo	Corey-Bloom et al. (1998)[27]	-2.751	(-3.694, -1.808)
		Rosler et al. (1999){Rosler, 1999 2016 /id}	-0.785	(-1.851, 0.281)
		Feldman & Lane (2007)[25]	-2.298	(-3.460, -1.137)
		Winblad et al. (2007)[26]	-1.943	(-2.858, -1.029)

TABLE 17 *Mixed treatment comparison – ADAS-cog at 21–16wk (mean change from baseline; classical ITT + LOCF data): results*

Technology	v. Placebo			Prob. most effective
	Effect	(95%CI)	Prob. more effective than placebo	
Placebo	-	-	-	0.000
Donepezil	-2.427	(-3.213, -1.686)	1.000	0.120
Galantamine	-2.972	(-3.648, -2.327)	1.000	0.867
Rivastigmine	-1.971	(-2.657, -1.271)	1.000	0.012
Memantine	-	-	-	-

TABLE 18 *Mixed treatment comparison – ADAS-cog at 21–16wk (mean change from baseline; OC populations only): input data*

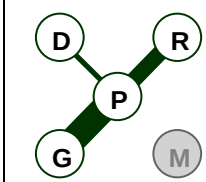
Evidence Network	Comparison	Study	WMD	(95%CI)
	Donepezil v. Placebo	Burns et al. (1999)[5]	-2.003	(-2.811, -1.195)
	Galantamine v. Placebo	Raskind et al. (2000)[19]	-3.853	(-5.129, -2.577)
		Tariot et al. (2000)[23]	-3.111	(-4.101, -2.121)
		Wilcock et al. (2000)[20]	-3.594	(-4.679, -2.508)
		Bullock et al. (2004)[24]	-3.100	(-4.620, -1.580)
		Brodaty et al. (2005)[22]	-2.894	(-3.775, -2.014)
	Rivastigmine v. Placebo	Corey-Bloom et al. (1998)[27]	-3.189	(-4.280, -2.098)
		Rosler et al. (1999){Rosler, 1999 2016 /id}	-1.224	(-2.527, 0.079)
		Feldman & Lane (2007)[25]	-2.118	(-3.338, -0.898)

TABLE 19 *Mixed treatment comparison – ADAS-cog at 21–16wk (mean change from baseline; OC populations only): results*

Technology	v. Placebo			Prob. most effective
	Effect	(95%CI)	Prob. more effective than placebo	
Placebo	-	-	-	0.000
Donepezil	-2.002	(-3.502, -0.518)	0.991	0.048
Galantamine	-3.267	(-4.027, -2.546)	1.000	0.913
Rivastigmine	-2.267	(-3.221, -1.245)	1.000	0.039
Memantine	-	-	-	-

MMSE

TABLE 20 *Mixed treatment comparison – MMSE at 12wk (mean change from baseline; LOCF data only): input data*

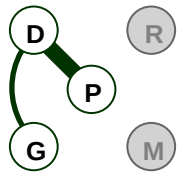
Evidence Network	Comparison	Study	WMD	(95%CI)
	Donepezil v. Placebo	Rogers et al. (1998)[4]	1.110	(0.514, 1.706)
		Nunez et al. (2003)[9;10]	0.830	(-0.071, 1.731)
		Holmes et al. (2004)[32]	1.700	(0.169, 3.231)
	Donepezil v. Galantamine	Jones et al. (2004)[32]	0.888	(0.004, 1.771)

TABLE 21 *Mixed treatment comparison – MMSE at 12wk (mean change from baseline; LOCF data only): results*

Technology	v. Placebo			Prob. most effective
	Effect	(95%CI)	Prob. more effective than placebo	
Placebo	-	-	-	0.017
Donepezil	1.115	(0.060, 2.286)	0.979	0.866
Galantamine	0.236	(-1.911, 2.466)	0.618	0.117
Rivastigmine	-	-	-	-
Memantine	-	-	-	-

TABLE 22 *Mixed treatment comparison – MMSE at 12wk (mean change from baseline; classical ITT or LOCF data): input data*

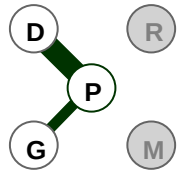
Evidence Network	Comparison	Study	WMD	(95%CI)
	Donepezil v. Placebo	Rogers et al. (1998)[4]	1.110	(0.514, 1.706)
		Nunez et al. (2003)[9;10]	0.830	(-0.071, 1.731)
		AD2000 (2004)[11]	0.930	(0.389, 1.471)
		Holmes et al. (2004)[12]	1.700	(0.169, 3.231)
	Donepezil v. Galantamine	Jones et al. (2004)[32]	0.888	(0.004, 1.771)

TABLE 23 *Mixed treatment comparison – MMSE at 12wk (mean change from baseline; classical ITT or LOCF data): results*

Technology	v. Placebo			Prob. most effective
	Effect	(95%CI)	Prob. more effective than placebo	
Placebo	-	-	-	0.005
Donepezil	1.038	(0.394, 1.775)	0.994	0.915
Galantamine	0.159	(-1.366, 1.763)	0.600	0.081
Rivastigmine	-	-	-	-
Memantine	-	-	-	-

TABLE 24 *Mixed treatment comparison – MMSE at 12–13wk (mean change from baseline; OC populations): input data*

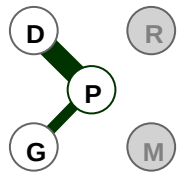
Evidence Network	Comparison	Study	WMD	(95%CI)
	Donepezil v. Placebo	Mohs et al. (2001)[13]	1.600	(0.889, 2.311)
		Winblad et al. (2001)[14]	0.800	(0.075, 1.525)
		Gauthier et al. (2002)[15]	2.000	(0.820, 3.180)
		Nunez et al. (2003)[9,10]	1.130	(0.146, 2.114)
		Seltzer et al. (2004)[16]	1.175	(0.100, 2.250)
	Rivastigmine v. Placebo	Agid et al. (1998)[29]	0.144	(-0.493, 0.782)
		Mowla et al. (2007)[30]	1.600	(1.099, 2.101)
	Donepezil v. Rivastigmine	Wilkinson et al. (2002)[33]	-0.490	(-1.825, 0.845)
	Donepezil v. Galantamine	Jones et al. (2004)[32]	0.753	(-0.215, 1.720)

TABLE 25 *Mixed treatment comparison – MMSE at 12–13wk (mean change from baseline; OC populations): results*

Technology	v. Placebo			Prob. most effective
	Effect	(95%CI)	Prob. more effective than placebo	
Placebo	-	-	-	0.001
Donepezil	1.222	(0.468, 1.988)	0.997	0.505
Galantamine	0.469	(-1.487, 2.449)	0.704	0.149
Rivastigmine	1.079	(0.075, 2.144)	0.980	0.346
Memantine	-	-	-	-

TABLE 26 *Mixed treatment comparison – MMSE at 24–26wk (mean change from baseline; LOCF data only): input data*

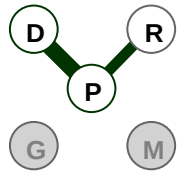
Evidence Network	Comparison	Study	WMD	(95%CI)
	Donepezil v. Placebo	Rogers et al. (1998)[7]	1.284	(0.604, 1.964)
		Gauthier et al. (2002)[15]	2.060	(0.880, 3.240)
		Seltzer et al. (2004)[16]	1.250	(0.171, 2.329)
	Rivastigmine v. Placebo	Feldman & Lane (2007)[25]	1.407	(0.809, 2.006)
		Winblad et al. (2007)[26]	0.932	(0.461, 1.403)

TABLE 27 *Mixed treatment comparison – MMSE at 24–26wk (mean change from baseline; LOCF data only): results*

Technology	v. Placebo			Prob. most effective
	Effect	(95%CI)	Prob. more effective than placebo	
Placebo	-	-	-	0.001
Donepezil	1.460	(0.581, 2.420)	0.995	0.741
Galantamine	-	-	-	-
Rivastigmine	1.137	(0.152, 2.160)	0.982	0.258
Memantine	-	-	-	-

TABLE 28 *Mixed treatment comparison – MMSE at 24–26wk (mean change from baseline; classical ITT or LOCF data): input data*

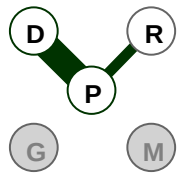
Evidence Network	Comparison	Study	WMD	(95%CI)
	Donepezil v. Placebo	Rogers et al. (1998)[7]	1.284	(0.604, 1.964)
		Gauthier et al. (2002)[15]	2.060	(0.880, 3.240)
		AD2000 (2004)[11]	0.500	(-0.250, 1.250)
		Seltzer et al. (2004)[16]	1.250	(0.171, 2.329)
		Mazza et al. (2006)[8]	1.450	(-3.720, 6.620)
	Rivastigmine v. Placebo	Feldman & Lane (2007)[25]	1.250	(0.670, 1.830)
		Winblad et al. (2007)[26]	0.932	(0.461, 1.403)

TABLE 29 *Mixed treatment comparison – MMSE at 24–26wk (mean change from baseline; classical ITT or LOCF data): results*

Technology	v. Placebo			Prob. most effective
	Effect	(95%CI)	Prob. more effective than placebo	
Placebo	-	-	-	0.001
Donepezil	1.169	(0.476, 1.978)	0.996	0.582
Galantamine	-	-	-	-
Rivastigmine	1.076	(0.102, 2.059)	0.981	0.418
Memantine	-	-	-	-

TABLE 30 *Mixed treatment comparison – MMSE at 24–26wk (mean change from baseline; OC populations): input data*

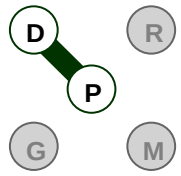
Evidence Network	Comparison	Study	WMD	(95%CI)
	Donepezil v. Placebo	Mohs et al. (2001)[13]	1.350	(0.188, 2.512)
		Winblad et al. (2001)[14]	1.490	(0.548, 2.432)
		Gauthier et al. (2002)[15]	2.000	(0.787, 3.213)
		Seltzer et al. (2004)[16]	1.200	(-0.086, 2.486)

TABLE 31 *Mixed treatment comparison – MMSE at 24–26wk (mean change from baseline; OC populations): results*

Technology	v. Placebo			Prob. most effective
	Effect	(95%CI)	Prob. more effective than placebo	
Placebo	-	-	-	0.003
Donepezil	1.507	(0.637, 2.371)	0.997	0.997
Galantamine	-	-	-	-
Rivastigmine	-	-	-	-
Memantine	-	-	-	-

SIB

TABLE 32 *Mixed treatment comparison – SIB at 12wk (mean change from baseline; OC populations): input data*

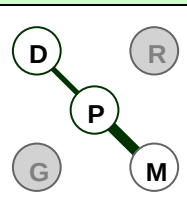
Evidence Network	Comparison	Pairwise Meta-Analysis	Study	WMD	(95%CI)
	Donepezil v. Placebo	-	Gauthier et al. (2002)[15]	3.900	(1.474, 6.326)
	Memantine v. Placebo	**Error! Reference source not ound.**	Reisberg et al. (2003)[34]	6.200	(3.138, 9.262)
			Van Dyck et al. (2007)[35]	2.475	(0.497, 4.453)

TABLE 33 *Mixed treatment comparison – SIB at 12wk (mean change from baseline; OC populations): results*

Technology	v. Placebo			Prob. most effective
	Effect	(95%CI)	Prob. more effective than placebo	
Placebo	-	-	-	0.000
Donepezil	3.884	(0.343, 7.414)	0.983	0.506
Galantamine	-	-	-	-
Rivastigmine	-	-	-	-
Memantine	3.849	(1.416, 6.509)	0.998	0.494

TABLE 34 *Mixed treatment comparison – SIB at 24–28wk (mean change from baseline; LOCF data only): input data*

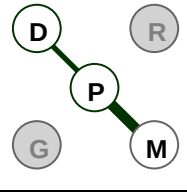
Evidence Network	Comparison	Study	WMD	(95%CI)
	Donepezil v. Placebo	Gauthier et al. (2002)[15]	4.425	(1.341, 7.509)
	Memantine v. Placebo	Reisberg et al. (2003)[34]	6.100	(2.989, 9.211)
		Van Dyck et al. (2007)[35]	0.500	(-2.272, 3.272)

TABLE 35 *Mixed treatment comparison – SIB at 24–28wk (mean change from baseline; LOCF data only): results*

Technology	v. Placebo			Prob. most effective
	Effect	(95%CI)	Prob. more effective than placebo	
Placebo	-	-	-	0.001
Donepezil	4.420	(0.268, 8.572)	0.981	0.701
Galantamine	-	-	-	-
Rivastigmine	-	-	-	-
Memantine	3.104	(0.263, 5.985)	0.983	0.298

TABLE 36 *Mixed treatment comparison – SIB at 24–28wk (mean change from baseline; OC populations): input data*

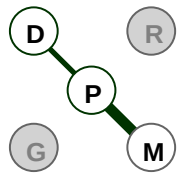
Evidence Network	Comparison	Study	WMD	(95%CI)
	Donepezil v. Placebo	Gauthier et al. (2002)[15]	5.325	(1.895, 8.755)
	Memantine v. Placebo	Reisberg et al. (2003)[34]	5.700	(2.137, 9.263)
		Van Dyck et al. (2007)[35]	0.600	(-2.591, 3.791)

TABLE 37 *Mixed treatment comparison – SIB at 24–28wk (mean change from baseline; OC populations): results*

Technology	v. Placebo			Prob. most effective
	Effect	(95%CI)	Prob. more effective than placebo	
Placebo	-	-	-	0.000
Donepezil	5.327	(1.061, 9.583)	0.992	0.821
Galantamine	-	-	-	-
Rivastigmine	-	-	-	-
Memantine	2.949	(-0.041, 5.957)	0.974	0.179

Behavioural

NPI

TABLE 38 *Mixed treatment comparison – NPI at 12–13wk (mean change from baseline; OC populations): input data*

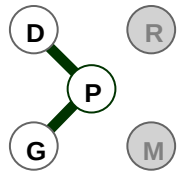
Evidence Network	Comparison	Study	WMD	(95%CI)
	Donepezil v. Placebo	Gauthier et al. (2002)[15]	-2.900	(-6.783, 0.983)
		Nunez et al. (2003)[9;10]	-3.160	(-5.947, -0.373)
	Galantamine v. Placebo	Tariot et al. (2000)[23]	-0.719	(-2.056, 0.618)
		Rockwood et al. (2001)[17]	-0.700	(-2.675, 1.275)

TABLE 39 *Mixed treatment comparison – NPI at 12–13wk (mean change from baseline; OC populations): results*

Technology	v. Placebo			Prob. most effective
	Effect	(95%CI)	Prob. more effective than placebo	
Placebo	-	-	-	0.003
Donepezil	-3.073	(-5.678, -0.458)	0.988	0.931
Galantamine	-0.713	(-2.525, 1.079)	0.815	0.066
Rivastigmine	-	-	-	-
Memantine	-	-	-	-

TABLE 40 *Mixed treatment comparison – NPI at 12–13wk (mean change from baseline; classical ITT or LOCF analysis): input data*

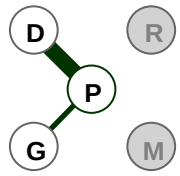
Evidence Network	Comparison	Study	WMD	(95%CI)
	Donepezil v. Placebo	Nunez et al. (2003)[9;10]	-2.870	(-5.406, -0.334)
		AD2000 (2004)[11]	1.250	(1.500, 4.000)
		Holmes et al. (2004)[12]	-6.200	(-11.374, -1.026)
	Galantamine v. Placebo	Rockwood et al. (2001)[17]	-0.900	(-2.688, 0.888)

TABLE 41 *Mixed treatment comparison – NPI at 12–13wk (mean change from baseline; classical ITT or LOCF analysis): results*

Technology	v. Placebo			Prob. most effective
	Effect	(95%CI)	Prob. more effective than placebo	
Placebo	-	-	-	0.020
Donepezil	-1.780	(-4.299, 0.602)	0.930	0.663
Galantamine	-0.886	(-4.237, 2.413)	0.720	0.316
Rivastigmine	-	-	-	-
Memantine	-	-	-	-

Global

CIBIC-plus

TABLE 42 *Mixed treatment comparison – CIBIC-plus at 12–16wk (classical ITT or LOCF analysis): input data*

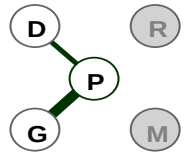
Evidence Network	Comparison	Study	WMD	(95%CI)
	Donepezil v. Placebo	Rogers et al. (1998)[4]	-0.350	(-0.527, -0.174)
	Galantamine v. Placebo	Rockwood et al. (2001)[17]	-0.335	(-0.524, -0.146)
		Rockwood et al. (2006)[21]	-0.450	(-0.797, -0.103)

TABLE 43 *Mixed treatment comparison – CIBIC-plus at 12–16wk (classical ITT or LOCF analysis): results*

Technology	v. Placebo			Prob. most effective
	Effect	(95%CI)	Prob. more effective than placebo	
Placebo	-	-	-	0.047
Donepezil	-0.352	(-2.125, 1.417)	0.808	0.458
Galantamine	-0.374	(-1.663, 0.866)	0.863	0.496
Rivastigmine	-	-	-	-
Memantine	-	-	-	-

TABLE 44 *Mixed treatment comparison – CIBIC-plus at 12–16wk (OC populations): input data*

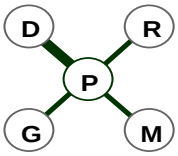
Evidence Network	Comparison	Study	WMD	(95%CI)
	Donepezil v. Placebo	Burns et al. (1999)[5]	-0.265	(-0.406, -0.125)
		Gauthier et al. (2002)[15]	-0.490	(-0.768, -0.212)
	Galantamine v. Placebo	Rockwood et al. (2001)[17]	-0.367	(-0.582, -0.152)
	Rivastigmine v. Placebo	Rosler et al. (1999){Rosler, 1999 2016 /id}	-0.007	(-0.186, 0.172)
	Memantine v. Placebo	Reisberg et al. (2003)[34]	-0.070	(-0.347, 0.207)

TABLE 45 *Mixed treatment comparison – CIBIC-plus at 12–16wk (OC populations): results*

Technology	v. Placebo			Prob. most effective
	Effect	(95%CI)	Prob. more effective than placebo	
Placebo	-	-	-	0.013
Donepezil	-0.351	(-1.697, 0.934)	0.843	0.330
Galantamine	-0.369	(-2.249, 1.522)	0.791	0.403
Rivastigmine	-0.007	(-1.871, 1.890)	0.510	0.113
Memantine	-0.072	(-1.958, 1.808)	0.578	0.142

TABLE 46 *Mixed treatment comparison – CIBIC-plus at 24–28wk (LOCF analyses only): input data*

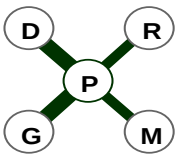
Evidence Network	Comparison	Study	WMD	(95%CI)
	Donepezil v. Placebo	Rogers et al. (1998)[7]	-0.400	(-0.593, -0.207)
		Burns et al. (1999)[5]	-0.340	(-0.484, -0.196)
		Gauthier et al. (2002)[15]	-0.545	(-0.858, -0.232)
	Galantamine v. Placebo	Raskind et al. (2000)[19]	-0.248	(-0.419, -0.077)
		Wilcock et al. (2000)[20]	-0.288	(-0.450, -0.127)
		Brodaty et al. (2005)[22]	-0.138	(-0.294, 0.018)
	Rivastigmine v. Placebo	Rosler et al. (1999){Rosler, 1999 2016 /id}	-0.284	(-0.538, -0.030)
		Feldman & Lane (2007)[25]	-0.502	(-0.704, -0.300)
	Memantine v. Placebo	Reisberg et al. (2003)[34]	-0.300	(-0.582, -0.018)
		Van Dyck et al. (2007)[35]	-0.300	(-0.515, -0.085)

TABLE 47 *Mixed treatment comparison – CIBIC-plus at 24–28wk (LOCF analyses only): results*

Technology	v. Placebo			Prob. most effective
	Effect	(95%CI)	Prob. more effective than placebo	
Placebo	-	-	-	0.000
Donepezil	-0.393	(-0.558, -0.247)	1.000	0.367
Galantamine	-0.223	(-0.364, -0.086)	0.995	0.008
Rivastigmine	-0.414	(-0.611, -0.205)	0.999	0.514
Memantine	-0.300	(-0.518, -0.086)	0.994	0.111

TABLE 48 *Mixed treatment comparison – CIBIC-plus at 24–28wk (classical ITT and LOCF analyses): input data*

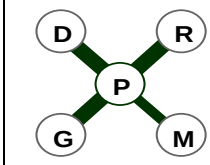
Evidence Network	Comparison	Study	WMD	(95%CI)
	Donepezil v. Placebo	Rogers et al. (1998)[7]	-0.400	(-0.593, -0.207)
		Burns et al. (1999)[5]	-0.340	(-0.484, -0.196)
		Gauthier et al. (2002)[15]	-0.545	(-0.858, -0.232)
	Galantamine v. Placebo	Raskind et al. (2000)[19]	-0.248	(-0.419, -0.077)
		Wilcock et al. (2000)[20]	-0.288	(-0.450, -0.127)
		Brodaty et al. (2005)[22]	-0.138	(-0.294, 0.018)
	Rivastigmine v. Placebo	Corey-Bloom et al. (1998)[27]	-0.275	(-0.471, -0.079)
		Rosler et al. (1999){Rosler, 1999 2016 /id}	-0.300	(-0.519, -0.081)
		Feldman & Lane (2007)[25]	-0.500	(-0.711, -0.289)
	Memantine v. Placebo	Reisberg et al. (2003)[34]	-0.300	(-0.582, -0.018)
		Van Dyck et al. (2007)[35]	-0.300	(-0.515, -0.085)

TABLE 49 *Mixed treatment comparison – CIBIC-plus at 24–28wk (classical ITT and LOCF analyses): results*

Technology	v. Placebo			Prob. most effective
	Effect	(95%CI)	Prob. more effective than placebo	
Placebo	-	-	-	0.000
Donepezil	-0.392	(-0.549, -0.251)	1.000	0.546
Galantamine	-0.222	(-0.356, -0.091)	0.997	0.010
Rivastigmine	-0.354	(-0.508, -0.203)	1.000	0.285
Memantine	-0.300	(-0.507, -0.100)	0.996	0.159

TABLE 50 *Mixed treatment comparison – CIBIC-plus at 24–28wk (OC populations): input data*

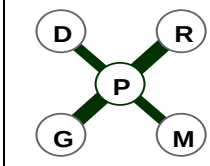
Evidence Network	Comparison	Study	WMD	(95%CI)
	Donepezil v. Placebo	Burns et al. (1999)[5]	-0.335	(-0.497, -0.174)
		Gauthier et al. (2002)[15]	-0.450	(-0.803, -0.097)
	Galantamine v. Placebo	Raskind et al. (2000)[19]	-0.281	(-0.480, -0.082)
		Wilcock et al. (2000)[20]	-0.407	(-0.592, -0.223)
		Brodaty et al. (2005)[22]	-0.156	(-0.327, 0.016)
	Rivastigmine v. Placebo	Corey-Bloom et al. (1998)[27]	-0.333	(-0.547, -0.119)
		Rosler et al. (1999){Rosler, 1999 2016 /id}	-0.259	(-0.558, 0.040)
		Feldman & Lane (2007)[25]	-0.403	(-0.620, -0.186)
	Memantine v. Placebo	Reisberg et al. (2003)[34]	-0.300	(-0.629, 0.029)
		Van Dyck et al. (2007)[35]	-0.300	(-0.555, -0.045)

TABLE 51 *Mixed treatment comparison – CIBIC-plus at 24–28wk (OC populations): results*

Technology	v. Placebo			Prob. most effective
	Effect	(95%CI)	Prob. more effective than placebo	
Placebo	-	-	-	0.000
Donepezil	-0.363	(-0.593, -0.151)	0.997	0.413
Galantamine	-0.277	(-0.439, -0.118)	0.997	0.077
Rivastigmine	-0.341	(-0.523, -0.157)	0.998	0.293
Memantine	-0.300	(-0.556, -0.048)	0.988	0.218

GDS

TABLE 52 *Mixed treatment comparison – GDS at 26–28wk (mean change from baseline; classical ITT or LOCF analysis): input data*

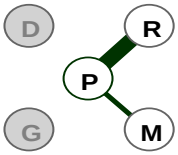
Evidence Network	Comparison	Study	WMD	(95%CI)
	Rivastigmine v. Placebo	Corey-Bloom et al. (1998)[27]	0.175	(0.065, 0.285)
		Rosler et al. (1999){Rosler, 1999 2016 /id}	0.120	(-0.042, 0.282)
		Feldman & Lane (2007)[25]	0.200	(0.087, 0.312)
	Memantine v. Placebo	Reisberg et al. (2003)[34]	-0.100	(-0.220, 0.020)

TABLE 53 *Mixed treatment comparison – GDS at 26–28wk (mean change from baseline; classical ITT or LOCF analysis): results*

Technology	v. Placebo			Prob. most effective
	Effect	(95%CI)	Prob. more effective than placebo	
Placebo	-	-	-	0.034
Donepezil	-	-	-	-
Galantamine	-	-	-	-
Rivastigmine	0.171	(-0.145, 0.471)	0.943	0.901
Memantine	-0.101	(-0.638, 0.434)	0.187	0.065

TABLE 54 *Mixed treatment comparison – GDS at 24–28wk (mean change from baseline; OC population): input data*

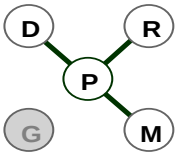
Evidence Network	Comparison	Study	WMD	(95%CI)
	Donepezil v. Placebo	Winblad et al. (2001)[14]	0.160	(-0.006, 0.326)
	Rivastigmine v. Placebo	Corey-Bloom et al. (1998)[27]	0.184	(0.068, 0.301)
	Memantine v. Placebo	Reisberg et al. (2003)[34]	-0.100	(-0.242, 0.042)

TABLE 55 *Mixed treatment comparison – GDS at 24–28wk (mean change from baseline; OC population): results*

Technology	v. Placebo			Prob. most effective
	Effect	(95%CI)	Prob. more effective than placebo	
Placebo	-	-	-	0.087
Donepezil	0.159	(-2.347, 2.677)	0.608	0.347
Galantamine	-	-	-	-
Rivastigmine	0.181	(-2.344, 2.690)	0.623	0.367
Memantine	-0.101	(-2.607, 2.420)	0.424	0.199

Appendix 10: Studies included by industry but excluded from the PenTAG clinical effectiveness systematic review

Table 56 Eisai/Pfizer submission

Studies included in their systematic review	Reason for exclusion from PenTAG systematic review
P. Bentham, R. Gray, J. Raftery, R. Hills, E. Sellwood, C. Courtney, D. Farrell, W. Hardyman, P. Crome, S. Edwards, C. Lendon, L. Lynch, and A. D. C. Grp. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. Lancet 363 (9427):2105-2115, 2004.	Included in the previous review
A. Burns, S. Gauthier, and C. Perdomo. Efficacy and safety of donepezil over 3 years: An open-label, multicentre study in patients with Alzheimer's disease. International Journal of Geriatric Psychiatry 22 (8):806-812, 2007.	Secondary study to studies included in the 2004 review
J. L. Cummings, T. McRae, and R. Zhang. Effects of donepezil on neuropsychiatric symptoms in patients with dementia and severe behavioral disorders. American Journal of Geriatric Psychiatry 14 (7):605-612, 2006.	Observational
H. H. Feldman, F. A. Schmitt, and J. T. Olin. Activities of daily living in moderate-to-severe Alzheimer disease: An analysis of the treatment effects of memantine in patients receiving stable donepezil treatment. Alzheimer Disease and Associated Disorders 20 (4):263-268, 2006.	Secondary study to studies included in the 2004 review
Mason C. Gasper and Brian R. Ott. Is Donepezil Therapy Associated with Reduced Mortality in Nursing Home Residents with Dementia? [References]. American Journal of Geriatric Pharmacotherapy (AJGP) .3 (1), 2005.	Observational
C. M. Persson, A. K. Wallin, S. Levander, L. Minthon, Cecilia M. Persson, Asa K. Wallin, Sten Levander, and Lennart Minthon. Changes in cognitive domains during three years in patients with Alzheimer's disease treated with donepezil. BMC Neurology 9:7, 2009.	Observational
M. W. Riepe, J. Kohler, and R. Horn. Donepezil in Alzheimer's disease: a clinical observational study evaluating individual treatment response. Current Medical Research and Opinion 23 (8):1829-1835, 2007.	Observational

F. A. Schmitt, C. H. Van Dyck, C. H. Wichems, and J. T. Olin. Cognitive response to memantine in moderate to severe Alzheimer disease patients already receiving donepezil: An exploratory reanalysis. Alzheimer Disease and Associated Disorders 20 (4):255-262, 2006.	Secondary study to studies included in the 2004 review
P. N. Tariot, M. R. Farlow, G. T. Grossberg, S. M. Graham, S. McDonald, and I. Gergel. Memantine Treatment in Patients with Moderate to Severe Alzheimer Disease Already Receiving Donepezil: A Randomized Controlled Trial. Journal of the American Medical Association 291 (3):317-324, 2004.	Included in the previous review
A. K. Wallin, N. Andreasen, S. Eriksson, S. Batsman, B. Nasman, A. Ekdahl, L. Kilander, M. Grut, M. Ryden, A. Wallin, M. Jonsson, H. Olofsson, E. Londos, C. Wattmo, Jonhagen M. Eriksdotter, L. Minthon, Swedish Alzheimer Treatment Study Group., Asa K. Wallin, Niels Andreasen, Sture Eriksson, Stellan Batsman, Birgitta Nasman, Anne Ekdahl, Lena Kilander, Mikaela Grut, Marie Ryden, Anders Wallin, Mikael Jonsson, Hasse Olofsson, Elisabeth Londos, Carina Wattmo, Maria Eriksdotter Jonhagen, Lennart Minthon, and Swedish Alzheimer Treatment Study Group. Donepezil in Alzheimer's disease: what to expect after 3 years of treatment in a routine clinical setting. Dementia & Geriatric Cognitive Disorders 23 (3):150-160, 2007.	Observational
Wimo, A., Winblad, B., Shah, S. N., Chin, W., Zhang, R., and McRae, T.Impact of donepezil treatment for Alzheimer's disease on caregiver time. Curr Med Res Opin 2004; 20(8): 1221-1225	Secondary study to studies included in the 2004 review

TABLE 57 *Lundbeck submission*

Study ID: Lundbeck	Studies included in their systematic review	Reason for exclusion from PenTAG systematic review
10158	A Randomised, Double-Blind, Parallel Group Study Examining the Efficacy and Safety of Memantine on Behavioural Symptoms in Patients with Moderate to Severe Dementia of the Alzheimer's Type	Ongoing study
10252	Open Label Extension to Study 10158 (Effect of Memantine on Behavioral Symptoms in Patients with Moderate to Severe Dementia of the Alzheimer's Type)	Observational
10112	A 1-Year Multicentre, Double-Blind Placebo-controlled Study to Evaluate the Disease-Modifying Effects of Memantine in Patients with Alzheimer's Disease of Moderate Severity	Poster presentation
10116	A Randomized, Double-Blind, Placebo Controlled Evaluation of the Efficacy and Tolerability of	Not English language (Chinese)

Study ID: Lundbeck	Studies included in their systematic review	Reason for exclusion from PenTAG systematic review
	Memantine in Chinese Patients with Dementia of Alzheimer's Type (including extension)	
10113	A Randomised, Double-Blind Study to Evaluate the Safety and Tolerability of Once Daily versus Twice Daily Memantine Treatment in Patients with Moderate to Severe Dementia of the Alzheimer's Type	No relevant comparators
10114	Evaluation of the safety and tolerability of randomised, double-blind switching of treatment from donepezil to memantine in patients with moderate to severe dementia of the Alzheimer's type	Commentary
99679	A Randomised, Double-Blind, Placebo-Controlled Evaluation of the Efficacy and Safety of Memantine in Patients with Mild to Moderate Dementia of the Alzheimer's Type	Wrong population - mild
99819	A Long Term Open Label Extension Study Evaluating the Safety and Tolerability of Memantine in Patients with Mild to Moderate Dementia of the Alzheimer's Type. Extension of 99679	Wrong population - mild
99817	A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Memantine in Patients with Dementia of the Alzheimer's Type	Conference abstract
Asubio IE-2101	Late Phase II Clinical Study of Sun Y7017 (Memantine Hydrochloride) in Patients with Moderately Severe to Severe Dementia of the Alzheimer's Type - Evaluation of Recommended Dose and Long-Term Safety (Extension Study for Dose-Finding and Long Term Safety): Double-blind period	Poster presentation
[redacted]	[redacted]	Unpublished study prior to 2004
[redacted]	[redacted]	Unpublished open label extension study
Asubio IE-3501	Phase III Study of SUN Y7017 (memantine hydrochloride) in Patients with Moderately Severe to Severe Dementia of the Alzheimer's Type	Unpublished Japanese study
Asubio MA-3301	Confirmatory Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of SUN Y7017 (Memantine Hydrochloride) in Patients with Mild to Moderate Dementia of the Alzheimer's Type	Wrong population - mild
[redacted]	[redacted]	Observational
MRZ 90001-0608	Prospective, open-label, single-arm, multicentre study to investigate the efficacy and safety of the once-daily (OD) Memantine treatment.	Observational

Study ID: Lundbeck	Studies included in their systematic review	Reason for exclusion from PenTAG systematic review
MRZ 90001-0716	Prospective, single-arm, multi-centre, open-label study to investigate the potential to reduce concomitant antipsychotics use in patients with moderate dementia of Alzheimer's type (DAT) treated with memantine	Observational
MRZ 90001-9605/1	Efficacy and Long Term Tolerability of Memantine in Patients with Moderately Severe to Severe Alzheimer's Disease (AD)	Included in the previous review
MRZ 90001-9605/2	A Randomized, Placebo-Controlled Study of Memantine in Patients with Moderate to Severe Alzheimer's Disease. Phase 3 open label extension.	Observational
MRZ 90001-AD-3001	Open-label, single-arm, multi-center validation study of the ROSA-Scale (Relevant Outcome Scale for Alzheimer Patients) in patients with dementia of Alzheimer's type (DAT) treated with memantine over a 3 months period	Observational
MRZ 9403	Efficacy and Long Term Tolerability of Memantine in Care-Dependent Patients with Moderately Severe to Severe Primary Dementia	Excluded from previous review due to population
MRZ 9104	Multicentre, Randomized Double-Blind, Comparative Study of the Efficacy and Tolerabilty of Akatinol Memantine and Placebo in Patients Suffering from Senile Demetia, Alzheimer Type.	No publications, date 1999
Forest MEM-MD-02	A Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Memantine in Patients with Moderate to Severe Dementia of the Alzheimer's Type (on ≥ 6 months Aricept therapy)	Included in previous review
Forest MEM-MD-03 A/B	A Long-Term Extension Study Evaluating the Safety and Tolerability of Four Memantine Dosing Regimens in Patients with Moderate to Severe Dementia of the Alzheimer's Type. Extension of MEM-MD-01 and MEM-MD-02 Phase A/B = 4 weeks double-blind + 24 weeks open	Observational
Forest MEM-MD-03 C	Extension of MEM-MD-01 and MEM-MD-02. Phase C = 52 weeks open	Observational
Forest MEM-MD-03 D	Extension of MEM-MD-01 and MEM-MD-02. Phase D = open continuation until memantine is commercially available	Observational
Forest MEM-MD-10	A Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Memantine in Patients with Mild to Moderate Dementia of the Alzheimer's Type (Monotherapy).	Population – mild Alzheimer's
Forest MEM-MD-11 A/B	A Long-Term Extension Study Evaluating the Safety and Tolerability of BID and QD Administration of Memantine in Patients with Mild to Moderate Dementia of the Alzheimer's Type. Extension of MEM-MD-10. Phase A/B = 8 weeks double-blind + 20 weeks open	Population – mild Alzheimer's

Study ID: Lundbeck	Studies included in their systematic review	Reason for exclusion from PenTAG systematic review
Forest MEM-MD-11 C	Extension of MEM-MD-10. Phase C = 52 weeks open	Observational
Forest MEM-MD-11 D	Extension of MEM-MD-10. Phase D = open continuation until memantine is commercially available	Observational
Forest MEM-MD-12 A	Open extension of MEM-MD-12: 28 weeks	Observational
Forest MEM-MD-12 B	Open extension of MEM-MD-12 A: continuation until memantine is commercially available	Observational
Forest MEM-MD-22	A Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Namenda in Nursing Home Patients with Moderate to Severe Alzheimer's Disease	Summary
Forest MEM-MD-23	A Randomized, Double-Blind, Placebo Controlled Evaluation of the Safety and Efficacy of Memantine in Patients With Moderate to Severe Alzheimer's Disease with Behavioral Disturbances	Summary
Forest MEM-MD-71	A Randomized, Double-Blind, Placebo-Controlled Evaluation of the Effectiveness of Memantine on Functional Communication in Patients with Moderate Dementia of the Alzheimer's Type	Summary
Lundbeck 11267	Memantine for Agitation and Aggression in Severe AD - Open-label, explorative study	Observational
Lundbeck 11875A	An open label, post-marketing, naturalistic, multi-centre study evaluating the safety and efficacy of Ebixa (Memantine) in the treatment of Chinese patients with Alzheimer's Disease	Ongoing
Lundbeck 12292A	Memantine on Aggression and Agitation of AD - Open-label study	Ongoing
Lundbeck 12484A	Memantine and changes of biological markers and brain PET imaging in Alzheimer's Disease - double-blind, randomized, placebo-controlled	Ongoing
Lundbeck 12484A	Memantine and changes of biological markers and brain PET imaging in Alzheimer's Disease - double-blind, randomized, placebo-controlled	Ongoing
Lundbeck 12732A	An open-label, observational, multi-centre study evaluating efficacy and safety profile of Memantine in Chinese patients with Alzheimer's Disease	Not started
Lundbeck 11784A	Psychiatric Symptoms and Caregiver Distress in patients with moderate to severe Alzheimer's Disease treated with Memantine - Study design: pre/post treatment study (no randomization, no blinding, no groups)	Observational

Study ID: Lundbeck	Studies included in their systematic review	Reason for exclusion from PenTAG systematic review
Lundbeck 11232	A randomised, double-blind placebo-controlled trial of Memantine in the treatment of the Agitation in Alzheimer's Dementia	Ongoing
Lundbeck 11786A	Impact on Aggressive Behaviour and Cognition of switching from Dopenezil to Memantine in patients with Moderate-to-Severe AD - Design: Open-label, pilot, observational, head-to-head.	Ongoing
Lundbeck 11829A	Memantine for the maintenance treatment of neurophsychiatric symptoms in people with Alzheimer's Disease living in care facilities: A double-blind, controlled comparison to neuroleptic medication (Maintenance of Neuropsychiatric Symptoms in AD: MAIN-AD)	Ongoing
Lundbeck 11967A	Donepezil and Memantine in moderate to severe Alzheimer's Disease (DOMINO Study) - Design: pragmatic, multi-centre, double-blind, randomized, placebo controlled (double-dummy), parallel group, 2X2 factorial clinical trial.	Ongoing
Lundbeck 10710	Memantine Effects on Cortical Excitability and its neurophysiological/neuropsychological effects on AD patients in combination with AChEI: A pilot study - Design: 1st phase open-label, 2nd phase partial blind	No publication or report
Lundbeck 10997	Behaviour and Cognition in AD patients treated with the NMDA receptor antagonist Memantine: correlation with the apoptotic mechanism	Ongoing
Lundbeck 10998	Effect of Memantine treatment on brain function and morphological structure in patients with moderate to severe Alzheimer's Disease: a structural MR and FMRI study. Experimental design.	Wrong outcomes
Lundbeck 10712	Effectiveness and Tolerability of Memantine treatment in outpatients with AD of mixed dementia. Multi centre, open-label trial.	Observational
Lundbeck 11198	Memantine therapy for treatment of Alzheimer's Disease	Commentary
Lundbeck 11830A	Investigating the effects of treatment on neurotrophic factors by means of functional magnetic resonance imaging (FMRI) in patients with Alzheimer's Disease - Design: double-blind, prospective, randomized.	Not started
MRZ 10001-0207	A randomized double-blind controlled trial to evaluate the efficacy and safety of an antidementive combination therapy (galantamine and memantine) in subjects with mild-to-moderate stage of probable AD." MEGA-COMBI-2".	Ongoing
MRZ-9605 MD-01 MD-02 MD-10 MD-12 Lu-	The meta-analysis population comprised the subgroup of patients from these studies (n=1,826) with a baseline MMSE score <20 (i.e., moderate to severe AD). Assessments were made in the key domains of	Pooled secondary analysis

Study ID: Lundbeck	Studies included in their systematic review	Reason for exclusion from PenTAG systematic review
99679	global response, function, cognition and behaviour.	
As above	Data from 6 randomized, double-blind, placebo-controlled, 6-month studies were pooled and a subgroup of patients (867 on placebo,959 on memantine) with moderate to severe AD (Mini-Mental State Examination < 20) was analyzed.	Pooled secondary analysis
As above	Data were pooled from six 24/28-week, randomised, placebo-controlled, double-blind studies. Of the 2,311 patients included in these studies, 1,826 patients with moderate to severe AD (MMSE <20) were included in this analysis. In this subgroup, 959 patients received memantine 20 mg/day and 867 received placebo. Behavioural symptoms were rated using the Neuropsychiatric Inventory (NPI) total and single-item scores at weeks 12 and 24/28.	Pooled secondary analysis
As above	Data from six multicentre, randomised, placebo-controlled, parallel-group, double-blind, 6-month studies were used as the basis for these post-hoc analyses. All patients with a Mini-Mental State Examination (MMSE) score of less than 20 were included. Analyses of patients with moderate AD (MMSE: 10–19), evaluated with the Alzheimer's disease Assessment Scale (ADAS-cog) and analyses of patients with moderate to severe AD (MMSE: 3–14), evaluated using the Severe Impairment Battery (SIB), were performed separately.	Pooled secondary analysis
As above	The current analysis combined data from six previously published studies and assessed the effect of memantine on various cognitive functions in 1826 patients (867 on placebo and 959 on memantine) with moderate to severe AD (MMSE <20). The Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog) and the Severe Impairment Battery (SIB) scores from all six studies were pooled and combined into three clusters representing discrete cognitive domains: language, memory, and praxis.	Pooled secondary analysis
As above	Data were pooled from patients with moderate to severe AD (MMSE score <20 at baseline) from six randomised, double-blind, placebo-controlled, 6-month clinical trials on the efficacy and safety of memantine in AD	Pooled secondary analysis
MRZ 9403 MRZ-9605	The aim of this additional analysis was to investigate how the global benefit reported in these earlier publications translates into specific functional effects, and the impact that these findings may have on AD patients and their caregivers.	Pooled secondary analysis
	Memantine for the Treatment of Alzheimer's Disease Tolerability and Safety Data from Clinical Trials Farlow et al, Drug Safety 2008; 31 (7)	Pooled secondary analysis

Study ID: Lundbeck	Studies included in their systematic review	Reason for exclusion from PenTAG systematic review
	Memantine for Agitation/Aggression and Psychosis in Moderately severe to Severe Alzheimer's Disease: A Pooled Analysis of 3 studies Wilcock et al, J Clin Psychiatry 69 (3) 2008	Pooled secondary analysis
	Treatment effects of Memantine on language in moderate to severe Alzheimer's disease patients Ferris et al, Alzheimer's & Dementia 5 (2009) 369–374	Pooled secondary analysis
	Memantine: A Review of its Use in Moderate to Severe Alzheimer's Disease McKeage, ADIS drug evaluation CNS Drugs 2009; 23 (10): 881-897	Review
	Memantine Therapy of Behavioral Symptoms in Community-Dwelling Patients with Moderate to Severe Alzheimer's Disease Grossberg et al, Dement Geriatr Cogn Disord 2009;27:164–172	Review
	Merz Pharma Ltd, a partner, has initiated two projects on the analyses of the prescription databases, General Practice Research Database (GPRD) in the UK and Insight Health in Germany and. The projects aim to analyze prescription patterns in Alzheimer's disease, including use of memantine, acetylcholinesterase inhibitors (AChEI) and concomitant use of antipsychotic medications in AD patients. In addition, GPRD data presents an opportunity to estimate a risk of hip fractures and of implantation of cardiac pacemakers by treatment group.	Ongoing
	Livingston G, Katona C, Roch B, Guilhaume C, Rive B. A dependency model for patients with Alzheimer's disease: its validation and relationship to the costs of care--the LASER-AD Study. Curr Med Res Opin 2004;20(7):1007-1016. Ryu SH, Katona C, Rive B, Livingston G. Persistence of and changes in neuropsychiatric symptoms in Alzheimer disease over 6 months: the LASER-AD study. Am J Geriatr Psychiatry. 2005 Nov;13(11):976-83. Livingston G, Katona C, François C, Guilhaume C, Cochran J, Sapin C. Characteristics and health status change over 6 months in people with moderately severe to severe Alzheimer's disease in the U.K. Int Psychogeriatr. 2006 Sep;18(3):527-38. Habermann S, Cooper C, Katona C, Livingston G. Predictors of entering 24-h care for people with Alzheimer's disease: results from the LASER-AD study. Int J Geriatr Psychiatry. 2009 Nov;24(11):1291-8.	Epidemiological
	Long-term effects of the concomitant use of memantine with cholinesterase inhibition in Alzheimer disease Lopez et al. J. Neurol. Neurosurg. Psychiatry 2009;80;600-607;	Observational
	Long-term Course and Effectiveness of Combination Therapy in Alzheimer Disease Atri et al, Alzheimer Dis	Observational

Study ID: Lundbeck	Studies included in their systematic review	Reason for exclusion from PenTAG systematic review
	Assoc Disord 2008;22:209–221)	
	Evaluation of the Impact of Memantine Treatment - Initiation on Psychotropics Use: A Study from the French National Health Care Database Vidal et al, Neuroepidemiology 2008;31:193–200 Memantine Therapy for Alzheimer Disease in Real-world Practice An Observational Study in a Large Representative Sample of French Patients Vidal et al, Alzheimer Dis Assoc Disord. 2008 Apr-Jun;22(2):125-30.	Observational
	Persistent treatment with cholinesterase inhibitors and/or memantine slows clinical progression of Alzheimer disease Rountree et al, Alzheimer's Research & Therapy 2009, 1:7	Observational
	Memantine in Moderately-Severe-to-Severe Alzheimer's Disease Clerici F et al, Drugs Aging. 2009;26(4):321-32.	Observational
	Alzheimer's disease behavioural symptoms increase ressource utilisation Orgogozo et al, Poster ICAD 2008.	Poster
	Psychiatric symptoms and caregiver distress in patients with moderate to severe Alzheimer's disease treated with memantine Martinez-Rivera et al, Poster EFNS 2008 European Journal of Neurology 15 (Suppl. 3), 222–390	Poster
	Adverse Events in a Cohort of Alzheimer's Disease Patients treated with Memantine Clerici et al, Poster ISoP 2007	Poster
	Real-world clinical effectiveness of combination therapy with ChEI and Memantine in AD Shaughnessy et al, Poster AAN 2007	Poster
	Memantine in Clinical Practice – Results of an Observational Study Calabrese et al, Dement Geriatr Cogn Disord 2007;24:111–117	Observational
	Memantine in Moderately-Severe-to-Severe Alzheimer's Disease Hartmann S et al, Int Clin Psychopharmacol. 2003 Mar;18(2):81-5.	Observational

Appendix 11: Ongoing trials

Register/ identifier number (if not available Study ID cited)	Sponsor/Collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status
ISRCTH96337233	West Midlands NHS Research & Development Executive	A reliable assessment of the efficacy and safety of donepezil and aspirin in Alzheimer's Disease (AD2000)	Prof Richard Gray (University of Birmingham Clinical Trials Unit)	UK	310		Completed - 2004
NCT00843518	Eli Lilly & Company	Treatment for aggression and agitation in patients with Alzheimer's Disease	Not specified	US	Not specified	Phase II	Recruiting
NCT00035204	J&J	A Double-Blind, randomized pilot study to evaluate the effects of galantamine and donepezil on sleep and attention and gastrointestinal (GI) tolerance in patients with mild to moderate alzheimer's disease	Not specified	Not specified	Not specified	Phase IV	Completed
NCT00523666	Ludwig-Maximilians - University of Munich	Diffusion Tensor Weighted MRI in Alzheimer's Disease: Prediction and Mapping of Symptomatic and Disease Modifying Treatment Effects of Galantamine (ReminylÂ®)	Stefan Teipel	Germany	Not specified	Phase IV	Recruiting
NCT01024660	AstraZeneca	The Effect of Cognitive Function as Measured by Repeated Cognitive Measures After 12 Weeks Treatment With Donepezil	Malene Jensen	Canada, Peru, South Africa, Poland	155	N/A	Recruiting
NCT00693004	Epix Pharmaceuticals, Inc.	A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of PRX-03140 as Monotherapy in Subjects With Alzheimer's Disease	Not specified	US	236	Phase II	Terminated
NCT00645190	Xian-Janssen Pharmaceutical Ltd.	A Randomized, Double Blind, Active Control, Flexible Dose, Multicenter Study to Evaluate Galantamine HBr in the Treatment of Alzheimer's Disease:Safety and Effectiveness of an Immediate-release Table Formulation	Not specified	Not specified	215	Phase III	Completed
NCT00100334	PRAECIS Pharmaceuticals Inc.	Multiple Dose Safety and Preliminary Pharmacodynamic Study of PPI-1019 in Subjects With Mild-Moderate Alzheimer's Disease	Not specified	US	24	Phase I / Phase II	Completed
NCT00645190	Xian-Janssen Pharmaceutical Ltd.	A Randomized, Double Blind, Active Control, Flexible Dose, Multicenter Study to Evaluate Galantamine HBr in the Treatment of Alzheimer's Disease:Safety and Effectiveness of an Immediate-release Table Formulation	Not specified	Not specified	215	Phase III	Completed

Register/ identifier number (if not available Study ID cited)	Sponsor/Collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status
NCT00190021	Beersheva Mental Health Center	Donepezil as Add-On Treatment of Psychotic Symptoms in Patients With Dementia of the Alzheimer's Type	Vladimir Lerner	Israel	80	Phase III	Not yet recruiting
NCT00099242	Novartis	Efficacy and Safety of the Rivastigmine Transdermal Patch in Patients With Probable Alzheimer's Disease	Not specified	US, Chile, Czech Republic, Denmark, Finland, Guatemala, Israel, Italy Korea (Republic of), Mexico, Norway, Peru, Poland, Portugal, Russian Federation, Slovakia, Sweden, Taiwan, Venezuela	1,040	Phase III	Completed
NCT00096473	Eisai Inc./Pfizer	A 24 Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Donepezil Hydrochloride (E2020) in Patients With Severe Alzheimer's Disease Followed by a 12 Week Open-Label Extension Period	Sharon Richardson, Honglan Li	USA	Not specified	Phase III	Completed
NCT00916383	Teikoku Pharma USA	A Randomized, Placebo-Controlled Study in Elderly Alzheimer's Subjects on an Established and Well Tolerated Dose of Aricept to Assess Skin Tolerability, Skin Irritation and Adhesion With Three Consecutive Seven-Day Applications of the 350 mg Donepezil Transdermal Patch-System	Not specified	USA	48	Phase II	Ongoing but not recruiting
NCT00711204	Eisai Inc./Pfizer	A 12-Week, Double-Blind, Placebo-Controlled Study To Evaluate The Impact Of Donepezil Hydrochloride (Aricept) On Behavioral And Psychological Symptoms In Patients With Severe Alzheimer's Disease	Thomas McRae (Pfizer)	USA	200	Phase IV	Terminated
NCT00478205	Eisai Inc./Eisai Limited	Double-Blind, Parallel-Group Comparison of 23 mg Donepezil Sustained Release (SR) to 10 mg Donepezil Immediate Release (IR) in Patients With Moderate to Severe Alzheimer's Disease	Jane Yardley, Eisai Limited	USA	1200	Phase III	Completed
NCT00216593	Janssen Pharmaceutica	Treatment of Severe Alzheimer's Disease in a Residential Home, Nursing	Janssen	Not specified	415	Phase	Complete

Register/ identifier number (if not available Study ID cited)	Sponsor/Collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status
	N.V., Belgium	Home, or Geriatric Residential Setting: Evaluation of Efficacy and Safety of Galantamine Hydrobromide in a Randomised, Doubleblind, Placebo-Controlled Study	Pharmaceutica N.V. Clinical Trial Janssen Pharmaceutica N.V.			III	d
NCT00235716	Department of Veterans Affairs/ Forest Laboratories/ DSM Nutritional Products, Inc.	CSP #546 - A Randomized, Clinical Trial of Vitamin E and Memantine in Alzheimer's Disease (TEAM-AD)	Maurice Dysken (Minneapolis Veterans Affairs Medical Center)	USA, Puerto Rico	840	Phase III	Recruiting
NCT00216593	Janssen Pharmaceutica N.V., Belgium	Treatment of Severe Alzheimer's Disease in a Residential Home, Nursing Home, or Geriatric Residential Setting: Evaluation of Efficacy and Safety of Galantamine Hydrobromide in a Randomised, Doubleblind, Placebo-Controlled Study.	Janssen Pharmaceutica N.V. Clinical Trial Janssen Pharmaceutica N.V.	Not specified	415	Phase III	Completed
NCT00814801	Janssen Pharmaceutical K.K.	Placebo-controlled Confirmatory Study of Galantamine (R113675) for Alzheimer's Type Dementia	Janssen Pharmaceutical K.K. Clinical Trial, Study Director, Janssen Pharmaceutical K.K.	Not specified	580	Phase III	Completed
NCT00183729	National Institute of Mental Health (NIMH)	Memantine for Enhancement of Rehabilitation Efficacy and Prevention of Major Depressive Disorder in Older Adults	Eric J. Lenze, MD (University of Pittsburgh)	USA	40	Phase IV	Active, not recruiting
ISRCTN24953404	East Kent Hospitals Research and Development Committee (UK) (funded by Lundbeck Pharmaceuticals UK)	A randomized, double-blind, placebo-controlled trial of memantine in the treatment of Agitation in Dementia (MAGD)	Dr Chris Fox (Folkestone Health Centre), Dr Art Artionou (Buckland Hospital, Dover)	UK	154	Not specified	Ongoing
ISRCTN55568578	Department of Health, London (funded by Avon and Wiltshire Mental Health Partnership NHS Trust)	Making Evidence-based Decisions Using Alzheimer Therapy (MEDUSA Therapy)	Dr Roger Bullock, (Kingshill Research Centre, Victoria Hospital, Swindon)	UK	75	Not specified	Completed
ISRCTN49545035	Institute of Psychiatry	DOnepezil and Memantine IN mOderate to severe Alzheimer's Disease	Prof Robert	UK	800	Not	Ongoing

Register/ identifier number (if not available Study ID cited)	Sponsor/Collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status
	(UK) (funded by Medical Research Council [UK] [grant ref: G0600989])	(DOMINO-AD)	Howard (Institute of Psychiatry, London, UK)			specified	
ISRCTN68407918	Kings College London (UK) (funded by Lundbeck Pharmaceuticals Ltd)	Memantine for the Long Term Management of Neuropsychiatric Symptoms in Alzheimer's disease (MAIN-AD)	Prof Clive Ballard (Kings College, London)	UK	300	Not specified	Ongoing
ISRCTN62185868	Kings College London (UK), (funded by Medical Research Council [UK])	A Randomised Placebo Controlled Trial of a Cholinesterase Inhibitor in the Management of Agitation in Dementia that is Unresponsive to a Psychological Intervention (CALM-AD)	Prof Robert Howard (Institute of Psychiatry, London, UK)	UK	285	Not specified	Completed
NCT00857649	H. Lundbeck A/S	A Randomised, Double-Blind, Parallel-group Study Examining the Efficacy and Safety of Memantine in Patients With Moderate to Severe Dementia of the Alzheimer's Type	Dr Sauge Gauthier and Dr Nathan Hermann	Canada	450	Phase III	Ongoing, not recruiting
NCT00857233	H. Lundbeck A/S	An open-label extension study examining the safety and tolerability of memantine in patients with moderate to severe dementia of the alzheimer's type having completed Study **10158**	Dr Sauge Gauthier and Dr Nathan Hermann	Canada	450	Phase III	Ongoing, not recruiting
NCT00862940	H. Lundbeck A/S	A 1-year Randomised, Double-blind Placebo-controlled Study to Evaluate the Effects of Memantine on Rate of Brain Atrophy in Patients With Alzheimer's Disease	Dr David Wilkinson	Not specified	278	Phase IV	Completed
(Lundbeck 99819)	H. Lundbeck A/S	A Long-term Open-label Extension Study Evaluating the Safety and Tolerability of Memantine in Patients with Mild to Moderate Dementia of the Alzheimer's Type	Prof Serge Bakchine	Not specified	Not specified	Phase III	Not specified
(Lundbeck 99817)	H. Lundbeck A/S	A Double-blind, Randomized, Placebo-controlled Study to Evaluate the Safety and Efficacy of Memantine in Patients with Dementia of the Alzheimer's Type	Dr Pei-Ning Wang, Dr Sui-Hing Yan	Not specified	Not specified	Phase III	Not specified
(Asubio IE-2101)		Late Phase II Clinical Study of Sun Y7017 (Memantine Hydrochloride) in Patients with Moderately Severe to Severe Dementia of the Alzheimer's Type: Evaluation of Recommended Dose and Long-term Safety (Extension Study for Dose-Finding and Long-term Safety)	Prof Akira Homma	Not specified	Not specified	Phase II	Not specified
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asubio (IE-3501)		Phase III Study of SUN Y7017 (Memantine Hydrochloride) in Patients with Moderately Severe to Severe Dementia of the Alzheimer's Type	Prof Akira Homma	Not specified	Not specified	Phase III	Not specified

Register/ identifier number (if not available Study ID cited)	Sponsor/Collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status
Asubio (MA-3301)		Confirmatory randomized, Double-blind, Placebo-controlled Parallel Group Study of SUN Y7017 (Memantine Hydrochloride) in Patients with Mild to Moderate Dementia of the Alzheimer's Type	Prof Akira Homma	Not specified	Not specified	Phase III	Not specified
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NCT00624026	Merz Pharmaceuticals GmbH	Prospective, Single-Arm, Multicenter, Open-Label Study to Investigate the Efficacy and Tolerability of the Once Daily (OD) Memantine Treatment	Prof Joerg Schulz	Germany	107	Phase IIIb	Completed
NCT00649220	Merz Pharmaceuticals GmbH	Prospective, Single-arm, Multi-centre, Open-label Study to Investigate the Potential to Reduce Concomitant Antipsychotics Use in Patients With Moderate to Severe Dementia of Alzheimer's Type (DAT) Treated With Memantine	Prof Ralf Ihl	Germany	27	Phase IV	Completed
(MRZ 90001-AD-3001)	Merz Pharmaceuticals GmbH	Open-label, Single-arm, Multicenter Validation Study of the ROSA-Scale (Relevant Outcome Scale for Alzheimer Patients) in Patients with Dementia of Alzheimer's Type (DAT) Treated with Memantine Over a 3-Month Period	Prof Vjera Holthoff	Not specified	Not specified	Phase IIIb	Not specified
MRZ 9104	Merz Pharmaceuticals GmbH	Multicentre, Randomized, Double-blind, Comparative Study of the Efficacy and Tolerability of Akatinol Memantine and Placebo in Patients Suffering from Senile Dementia, Alzheimer Type	Prof Derouesne	Not specified	Not specified	Phase II	Not specified
(Forest MEM-MD-03 C)	Forest Laboratories	Extension of MEM-MD-01 and MEM-MD-02 Phase C = 52 Weeks Open	Not specified	Not specified	Not specified	Phase III	Not specified
(Forest MEM-MD-03 D)	Forest Laboratories	Extension of MEM-MD-01 and MEM-MD-02 Phase D = Open Continuation Until Memantine is Commercially Available	Not specified	Not specified	Not specified	Phase III	Not specified
(Forest MEM-MD-11 A/B)	Forest Laboratories	A Long-term Extension Study Evaluating the Safety and Tolerability of BID and QD Administration of Memantine in Patients with Mild to Moderate Dementia of the Alzheimer's Type. Extension of MEM-MD-10. Phase A/B = 8 Weeks Double_Blind + 20 Weeks Open	Not specified	Not specified	Not specified	Phase III	Not specified
(Forest MEM-MD-11 C)	Forest Laboratories	Extension of MEM-MD-10. Phase C = 52 Weeks Open	Not specified	Not specified	Not specified	Phase III	Not specified
(Forest MEM-MD-11 D)	Forest Laboratories	Extension of MEM-MD-10. Phase D = Open Continuation Until Memantine is Commercially Available	Not specified	Not specified	Not specified	Phase III	Not specified
(Forest MEM-MD-12 A)	Forest Laboratories	Open Extension of MEM-MD-12. 28 Weeks	Not specified	Not specified	Not specified	Phase III	Not specified
(Forest MEM-MD-12 B)	Forest Laboratories	Open Extension of MEM-MD-12 A. A Continuation Until Memantine is Commercially Available	Not specified	Not specified	Not specified	Phase III	Not specified
(Forest MEM-MD-22)	Forest Laboratories	A Randomized, Double-blind, Placebo-Controlled Evaluation of the Safety and Efficacy of Namenda in Nursing Home Patients with Moderate to Severe Alzheimer's Disease	Not specified	Not specified	Not specified	Phase IV	Not specified

Register/ identifier number (if not available Study ID cited)	Sponsor/Collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status
(Forest MEM-MD-23)	Forest Laboratories	A Randomized, Double-blind, Placebo-controlled, Evaluation of the Safety and Efficacy of Memantine in Patients with Moderate to Severe Alzheimer's Disease with Behavioral Disturbances	Not specified	Not specified	Not specified	Phase III	Not specified
NCT00401167	Sunnybrook Health Sciences Centre/ H. Lundbeck A/S	Phase IV-An Open-Label Prospective Study of Memantine in Institutionalized Patients With Severe Alzheimer's Disease and Significant Behavioural and Psychological Symptoms of Dementia	Nathan Herrmann MD	Canada	32	Phase IV	Completed
(Lundbeck 11875A)	Lundbeck A/S	An Open-label, Post-marketing, Naturalistic, Multi-centre Study Evaluating the Safety and Efficacy of Ebixa (Memantine) in the Treatment of Chinese Patients with Alzheimer's Disease	Hong Zhen	Not specified	Not specified	Not specified	Ongoing
(Lundbeck 12292A)	Lundbeck A/S	Memantine on Aggression and Agitation of AD – Open-label Study	Xin Yu, Wang Hu	Not specified	Not specified	Not specified	Ongoing
NCT00800709	Shanghai Mental Health Center/Lundbeck A/S	Memantine and Changes of Biological Markers and Brain PET Imaging in Alzheimer's Disease – Double-blind, Randomized, Placebo-controlled	Xiao Shi Fu	China	26	Phase IV	Recruiting
(Lundbeck 12732A)	Lundbeck A/S	An Open-label, Observational, Multicentre Study Evaluating Efficacy and Safety Profile of Memantine in Chinese Patients with Alzheimer's Disease	Yinhua Wang	Not specified	Not specified	Not specified	Ongoing
(Lundbeck 13143A)	Lundbeck A/S	A randomized, Double-blind, Placebo-controlled Study to Investigate the Improvement of Language Function in Chinese AD Patients with Memantine	Dantao Peng	Not specified	Not specified	Not specified	Not yet initiated
(Lundbeck 11232)	Lundbeck A/S	A Randomized, Double-blind, Placebo-controlled Trial of Memantine in the Treatment of the Agitation in Alzheimer's Dementia	Fox	Not specified	Not specified	Not specified	Ongoing
(Lundbeck 11786A)	Lundbeck A/S	Impact on Aggressive Behaviour and Cognition of Switching from Donepezil to Memantine in Patients with Moderate-to-Severe AD- Design: Open-label, Pilot, Observational, Head-to-head	Huertas	Not specified	Not specified	Not specified	Ongoing
(Lundbeck 10710)	Lundbeck A/S	Memantine Effects on Cortical Excitability and its Neurophysiological/Neuropsychological Effects on AD Patients in Combination with AChEI: A Pilot Study – Design: 1st Phase Open-label, 2nd Phase Partial Blind	Stefani	Not specified	Not specified	Not specified	Completed
(Lundbeck 10997)	Lundbeck A/S	Behaviour and Cognition in AD Patients Treated with the NMDA Receptor Antagonist Memantine: Correlation with Apoptotic Mechanism	Spalleta	Not specified	Not specified	Not specified	Ongoing
(Lundbeck 11830A)	Lundbeck A/S	Investigating the Effect of Treatment on Neurotrophic Factors by Means of Functional Magnetic Resonance Imaging (FMRI) in Patients with Alzheimer's Disease – Design: Double-blind, Prospective randomized	Tamer Aker	Not specified	Not specified	Not specified	Not yet initiated
(MRZ 10001-0207)	Merz Pharmaceuticals	A Randomized, Double-blind, Controlled Trial to Evaluate the Efficacy and	Heuser	Not specified	Not	Not	Ongoing

Register/ identifier number (if not available Study ID cited)	Sponsor/Collaborators	Trial name	Investigator	Country	Established/ anticipated sample size	Phase	Status
	GmbH	Safety of an Antidementive Combination Therapy (Galantamine and Memantine) in Subjects with Mild-to-Moderate Stage of Probable AD (MEGA-COMBI-2)			specified	specified	

Appendix 12: PRISMA statement checklist

TABLE 58 *PRISMA comparison of the quality of included clinical effectiveness systematic reviews A–D*

Section/topic	Item	Checklist item	A	B	C	D
Title						
Title	1	Identify the report as a systematic review, meta-analysis or both	✗	✗	✓	✗
Abstract						
Structured summary	2	Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, interventions, study appraisal and synthesis methods, results, limitations, conclusions and implications of key findings, systematic review registration number	✓	✓	✓	✓
Introduction						
Rationale	3	Describe the rationale for the review in the context of what is already known	✓	✓	✓	✓
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes and study design	✓	~	~	✓
Methods						
Protocol & registration	5	Indicate if a review protocol exists, if and where it can be accessed and if available, provide registration information including registration number	~	✗	✗	✓
Eligibility criteria	6	Specify study characteristics and report characteristics used as criteria for eligibility, giving rationale	✓	✓	✓	✓
Information sources	7	Describe all information sources in the search and date last searched	✓	✓	✓	✓
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	✗[1]	✗	✗	✓
Study selection	9	State the process for selecting studies	✓	~	✓	✓
Data collection process	10	Describe method of data extraction from reports and any processes for obtaining and confirming data from investigators	✓	✓	✓	✓
Data items	11	List and define all variables for which data are sort and any assumptions and simplifications made	✓	✓	✓	✓
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies and how this information is to be used in any data synthesis	✓	✗	✗	✓
Summary measures	13	State the principal summary measures	✓	✓	✓	✓
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measure of consistency for each meta-analysis	✓	✓	✓	✓
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence	✗	✗	✓	✗
Additional analyses	16	Describe methods of additional analyses, if done, indicating which were pre-specified	✗	-	-	-

[1] Information provided about where to find the search strategy.

Section/topic	Item	Checklist item	A	B	C	D
Results						
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally from a flow diagram	✗	✓	✓	✓
Study characteristics	18	For each study, present characteristics for which data were extracted and provide the citations	✓	✓[2]	✓	✓
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessments	✓	✗	✗	✓
Results of individual studies	20	For all outcomes considered, present for each study (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	✓	✓	~	✓
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measure of consistency	✓	✓	~	✓
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies	✗	✗	✗	✗
Additional analysis	23	Give results of additional analyses, if done	✓	-	-	-
Discussion						
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome: consider their relevance for key groups	✓	✓	✓	✓
Limitations	25	Discuss limitation at study and outcome level and at review level	~	~	✓	✓
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implication for future research	✓	✓[3]	✓[4]	✓
Funding						
Funding	27	Describe sources of funding for the systematic review and other support and role of funders for the systematic review	~	✓	✓	✗

A Birks 2009, B Raina 2008, C Hansen 2007, D Institute for Quality and Efficiency in Health Care 2007,

✓ item present, ✗ item absent, ~ partially complete, - not applicable

[2] Only available on-line

[3] No research recommendations given

[4] No research recommendations given

Appendix 13: Summary Tables of results from the Institute of Quality and Efficiency in Health Care.

TABLE 59 *Summary of results on therapy goals from placebo-controlled studies*

Therapy goal	Donepezil	Galantamine	Rivastigmine
Patient-relevant therapy goals			
Activities of daily living	↑	↑	↑
Psychopathological symptoms	⇔	↑	No data available
Cognitive function	↑↑	↑↑	↑↑
Health-related quality of life	⇔	No data available	No data available
Nursing home care (institutionalisation)	No data available	No data available	No data available
Mortality	(⇔)	(⇔)	(⇔)
Adverse events	↓↓	↓↓	↓↓
Therapy goals relevant to relatives			
Quality of life of (caregiving) relatives	⇔	↑	No data (or only uncertain data) available
Degree of care provided	⇔	↑	No data available
Additional information			
Clinical disease stage	↑↑	↑↑	↑↑
Dose-effect relationship			
	Lower efficacy (cognition) and fewer adverse effects for low (5 mg) or flexible dose	No favourable effect, and not consistently more adverse effects with the 8 mg dose; otherwise no differences	Uncertain effect for 1–4 mg

↑↑, ↓↓ = Evidence of a favourable or unfavourable effect.
↑, ↓ = Indication of a favourable or unfavourable effect.
⇔ = No indication of a difference
( ) = Few data available

TABLE 60 *Summary of results on therapy goals from comparative studies in AChEIs*

Therapy goal	DON vs. GAL	DON vs. RIV	GAL vs. RIV
Patient-relevant therapy goals			
Activities of daily living	(⇔)	(↓)[a]	No data available
Psychopathological symptoms	(⇔)	⇔	(⇔)
Cognitive function	(⇔)	⇔	No data available
Health-related quality of life	No data available	No data available	No data available
Placement in a nursing home (institutionalisation)	No data (or only uncertain data) available	No data available	No data available
Mortality	(⇔)	⇔	No data available
Adverse events	(⇔)	↑↑	(⇔)
Therapy goals relevant to relatives			
Quality of life of (caregiving) relatives	No data available	No data available	No data available
Degree of care provided	No data available	No data available	No data available
Additional information			
Clinical disease stage	No data available	No data available	No data available
Comments	In the larger study, possibly less favourable dose for DON	Possibly less favourable dose for DON	

a: Results affected by high discontinuation rates.

↑↑, ↓↓ = Evidence of a favourable or unfavourable effect.
↑, ↓ = Indication of a favourable or unfavourable effect.
⇔ = No indication of a difference
( ) = Few data available

DON = donepezil, GAL = galantamine, RIV = rivastigmine

Appendix 14: Memantine ± AChEI *v.* placebo ± AChEI

Memantine ± AChEI *v.* placebo ± AChEI

If, as per the 2004 review, it is assumed that evidence on memantine monotherapy is equivalent to that detailing combination therapy including memantine, a larger evidence base can be assembled. The following analysis combines evidence on memantine monotherapy v. placebo (as detailed and explored in Section 4.6.4) with that on memantine + AChEIs v. placebo + AChEIs (Section 4.8)

Cognition

New data

Data from newly identified RCTs are presented in Section 4.6.4 (memantine monotherapy *v.* placebo) and Section 4.8 (memantine + AChEI *v.* placebo + AChEI).

Synthesis with existing evidence-base

ADAS-cog

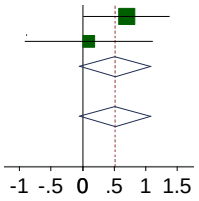
Because ADAS-cog scores are only reported by one relevant study (Porsteinsson and colleagues[36]; see ¶4.8 it is not possible to undertake any synthesis on this outcome.
An additional source of data is Mecocci and colleagues' pooled IPD study,[37] which includes the participants from Porsteinsson and colleagues' RCT[36] and also relevant individuals from two trials that could not be included in this review because the primary publications also reported participants from beyond the UK licensed indication of memantine[38;39]). This analysis suggests that, following 24–28 weeks of treatment with memantine ± AChEIs, a benefit of 1.55 points (95%CI 0.487, 2.613) over individuals taking placebo ± AChEIs is seen.

MMSE

A synthesis of data from the existing evidence with the new study showed there was no significant cognitive benefit from memantine either combined with an AChEI or on its own compared with placebo, either on its own or with an AChEI, when measured by the MMSE at 24 to 28 weeks follow up (see *Figure 56).*

FIGURE 56 *Random-effects meta-analysis: MMSE at 24–28wk (mean change from baseline) – memantine ± AChEI v. placebo ± AChEI*

	Memantine ± AChEI			Placebo ± AChEI					
	N	mean	SD	N	mean	SD	WMD	(95%CI)	Wght
LOCF analysis									
Reisberg et al. (2003)[34]	124	-0.50	2.40	124	-1.20	3.02	0.700	(0.021, 1.379)	69.1
Porsteinsson et al. (2008)[36]	210	16.50	5.38	198	16.40	5.08	0.100	(-0.915, 1.115)	30.9
subtotal (Q=0.93 [p on 1 d.f.=0.336]; I^2=0.0%; τ^2=0.000)							**0.515**	**(-0.050, 1.079)** p=0.074	100.0
Overall pooled estimate (Q=0.93 [p on 1 d.f.=0.336]; I^2=0.0%; τ^2=0.000) Small-study effects: not calculable							**0.515**	**(-0.050, 1.079)** p=0.074	

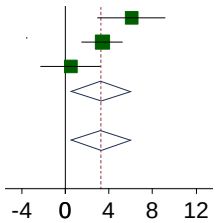


Severe Impairment Battery

In contrast, a significant benefit was seen when cognitive outcomes were measured with the SIB. The overall pooled estimate has been calculated as WMD=3.27 (95%CI 0.55, 6.04), p=0.021 (see *Figure 57).*

FIGURE 57 *Random-effects meta-analysis: SIB at 24–28wk (mean change from baseline) – memantine ± AChEI v. placebo ± AChEI*

	Memantine ± AChEI			Placebo ± AChEI					
	N	mean	SD	N	mean	SD	WMD	(95%CI)	Wght
LOCF analysis									
Reisberg et al. (2003)[34]	124	-4.00	11.34	123	-10.10	13.50	6.100	(2.989, 9.211)	29.5
Tariot et al. (2004)[40]	198	0.90	9.43	196	-2.50	9.66	3.400	(1.515, 5.285)	38.6
Van Dyck et al. (2007)[35]	170	-2.00	13.04	165	-2.50	12.85	0.500	(-2.272, 3.272)	31.9
subtotal (*Q*=7.03 [*p* on 2 d.f.=0.030]; I^2=71.5%; τ^2=4.256)							**3.270**	**(0.500, 6.041)** *p*=0.021	**100.0**
Overall pooled estimate (*Q*=7.03 [*p* on 2 d.f.=0.030]; I^2=71.5%; τ^2=4.256) Small-study effects: Egger's *p*=0.933							**3.270**	**(0.500, 6.041)** *p*=0.021	



IPD: Mecocci et al. (2009)[37] 3.175 (95%CI 1.566, 4.784)

Functional

New data

For data on functional outcomes in newly identified studies of memantine ± AChEIs *v.* placebo ± AChEIs, see *Section 4.8.1.2.2* and *Table 45*

Synthesis with existing evidence-base

Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory

When we meta-analyzed the data for function outcome measures from new and existing studies we found more favourable results for memantine when considered on its own and in combination with an AChEI. When measured with the ADCS-ADL at 12 weeks and 24-28 weeks the overall pooled estimates showed significant gain from memantine, 12 weeks; WMD= 1.03 (95%CI 0.29,1.77), p=0.006 and 24-28 weeks; WMD= 1.41 (95%CI 0.51, 2.30, p=0.002 (see *Figure 58* and *Figure 59*).

FIGURE 58 *Random-effects meta-analysis: ADCS-ADL$_{19}$ at 12wk (mean change from baseline) – memantine ± AChEI v. placebo ± AChEI*

	Memantine ± AChEI			Placebo ± AChEI				
	N	mean	SD	N	mean	SD	WMD (95%CI)	Wght
OC population								
Reisberg et al. (2003)[34]	107	-0.60	6.21	106	-2.10	5.15	1.500 (-0.031, 3.031)	23.4
Tariot et al. (2004)[40]	185	-0.47	5.64	170	-1.75	5.87	1.285 (0.085, 2.485)	38.2
Van Dyck et al. (2007)[35]	147	0.00	5.46	150	-0.49	5.05	0.488 (-0.709, 1.684)	38.4
subtotal (Q=1.33 [p on 2 d.f.=0.515]; I^2=0.0%; τ^2=0.000)							**1.029 (0.288, 1.771)**	**100.0**
							p=0.006	
Overall pooled estimate							**1.029 (0.288, 1.771)**	
(Q=1.33 [p on 2 d.f.=0.515]; I^2=0.0%; τ^2=0.000)							p=0.006	
Small-study effects: Egger's p=0.585								

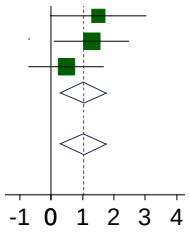


FIGURE 59 *Random-effects meta-analysis: ADCS-ADL$_{19}$ at 24–28wk (mean change from baseline) – memantine ± AChEI v. placebo ± AChEI*

	Memantine ± AChEI			Placebo ± AChEI				
	N	mean	SD	N	mean	SD	WMD (95%CI)	Wght
LOCF analysis								
Reisberg et al. (2003)[34]	124	-3.10	6.79	123	-5.20	6.33	2.100 (0.463, 3.737)	30.0

Tariot et al. (2004)[40]	198	-2.00	7.04	197	-3.40	7.16	1.400	(0.000, 2.800)	41.0
Van Dyck et al. (2007)[35]	171	-2.00	7.85	165	-2.70	7.71	0.700	(-0.963, 2.363)	29.0
subtotal (Q=1.38 [p on 2 d.f.=0.501]; I^2=0.0%; τ^2=0.000)							**1.407**	**(0.510, 2.303)**	**100.0**
								p=0.002	
Overall pooled estimate							**1.407**	**(0.510, 2.303)**	
(Q=1.38 [p on 2 d.f.=0.501]; I^2=0.0%; τ^2=0.000)								p=0.002	
Small-study effects: Egger's p=0.955									

favours placebo ± AChEI ***favours memantine ± AChEI***

Behavioural and mood

New data

Behavioural outcome data reported in included RCTs of memantine ± AChEIs in comparison with placebo ± AChEIs are tabulated in *Table 28* and *Table 46*

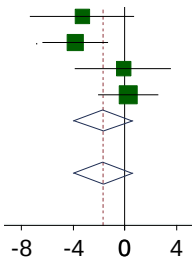
Synthesis with existing evidence-base

NPI

A meta-analysis of data from new and existing studies using the NPI at 24-28 weeks showed no significant gain from memantine.

FIGURE 60 *Random-effects meta-analysis: NPI at 24–28wk (mean change from baseline) – memantine ± AChEI v. placebo ± AChEI*

	Memantine ± AChEI			Placebo ± AChEI					
	N	**mean**	**SD**	**N**	**mean**	**SD**	**WMD**	**(95%CI)**	**Wght**
LOCF analysis									
Reisberg et al. (2003)[34]	120	0.50	15.76	119	3.80	16.06	-3.300	(-7.334, 0.734)	18.9
Tariot et al. (2004)[40]	193	-0.10	11.20	189	3.70	14.00	-3.800	(-6.346, -1.254)	29.3
Van Dyck et al. (2007)[35]	161	1.00	16.50	154	1.10	17.37	-0.100	(-3.845, 3.645)	20.6
Porsteinsson et al. (2008)[36]	212	0.70	12.01	209	0.40	12.29	0.300	(-2.022, 2.622)	31.2
subtotal (Q=6.74 [p on 3 d.f.=0.081]; I^2=55.5%; τ^2=2.943)							**-1.664**	**(-3.947, 0.619)**	**100.0**
								p=0.153	
Overall pooled estimate							**-1.664**	**(-3.947, 0.619)**	
(Q=6.74 [p on 3 d.f.=0.081]; I^2=55.5%; τ^2=2.943)								p=0.153	
Small-study effects: Egger's p=0.817									



favours memantine ± AChEI ***favours placebo ± AChEI***

This result closely reflects the findings of Gauthier and colleagues' analysis of pooled IPD from six trials (including the four included here),[41] in which the WMD at 24–28wk (LOCF analysis) was -1.675 (95%CI: -3.270, -0.080). This publication also provides information on the individual items making up the NPI. At 24 weeks, participants taking memantine ±

AChEIs showed more improvement (or less deterioration) then those taking placebo ± AChEIs on all 12 single items of the NPI, with the difference achieving conventional levels of statistical significance (p<0.05 by Kruskall–Wallis test without adjustment for multiplicity of testing) on three items: delusions, agitation/aggression, and irritability.

An additional pooled IPD analysis[42] concentrates on treatment effect of memantine ± AChEIs on agitation and psychotic symptoms, concluding that therapy with memantine confers benefit on the NPI cluster (agitation/aggression, delusions, and hallucinations) score at both 12wk (-0.8 points *v.* 0.5 points; p=0.0014) and 24–28wk (-0.7 points *v.* 0.7 points; p=0.0004). This effect was substantially driven by a large difference on the agitation item: while the proportions of responders in the single items delusions and hallucinations were numerically higher for participants receiving memantine, the difference from placebo did not reach statistical significance.

Global effect

New data

Data from newly identified RCTs are presented in *Table 29* (memantine monotherapy *v.* placebo) and Section 4.8.1.2.4 (memantine + AChEI *v.* placebo + AChEI).

Synthesis with existing evidence-base

Clinician Interview-Based Impression of Change

When the new data from mono and combined therapies were synthesized with the existing data, the overall pooled estimate showed a significant gain from memantine, WMD=-0.21 (95%CI -0.34, -0.080), p=0.002 (see *Figure 61).*

FIGURE 61 *Random-effects meta-analysis: CIBIC-plus at 24–28wk (mean change from baseline) – memantine ± AChEI v. placebo ± AChEI*

	Memantine ± AChEI			Placebo ± AChEI				
	N	mean	SD	N	mean	SD	WMD (95%CI)	Wght
LOCF analysis								
Reisberg et al. (2003)[34]	118	4.50	1.12	118	4.80	1.09	-0.300 (-0.582, -0.018)	17.1
Tariot et al. (2004)[40]	198	4.41	1.04	196	4.66	1.05	-0.250 (-0.457, -0.043)	26.8
Van Dyck et al. (2007)[35]	171	4.30	1.00	163	4.60	1.00	-0.300 (-0.515, -0.085)	25.5
Porsteinsson et al. (2008)[36]	214	4.38	1.00	213	4.42	0.96	-0.040 (-0.226, 0.146)	30.6
subtotal (Q=4.39 [p on 3 d.f.=0.223]; I^2=31.6%; τ^2=0.006)							**-0.207 (-0.338, -0.075)**	**100.0**

		p=0.002
Overall pooled estimate		**-0.207 (-0.338, -0.075)**
(*Q*=4.39 [*p* on 3 d.f.=0.223]; I^2=31.6%; τ^2=0.006)		*p*=0.002
Small-study effects: Egger's *p*=0.321		
	favours memantine ± AChEI	***favours placebo ± AChEI***

Safety

A pooled IPD paper by Farlow and colleagues provides extensive detail on the safety profile of memantine±AChEI, as investigated in trials with placebo±AChEI control arms.[43] In total 1,242 individuals who received memantine are compared with 1,242 who did not. Their findings showed that overall the proportion of adverse events in those with moderate to severe Alzheimer's was the same in treatment and control arms (68%). Agitation (12%) and falls (7%) caused the greatest percentage of adverse events in the memantine group, with agitation being the most frequently cited cause for discontinuation due to an AE, n=51 (2%). Agitation (18%) and falls (8%) were also the most frequent AE reported by the control group, again agitation was the most likely cause of AE related discontinuation, n=72 (14%).[43]

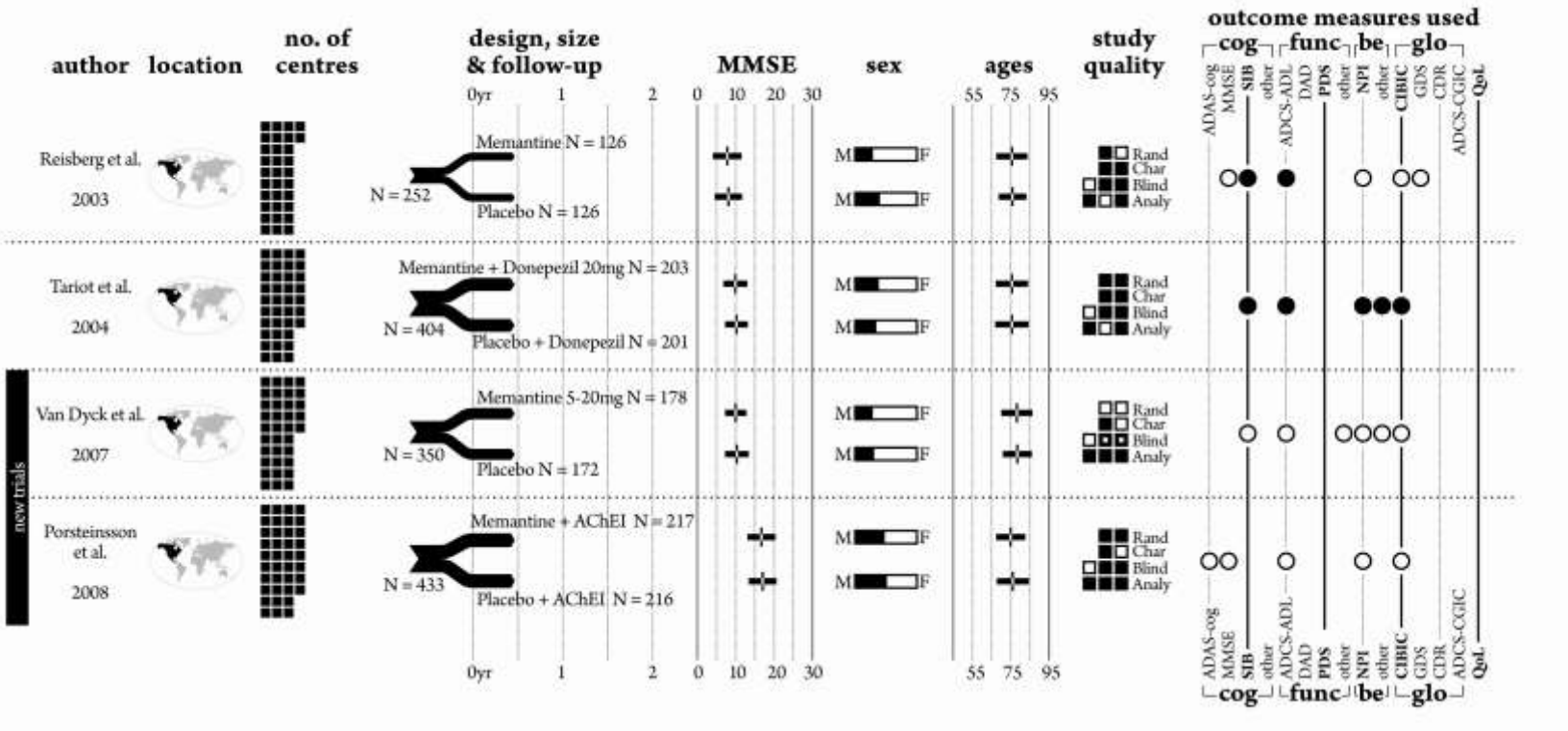
Summary: memantine ± AChEI v. placebo ± AChEI

When data from monotherapy and combination therapy were combined in meta-analysis the results from cognitive outcomes varied. Analyses using the ADAS-cog and the SIB showed significant benefits from memantine ± AChEI, whilst that using the MMSE did not. Functional and global outcomes were also shown to favour memantine ± AChEI, although, there was no similar benefit shown from behavioural outcomes.

Graphical summary of memantine± AChEI v. placebo ± AChEI

The summary graphic in **FIGURE 62** clearly shows the difference in results in studies included in the new and previous reviews. The main difference between these two groups of studies is that those in the 2004 review were not analysed by full ITT and those included in the 2010 review were. The lack of ITT analysis may introduce bias.

FIGURE 62 *Summary of all studies included in the 2004 and 2010 reviews- memantine ± AChEI v. placebo ±AChEI*



Appendix 15: Update on evidence about the care cost of Alzheimer's disease in the UK

In relation to Alzheimer's patients in the UK, there have been three major reports published since 2004 which contain care cost estimates: the *Dementia UK* report in 2007 (by the personal and Social Services Research Unit at the London School of Economics, the Institute of Psychiatry and the Alzheimer's Society),[44] a report by the National Audit Office in 2007 on improving services for people with dementia,[45] and a more recent (2010) cost of illness study by a health economics.[46] The 2010 study estimates that dementia will cost the UK economy £23 billion this year – and approximately 60% of this cost would be attributable to Alzheimer's disease.[46] This translates to approximately £27,600 per patient per year.
We also reviewed a number of recent papers about the cost of Alzheimer's disease for patients outside the UK, including a recent systematic review of cost-of-illness studies which focused on the stage dependency of costs,[47] and a recent systematic review of the cost of dementia in Europe.[48]

1. **Which clinical events, or main stages of Alzheimer's disease progression - or changes in a patient's living situation - lead to a step-change in health or social care costs?**

In the UK, the main marker of Alzheimer's disease progression which leads to a step-change in health/social care costs appears to be the events that trigger the transition from home or community care to institutional care (*Dementia UK* report; Knapp et al., 2007).[44] When deterioration in the condition necessitates a move into long-term institutional care, the cost of care then shifts to the state - either via the NHS or social services, NAO report, 2007. [45] This shift in cost carrying is evident in *Figure 64*, showing the annual cost of services in the UK used by people with late-onset dementia by disease severity and care setting (Dementia UK, Knapp et al 2007). While still living in the community, care for individuals with severe Alzheimer's disease, informal care costs are estimated at £27,096 per annum, compared to combined NHS, SSD and accommodation costs of £10,377. When community care moves to residential care, informal care costs drop to an estimated £938 per annum, compared to combined NHS, SSD and accommodation costs of £30,358 p.a. – of which accommodation costs constitute the majority at £28,646 p.a.

The transition from community care to institutional care is clearly related to an increase in disease severity, and this increase in severity is related to a rise in costs – however, the relationship between disease progression and increase in costs is not clear cut (Lowin et al, 2001; Souetre et al., 1999).[49;50] A report on Alzheimer's and dementia by the Parliamentary Office of Science and Technology (POST) stated that the greatest impact caused by Alzheimer's and dementia on sufferers, carers and society is concentrated in individuals in the severe stages of disease progression, that is between 17 and 28% of people with dementia over 65 yrs old.).[51] The POST report also highlighted that in 2007, 62-75% of residents in care institutions had dementia (Parliamentary Office of Science and Technology, 2007)

Kavanagh & Knapp (2002) showed that cognitive disability, in the context of its cost-raising impact, needs to be understood in the context of comorbid disabilities and their complex interactions rather than viewed in isolation.[52] Specifically, when analysing cognitive disability alongside non-disability variables, cognitive disability is strongly significant ($P<0.001$) and the coefficient (4.286, $R^2=0.062$) is three times larger than when analysed with individual disability domains (continence disability, hearing morbidity, summary mental disability, summary physical disability, summary physical ability x living alone and whether patients had had a recent underlying condition) as independent variables (1.438, $R^2=0.136$). However, the overall goodness of fit is worse when analysing cognitive disability with non-disability variables as can be seen from the R^2 values.

2. Which markers or measures of Alzheimer's disease progression (e.g. cognitive function, functional ability, behavioural or psychotic symptoms, physical health), either individually or in combination, are most predictive of health and/or social care costs?

Patients are commonly assessed for cognitive function using the Mini Mental State Examination (MMSE) and are allocated into distinct severity groups. A less commonly-used measure of cognitive and behavioural function is the Office of Population Censuses and Surveys (OPCS disability instrument; Kavanagh & Knapp, 2002).[52] In this instance, the researchers reviewed survey data already gathered for a 1988 study (Martin et al., 1988 referenced in Kavanagh & Knapp, 2002) which measured disability across 13 domains including locomotion, dexterity, continence, intellectual functioning, consciousness and disfigurement. Kavanagh and Knapp reported that the instrument has good inter-rater reliability and is highly correlated with the Barthel Index although more comprehensive. They found that the link between cognitive disability and cost was sensitive to the inclusion or exclusion of behavioural disability.

The Barthel ADL Index is used to assess functional status on a scale of 0-20 with zero indicating the greatest impairment. There has been a more detailed scale developed which rates ten items individually on a 0-10 scale (with a maximum score of 100). Wolstenholme et al. (2002) report that both the MMSE and the Barthel Index are significant predictors of time to institutionalisation and cost of care, but changes in the Barthel Index are particularly important in predicting costs outside institutional care.[53]

Wolstenholme et al. (2002) also examined associations between costs and cognitive assessment scores, reporting from a regression-based analysis that each one-point decline in the MMSE score was associated with a cost of care increase of £56 every four months, whereas each one-point decline in the Barthel score was associated with a cost of care increase of £586 every four months.

On a neurological level, structural imaging (MRI or CT scanning) and functional imaging (PET and SPET scans) are sometimes carried out in order to exclude other cerebral pathologies and to help establish the type of dementia. Individual monitoring over time can indicate disease progression and PET scanning with the use of a dye can indicate amyloid plaques in Alzheimer's, again allowing monitoring of disease progression (Parliamentary Office of Science and Technology, 2007). However, access to resources is limited and NICE estimates that the additional national cost of implementing its recommendation on structural imaging will be £20.22 million (Improving services and support for people with dementia, 2007 – NAO).

3. In England and Wales, what are the typical stages or pathways of care for people with Alzheimer's disease?

This has been largely summarized in the Background section of the main report.

Q5. In England and Wales, to what extent are the costs of caring for people with Alzheimer's disease borne by (i) the NHS (ii) Personal Social Services (iii) local authorities (iv)other organisations such as voluntary organisations?

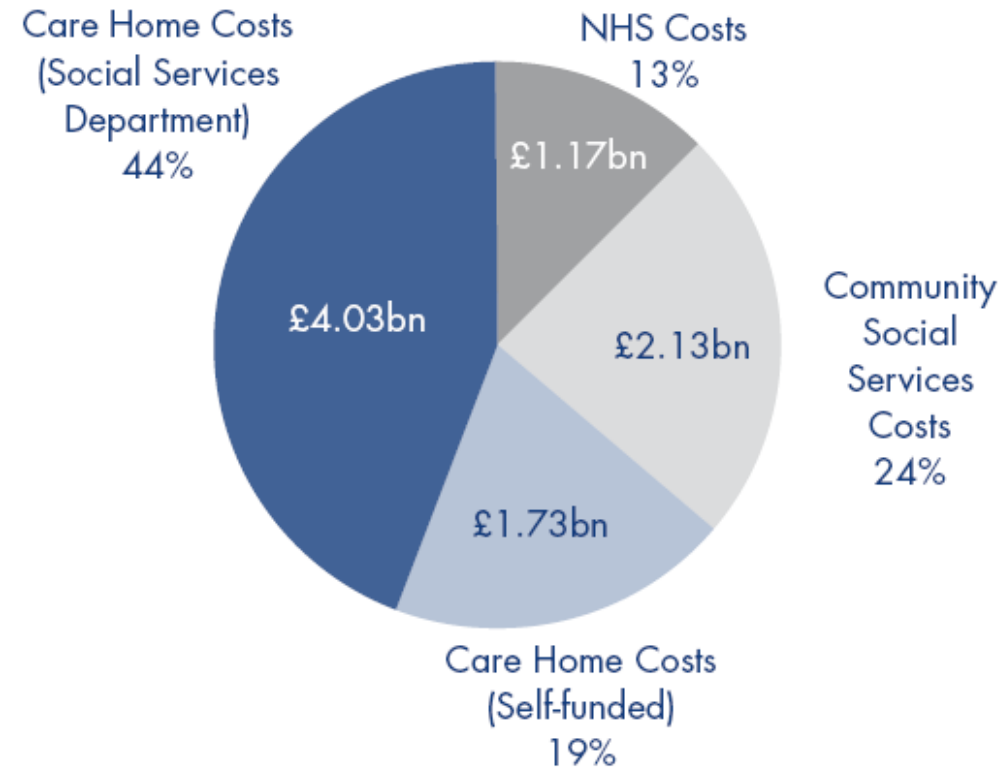
Within the community, informal care costs are typically borne by the patient and/or carers and these make up the majority of the financial burden for mild, moderate and severe late-onset dementia (Knapp et al., 2007).[44] In their 2007 document 'Dementia UK: The Full Report', Knapp and colleagues assessed mean annual informal care costs for those with late-onset dementia in 2005/06 as rising from £9,246 for individuals with mild impairment, to £17,223 for people - with moderate symptoms and finally to £27,096 for people with severe impairment.

Whilst informal care costs reduce when individuals with Alzheimer's disease move into residential care,[44] only Wolstenholme and colleagues (2002) were able to attach a clear accommodation and care cost increase of around £8,000 per four month period for patients in institutional care, assuming all other cost variables hold constant.[53] This is at least partly due to the lack of a 'single assessment process' (POST 278, 2007) with a clear care pathway catering for people with Alzheimer's disease throughout their disease progression and across all the agencies involved at various stages.

However, Figure 63 gives a clear picture of the split between the NHS (13%), Social Services (care home costs at 44%), local authorities and other organisations such as voluntary organisations (community social services costs at 24%) and individuals (self-funded care home costs at 19%) in caring for dementia in 2007 (from Knapp et al., 2007).[44]

Further breakdown of individual costs is given in Figure 66, although the allocation of these costs is by type of resource (e.g. health care costs, social care costs) rather than by funding organisation (Luengo-Fernandez et al., 2010).[46]

FIGURE 63 *The total estimated direct cost of dementia is £9.1 billion, the bulk of which relates to the cost of care home places*



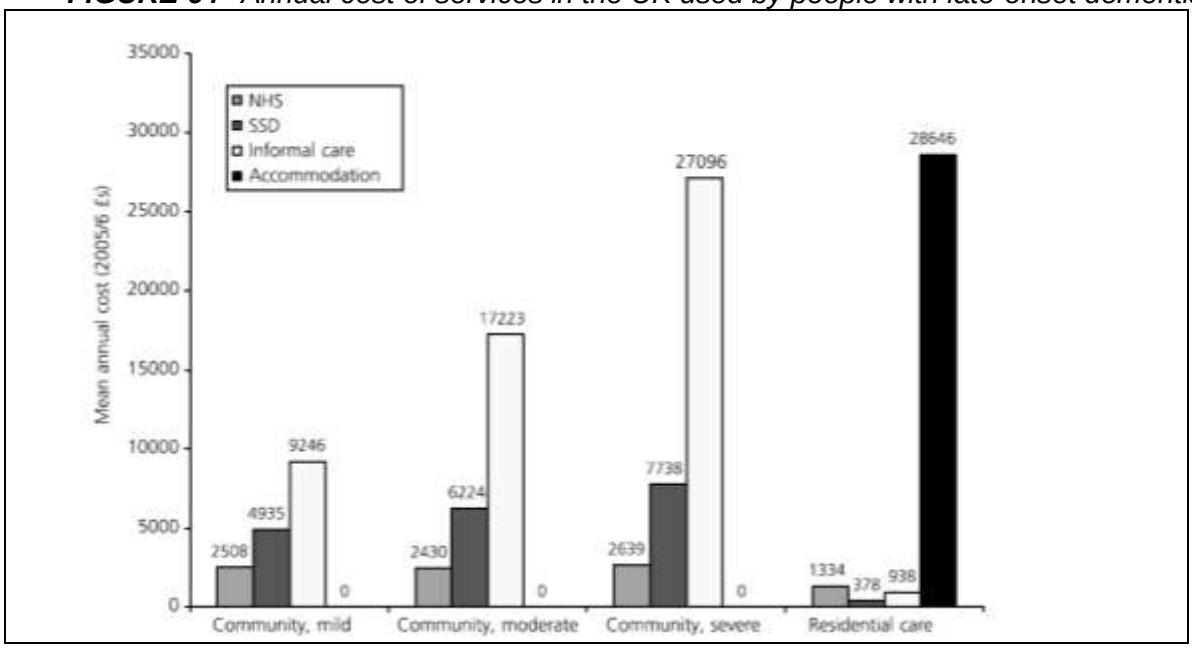
Source: Knapp et al. (2007) Dementia UK: Report to the Alzheimer's Society, King's College London and London School of Economics and Political Science

NOTE

£5.76 billion, equivalent to almost two thirds of the direct costs of dementia (i.e. excluding informal care costs), borne by families, the NHS and social services, relates to the provision of care home places for people with dementia. NHS costs and social services costs account for the remaining one third of direct costs.

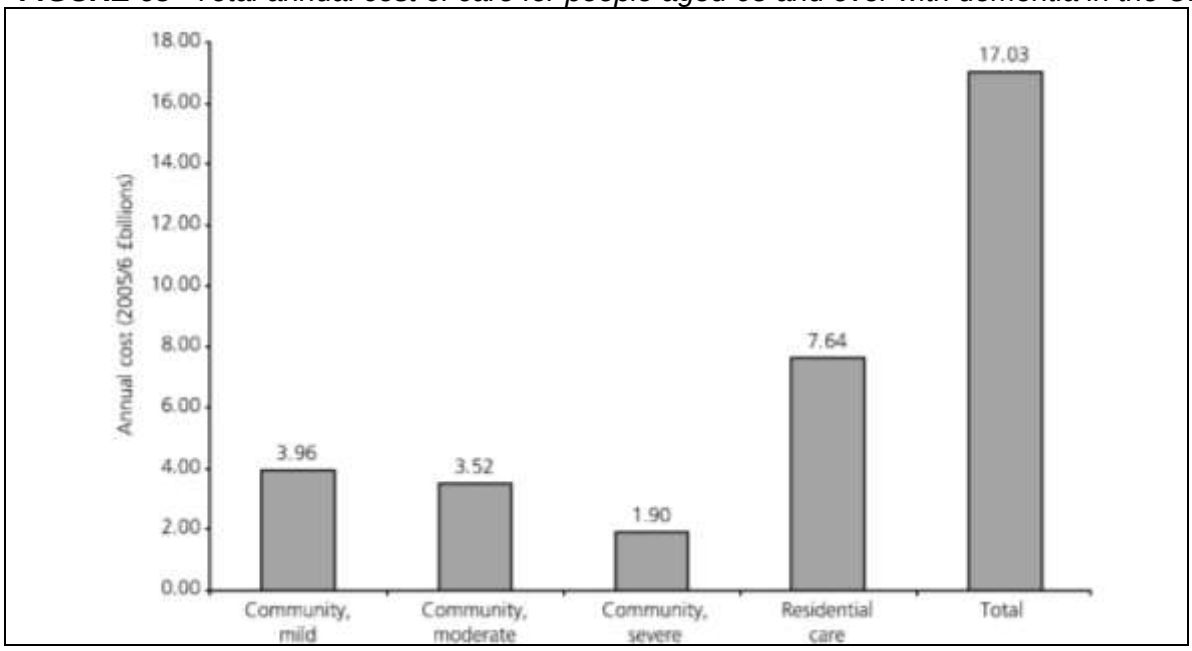
Source: Improving services and support for people with dementia, National Audit Office, 2007.

FIGURE 64 *Annual cost of services in the UK used by people with late-onset dementia*



source: Dementia UK: The Full Report by the Alzheimer's Society 2007[44]

FIGURE 65 *Total annual cost of care for people aged 65 and over with dementia in the UK*



source: Dementia UK: The Full Report by the Alzheimer's Society 2010[44]

FIGURE 66 *Cost of dementia in 2010 in the UK*

Type of resource used	Unit of measurement	Units of resources consumed	Average unit cost, £	Total cost, thousands, £
HEALTH CARE				
Primary care	Nurse home visits	2,492,220	26	64,798
	Nurse surgery visits	186,753	9	1,681
	GP home visits	3,567,046	58	206,889
	GP surgery visits	1,161,197	36	41,803
	GP telephone visits	83,939	22	1,847
	Total			317,017
A&E	Attendances	298,867	89	26,737
Outpatient care	Attendances	489,766	112	55,044
Inpatient care	Hospital bed-days	1,485,471	311	462,590
	Hospital day cases	209	2,755	576
Medications				228,399
Private care	Private part of total health expenditure	12.70%		109,469
Health care cost subtotal				**£1,199,832**
SOCIAL CARE				
Long-term care	Years in long-term care accommodation	304,850	29,822	9,091,177
Social care cost subtotal				**£9,091,177**
NON-HEALTH/SOCIAL CARE				
Informal care	Hours of care provided by economically active carers	512,457,980	13	6,671,816
	Hours of care provided by economically inactive carers	996,638,065	6	5,710,736
Mortality	Working years lost (men)	2,025	32,838*	22,515
	Working years lost (women)	1,933	18,958*	5,994
Morbidity (friction adjusted)	Certified incapacity days	160,603	104	16,743
	Work days lost	38,380	104	4,001
Non-health/social care subtotal (friction adjusted)				**£12,431,804**
Total economic burden (friction adjusted)				**£22,722,813**

*Future earnings discounted using an annual rate of 3.5%.

Source: Dementia 2010. Alzheimer's Research Trust..[46]

Appendix 16: Consideration of a two-dimensional Markov model for Alzheimer's disease

The feasibility of a two-dimensional Markov model has been considered. Limitations for the development of such a model include structural uncertainty (such as how to translate the treatment effect measured and reported in RCTs to transition probabilities and/or state occupancy proportions for the Markov model) in addition to limitations of data availability.

Background

Important predictors of QoL and cost were assessed to identify the variables most likely to be considered for the 2-dimensional model: with institutionalisation the variable associated with largest cost changes, but unclear evidence as to the role of cognition, function and behaviour on the QoL of someone with AD (with behaviour and carer-related variables being found to be related to probability of institutionalisation). Further investigation reviewed the relationships between cognition, behaviour and function and the different measures used to reflect these variables. The review suggested some evidence for a correlation between cognition and functional status, whereas for cognition and behavioural status the evidence was unclear. Thus, leading to cognition and behavioural status as prime candidates for the 2-dimensional model, although functional status was not totally ruled out.

Two-dimensional Markov model: cognitive status v. behavioural or functional status

Best supportive care cohort – AD progression

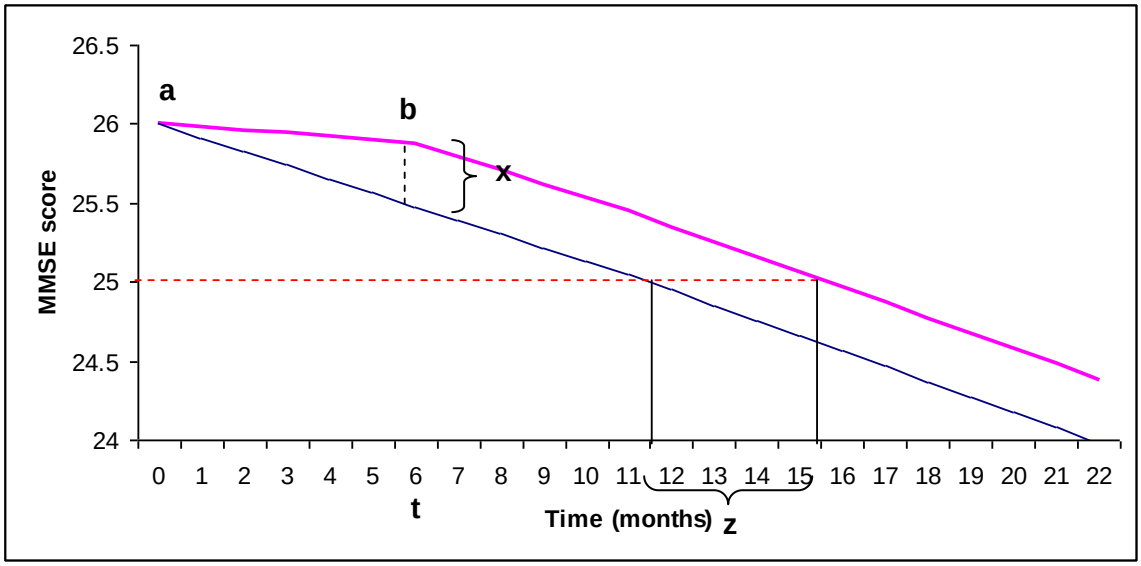
Requested IPD for control groups from manufacturers to model disease progression along two dimensions. Also requested IPD from two UK longitudinal studies: LASER-AD and Oxfordshire dataset. The majority of people in the LASER-AD study were treated with cholinesterase inhibitors, however the data are of use for characterising disease progression in more severe patients.

Treatment effect

As noted below, the majority of available evidence on treatment effect is reported as mean difference between untreated and treated at a particular time-point. There is very little, if any, data reported by cognition and another variable, e.g. only mean difference in MMSE score of 0.4 at 6 months, mean difference in NPI of 0.3, rather than of those with poor functional/behavioural status the mean difference in MMSE was 0.3 while for those with good functional/behavioural status the mean difference in MMSE was 0.6. We therefore have the problem of translating these mean differences into transition probabilities or state occupancy proportions (as in the one-dimensional model), but also have the added problem of coinciding treatment effects on cognition with treatment effects on functional or behavioural status.

Assuming the one-dimensional model, there are many questions in assuming how this measure of effectiveness is incorporated into transition probabilities for the treated cohort. One approach is to calculate the expected MMSE score at time t for a treated individual (point b on *Figure 67*) which is the expected score for an untreated individual plus the mean difference, (see *Figure 67*), assuming that decline between start of treatment and time t is constant (see line ab in *Figure 67*). It is then assumed that decline after time t continues at the same rate as that in the untreated individual, but that the treated individual is constantly x points above the untreated individual (see explanation of treatment effect for the one-dimensional Markov model below for discussion of this assumption if the Mendiondo and colleagues[54] disease progression eqn is used). The time to one-point change in the treated individual is then calculated as the time to a one-point change in the untreated individual plus z, the additional time spent at that MMSE score due to the treatment effect. Thus, allowing treatment to slow progression.

FIGURE 67 *Alzheimer's disease progression based on MMSE for an untreated individual (thin line) and for a treated individual (thick line)*



However, this extended time at MMSE scores only applies to earlier transitions, therefore some 'memory' has to be built into the model, where already there are 32 states. Of course, for a two-dimensional model, the number of states is two-fold, although aggregation of cognition states may be possible if not using the Mendiondo and colleagues equation for disease progression.

It is also important to note that in applying the treatment effect to baseline data from elsewhere (e.g. IPD from UK study or the Mendiondo and colleagues eqn), it is quite possible that an improvement in MMSE score is modelled rather than just allowing for a slowing of decline. It is unclear whether the evidence base agrees with an assumption than treatment can increase MMSE score, rather than delay decline.

Utilities

Utility data for MMSE is available. Utility data for functional status are also available but are not independent of cognition score. Only utility data concerning depression can be identified for any type of behavioural symptom.

Costs

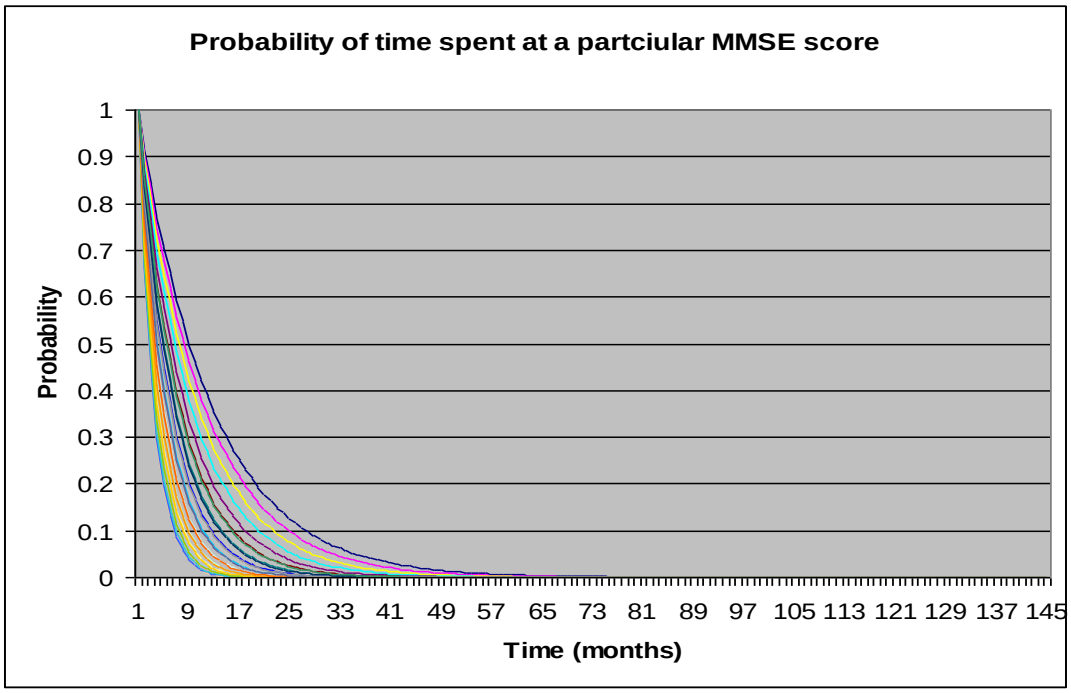
1-dimensional Markov model: cognitive status

Great deal of evidence to suggest that MMSE alone is not a good basis for summarising AD progression. Has MMSE been validated for AD?

Best supportive care cohort – AD progression

The Mendiondo and colleagues[54] model can be used to inform AD progression in terms of the time to next point change on MMSE scale. Assuming a constant rate and an exponential function, the time-dependent probabilities for transition across MMSE scores can be obtained (see Figure 68).

FIGURE 68 *Probability of time spent at a particular MMSE score*



Treatment effect

Treatment effects are commonly reported as mean difference in MMSE between treated and untreated people with AD, e.g. at 6 months the mean difference is 0.4 point. See above for a description of the issues associated with translating the treatment effect into the decision model.

Additionally, as Figure 68 demonstrates, the probability of moving to the next MMSE score depends upon severity, and therefore assuming a decline of the same rate as the untreated individual for a treated individual after time t does not follow the Mediondo and colleagues eqn.

Utilities

Utility data by MMSE are available, including EQ-5D.

Costs

Cost data by MMSE are available.

Appendix 17: Previous criticisms of the SHTAC Alzheimer's disease model

FIGURE 69 *List of criticisms of SHTAC decision model*

	Criticism of SHTAC model	Addressed in PenTAG model	Method used to try and address the criticism	Relevant section of report
Alzheimer's disease progression:				
1	Generalisability of risk equations	Yes	Used a UK-based dataset[53] to model progression in Alzheimer's disease	Health state occupancy (section 7.3.8)
2	Implicit assumption in SHTAC model that FTC = severe Alzheimer's disease	Yes	This assumption has been justified using the IPD from Wolstenholme et al[53], which suggests MMSE of 9 reached at 0.04 years prior to institutionalization	Model assumptions (section 7.3.4)
3	Baseline characteristics - change cohort characteristics	Yes	Base case baseline characteristics are taken from the Wolstenholme IPD. Baseline characteristics from LASER-AD were used in sensitivity analyses	Modelled population (Section 7.3.3)
Cost data:				
4	Query the costs used: Inaccurate, out-of-date, not UK based	No	The only sources of evidence for resource use and costs are from many years ago. Cost data have been inflated to 2009 prices.	Cost of health and social care received by AD patients (section 7.3.10.2)
5	pre-FTC too heterogeneous a state for a single cost value	Yes	The relationship between costs and time to pre institutionalization has been modeled allowing costs in the pre-institutionalized state to be dependent on time to institutionalization	Cost of health and social care received by AD patients (section 7.3.10.2)
6	Query the proportion of people in FTC that are institutionalized	No longer relevant	This is no longer relevant as the UK data use time to institutionalization, rather than full-time care	

7	Query the exclusion of costs for those in institutionalized care who pay privately	Not completely	Based on the Dementia UK report a number of assumptions have been made and assessed	Cost of health and social care received by AD patients (section 7.3.10.2)
8	No inclusion of carer's costs	Not	No data on the NHS/PSS costs for carer's of people with AD could be identified	Cost estimates (section 7.3.10)
Quality of life data:				
9	No daily health benefit associated with treatment	Yes	The relationship between MMSE and time to institutionalization has been modeled allowing health benefit to accrue in the pre-institutionalized state	Quality of life of the individual with Alzheimer's disease (section 7.3.9.1)
10	No benefit for those going straight from pre-FTC to death (related to above point)	Yes	as above	Quality of life of the individual with Alzheimer's disease (section 7.3.9.1)
11	pre-FTC too heterogeneous a state for a single utility value	Yes	as above	Quality of life of the individual with Alzheimer's disease (section 7.3.9.1)
12	Query the values used	Yes	Utility values by MMSE assessed to be reasonably similar across different studies and the different utility values by MMSE will be investigated in sensitivity analyses	Quality of life of the individual with Alzheimer's disease (section 7.3.9.1)
13	No inclusion of carer's quality of life	Yes	Incorporated carer's utility as a sensitivity analysis. Evidence from one study only.	Quality of life of the carer (section 7.3.9.2)
Treatment and effectiveness:				
14	Assume treatment stops once enter FTC	Yes	Analysis of the Wolstenholme IPD suggests that institutionalization is a good proxy for severe Alzheimer's disease (see point 2 above)	Model assumptions (section 7.3.4)
15	No consideration of treatment drop-out, non-responders, adverse events	Yes	The PenTAG model allows for a proportion of the total cohort to discontinue treatment each month from the start of treatment. This assumption is constant across all drugs	Treatment discontinuation (section 7.3.7.2)
16	No treatment effect observed in psychiatric symptoms	No	Baseline characteristics for the prediction of institutionalization from the UK data do not include variables for psychiatric symptoms, therefore no treatment effects on psychiatric symptoms are assumed. However, the PenTAG model does incorporate a treatment on psychiatric or behavioural	Clinical effectiveness (section 7.3.7)

			symptoms in addition to cognitive symptoms	
17	No treatment benefit beyond 6 months	To an extent	For consistency across drugs, trial data with 6 months follow-up have been used. Sensitivity analyses for donepezil have incorporated longer term follow-up	Clinical effectiveness (section 7.3.7)
18	Placebo effect observed in trials	No		
19	Responder analyses not included	No	No data identified from the RCTs	
Modelling:				
20	Time horizon longer than 5 years	Yes	Time horizon is 20 years, where it is estimated that <5% of the cohort are still alive	Time horizon (section 7.3.5)
21	Constant mortality assumed	Yes	Mortality in the PenTAG model is based on age, starting MMSE and ADL, and is the same for treated and untreated patients in the base case analysis	Health state occupancy (section 7.3.8)
22	Over-estimated' mortality	Not addressed directly but see 21 above		
23	Lots of queries regarding the PSA	Yes	Only parameters with uncertainty have associated distributions in the PSA	Results section
24	Inclusion of multi-way sensitivity analyses	Not undertaken formally	Some multiway sensitivity analyses were undertaken for comparison with the SHTAC, Eisai/Pfizer and Lundbeck models	SHTAC, Eisai/Pfizer & Lundbeck comparisons
25	Individual vs population characteristics	Not addressed directly	Cohorts are split by age groups	Model assumptions (Section 7.3.4)
26	No monitoring of MMSE/ADL etc - cannot model current NICE guidance	Yes	Inclusion of time to pre institutionalization by MMSE allows assessment of disease progression over time by MMSE	Quality of life (section 7.3.9)
27	Accounted costs during initial treatment period, but not any health benefits	Yes	Both costs and health benefits in the initial treatment period are accounted for (i.e. during the 6 months up to the point of estimation of the treatment effect)	Model assumptions (Section 7.3.4)

Appendix 18: Published utility values for Alzheimer's disease

FIGURE 70 *Utility values from relevant literature*

Source	Health state utility scale	Sample	Factor	Category	Utility
Kerner et al [55]	QWB	Spousal proxy			0.51 (SD 0.06)
Miller et al 2008 [56]	HUI-3	Carer-proxy	Time	Baseline	0.184 (range -0.291, 1)
				3 months	0.162
				6 months	0.148
				9 months	0.123
Sano et al 1999 [57]	TTO	Alzheimer's disease experts	CDR	Mild (CDR=1)	0.67 (SD 0.32)
				Severe (CDR=3)	0.31 (SD 0.27)
		Students	CDR	Mild (CDR=1)	0.58 (SD 0.23)
				Severe (CDR=3)	0.29 (SD 0.21)
	VAS	Alzheimer's disease experts	CDR	Mild (CDR=1)	0.75 (SD 0.14)
				Severe (CDR=3)	0.26 (SD 0.18)
		Students	CDR	Mild (CDR=1)	0.65 (SD 0.17)
				Severe (CDR=3)	0.30 (SD 0.13)
Ekman et al 2007 [58]	TTO	Members of public in Sweden aged 45-84 years	CDR	Mild cognitive impairment (CDR=0.5)	0.82 (SD 0.21)
				Mild (CDR=2)	0.62 (SD 0.25)
				Moderate (CDR=3)	0.4 (SD 0.26)
				Severe (CDR=3)	0.25 (SD 0.28)
Naglie et al 2006 [59]		Patient utility scores	Health status tool	EQ-5D	0.86
				QWB	0.60
				HUI-3	0.73
				VAS (from EQ-5D)	0.81
		Carer-proxy scores	Health status tool	EQ-5D	0.62
				QWB	0.42
				HUI-3	0.23
				VAS (from EQ-5D)	0.59
Andersen et al [60]	EQ-5D mapped from health status and ADL	Obtained from interviews with patients and carer	MMSE	MMSE > 20	0.636 (SD 0.2109)
				9 < MMSE < 20	0.596 (SD 0.2152)
				MMSE < 10	0.486 (SD 0.2191)
			Dependency	Independent	0.641 (SD 0.1952)
				Dependent	0.343 (SD 0.2324)
			Residential status	Community	0.621 (SD 0.2173)
				Institution	0.564 (SD 0.1861)
Wlodarczyk et al 2004 [61]	AQoL (extracted from figures 1 and 2) [95% CIs available and yet to be extracted]	Carer-proxy	MMSE	0-10	0.4
				10-15	0.46
				15-20	0.475
				20-25	0.52
				25+	0.59
			IADL	0-2	0.36
				3-5	0.5
				6-8	0.62
		Patient	MMSE	0-10	0.52
				10-15	0.54
				15-20	0.61
				20-25	0.68
				25+	0.71
			IADL	0-2	0.53
				3-5	0.62
				6-8	0.77

Source	Health state utility scale	Sample	Factor	Category	Utility
Karlawish et al [62]	EQ-5D	Patient self-ratings	MMSE	24-29	0.78 (SD 0.261)
				20-23	0.8 (SD 0.228)
				11-19	0.885 (SD 0.132)
			IADL	8-10	0.885 (SD 0.136)
				11-14	0.835 (SD 0.249)
				15-27	0.744 (SD 0.233)
			BADL	6	0.851 (SD 0.21)
				7-14	0.761 (SD 0.226)
	HUI-2	Patient self-ratings	MMSE	24-29	0.886 (SD 0.133)
				20-23	0.846 (SD 0.19)
				11-19	0.916 (SD 0.105)
			IADL	8-10	0.941 (SD 0.084)
				11-14	0.894 (SD 0.129)
				15-27	0.811 (SD 0.191)
			BADL	6	0.928 (SD 0.087)
				7-14	0.795 (SD 0.20)
Karlawish et al [63]	EQ-5D	Carer-proxy ratings	MMSE	24-29	0.72 (SD 0.202)
				20-23	0.63 (SD 0.251)
				11-19	0.604 (SD 0.233)
			IADL	8-18	0.753 (SD 0.219)
				19-24	0.7 (SD 0.183)
				25-31	0.476 (SD 0.208)
			BADL	6	0.789 (SD 0.116)
				7-8	0.646 (SD 0.247)
				9-22	0.519 (SD 0.233)
	HUI-2	Carer-proxy ratings	MMSE	24-29	0.763 (SD 0.158)
				20-23	0.703 (SD 0.201)
				11-19	0.707 (SD 0.172)
			IADL	8-18	0.791 (SD 0.164)
				19-24	0.77 (SD 0.123)
				25-31	0.595 (SD 0.185)
			BADL	6	0.791 (SD 0.144)
				7-8	0.752 (SD 0.154)
				9-22	0.635 (SD 0.196)
Neuman et al 1999 [64]	HUI-2	Carer-proxy	CDR	0.5	0.73
				1	0.69
				2	0.53
				3	0.38
				4	0.27
				5	0.14
Jonsson et al 2006 [65]	EQ-5D	Self ratings (both self and carer ratings available)	MMSE	26-30	0.84
				21-25	0.85
				15-20	0.83
				10-15	0.73
				0-9	0.78
		Carer-proxy (both self and carer ratings available)	MMSE	26-30	0.7
				21-25	0.65
				15-20	0.52
				10-15	0.51
				0-9	0.4
		Only carer proxy ratings available	MMSE	26-30	0.5
				21-25	0.19
				15-20	0.21
				10-15	0.39
				0-9	0.22
		Only self ratings available	MMSE	26-30	0.81
				21-25	0.78
				15-20	0.82
				10-15	1
				0-9	0.94

Appendix 19: Figures from the statistical analysis of IPD from Wolstenholme and colleagues

FIGURE 71 *Inflated cost per month as a function of time until pre institutionalization for each of 92 AD patients*

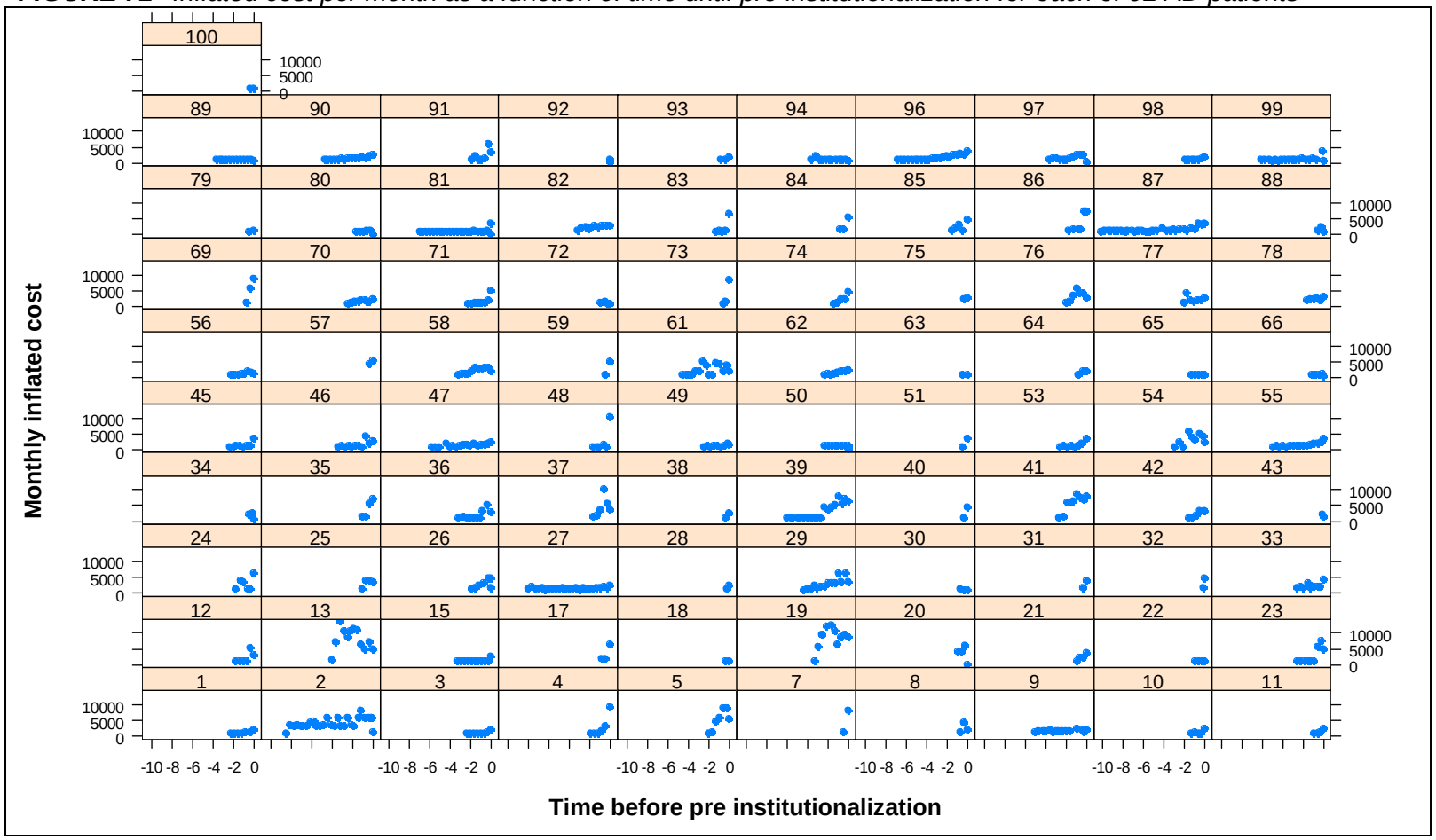
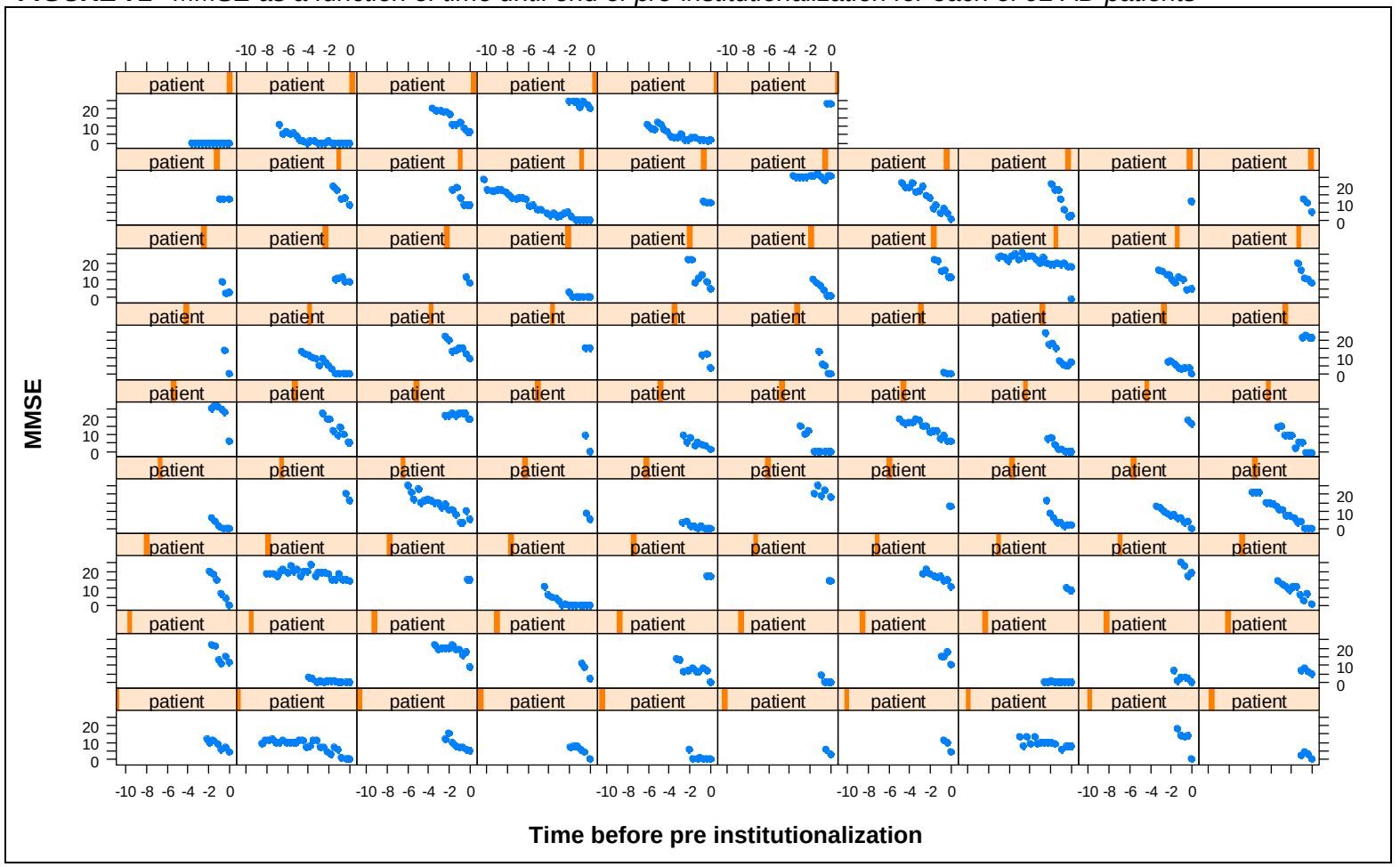


FIGURE 72 *MMSE as a function of time until end of pre-institutionalization for each of 92 AD patients*



Appendix 20: Graphical presentation of distributions for PSA

FIGURE 73 *Density plots of the effectiveness parameters included in the PSAs (refer to Section 8)*

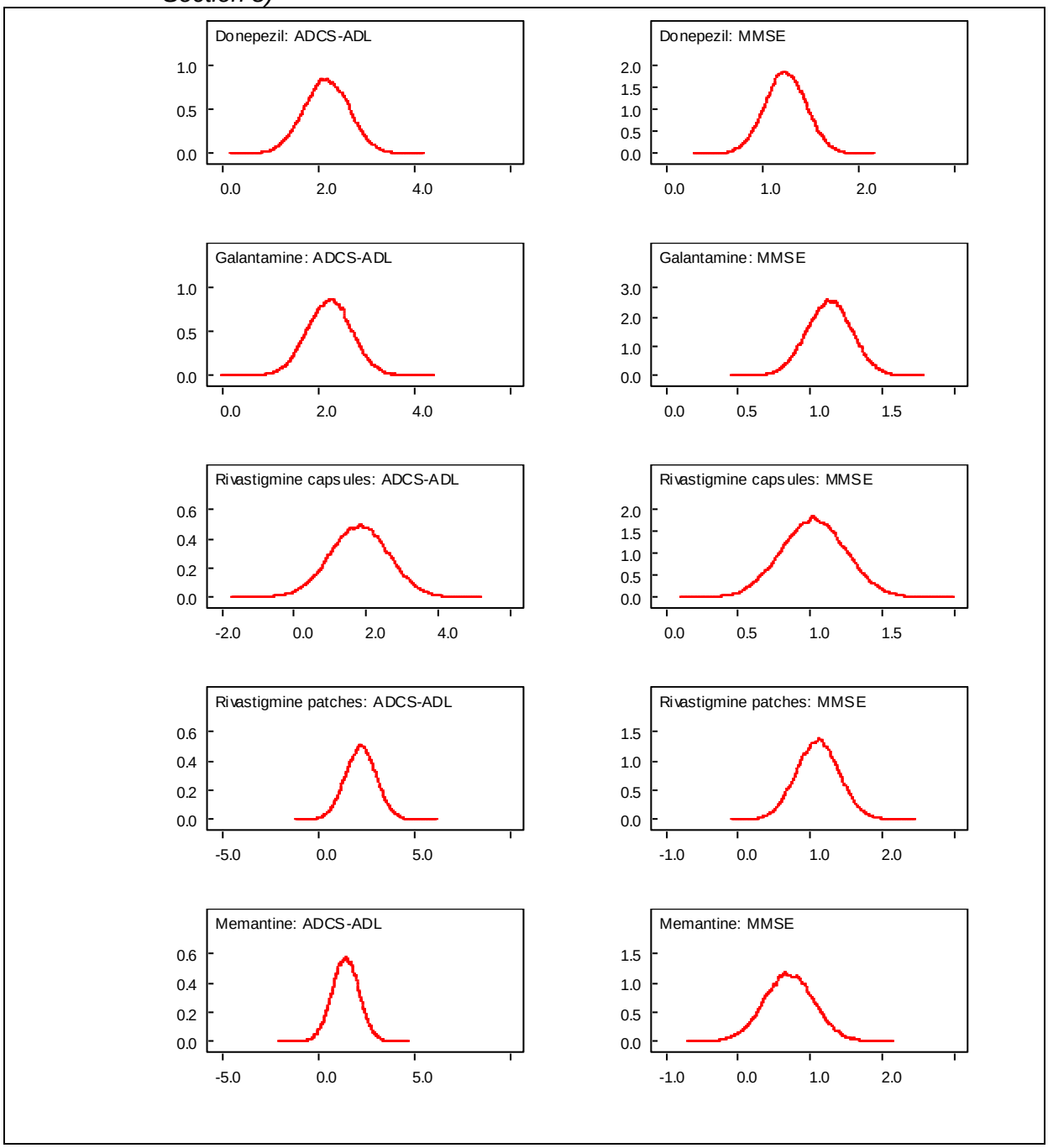


FIGURE 74 *Density plots of the uncertain cost parameters included in the PSAs*

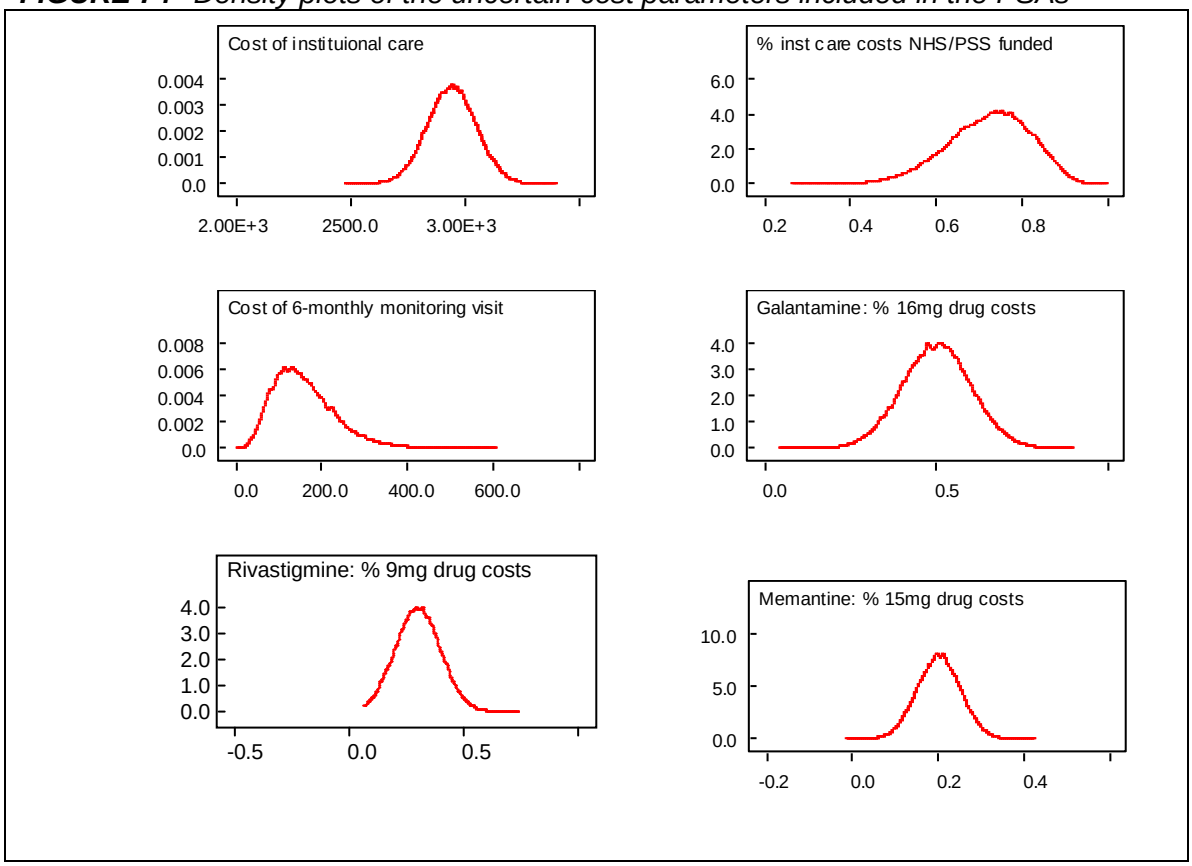


FIGURE 75 *Density plots of the utility estimates included in the PSAs*

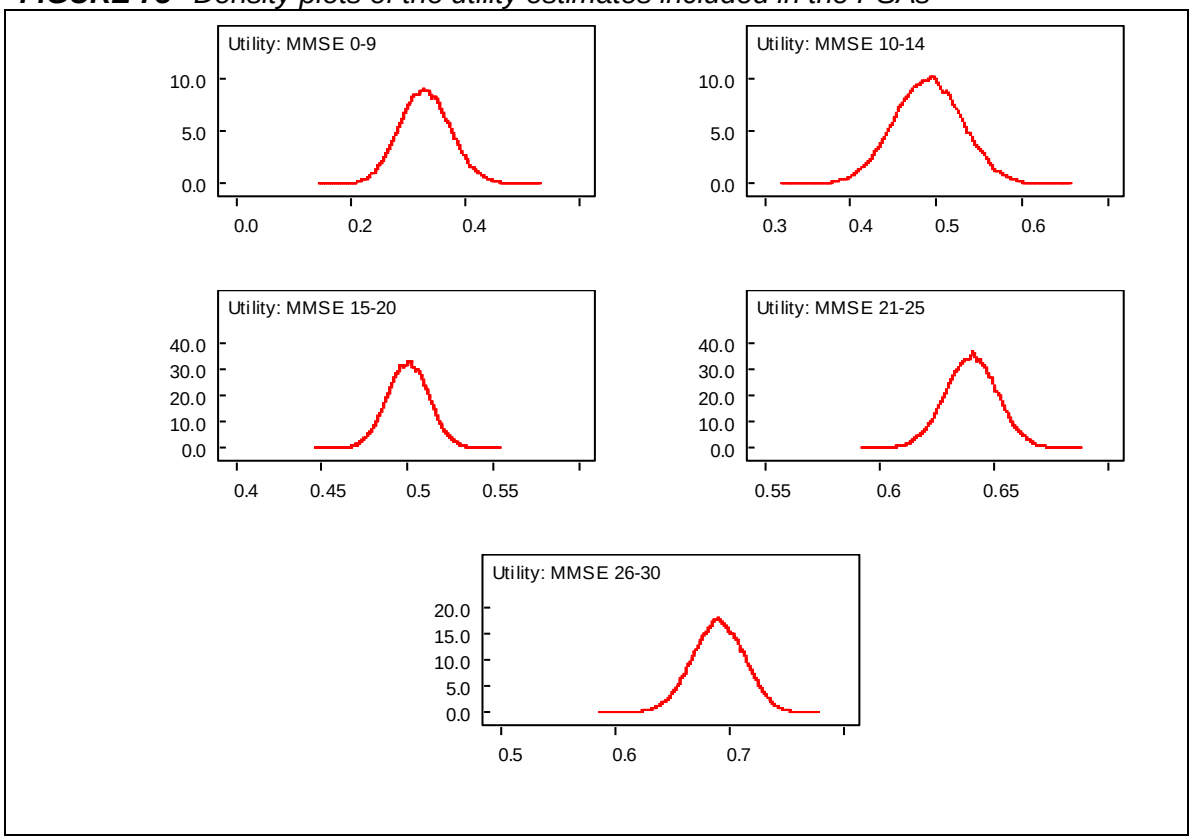
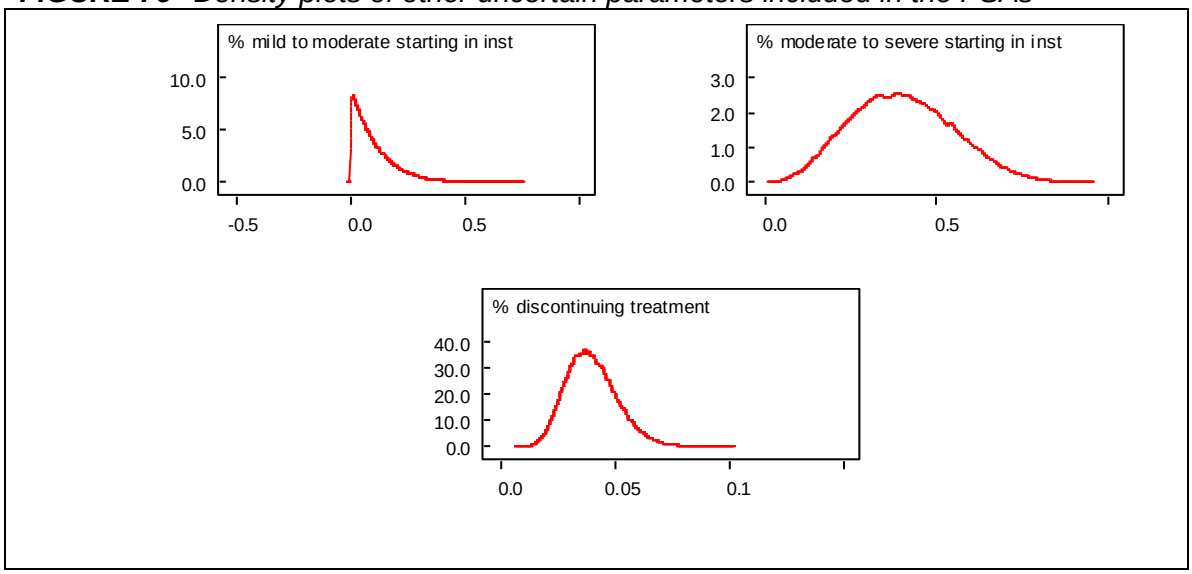


FIGURE 76 *Density plots of other uncertain parameters included in the PSAs*



Appendix 21: Tornado plots for AChEI versus best supportive care

Tornado plots for comparisons between best supportive care and donepezil (**FIGURE 77**), rivastigmine capsules (**FIGURE 78**) and galantamine (**FIGURE 79**) in base case analyses for people with mild to moderate Alzheimer's disease.

FIGURE 77 *Donepezil versus best supportive care*

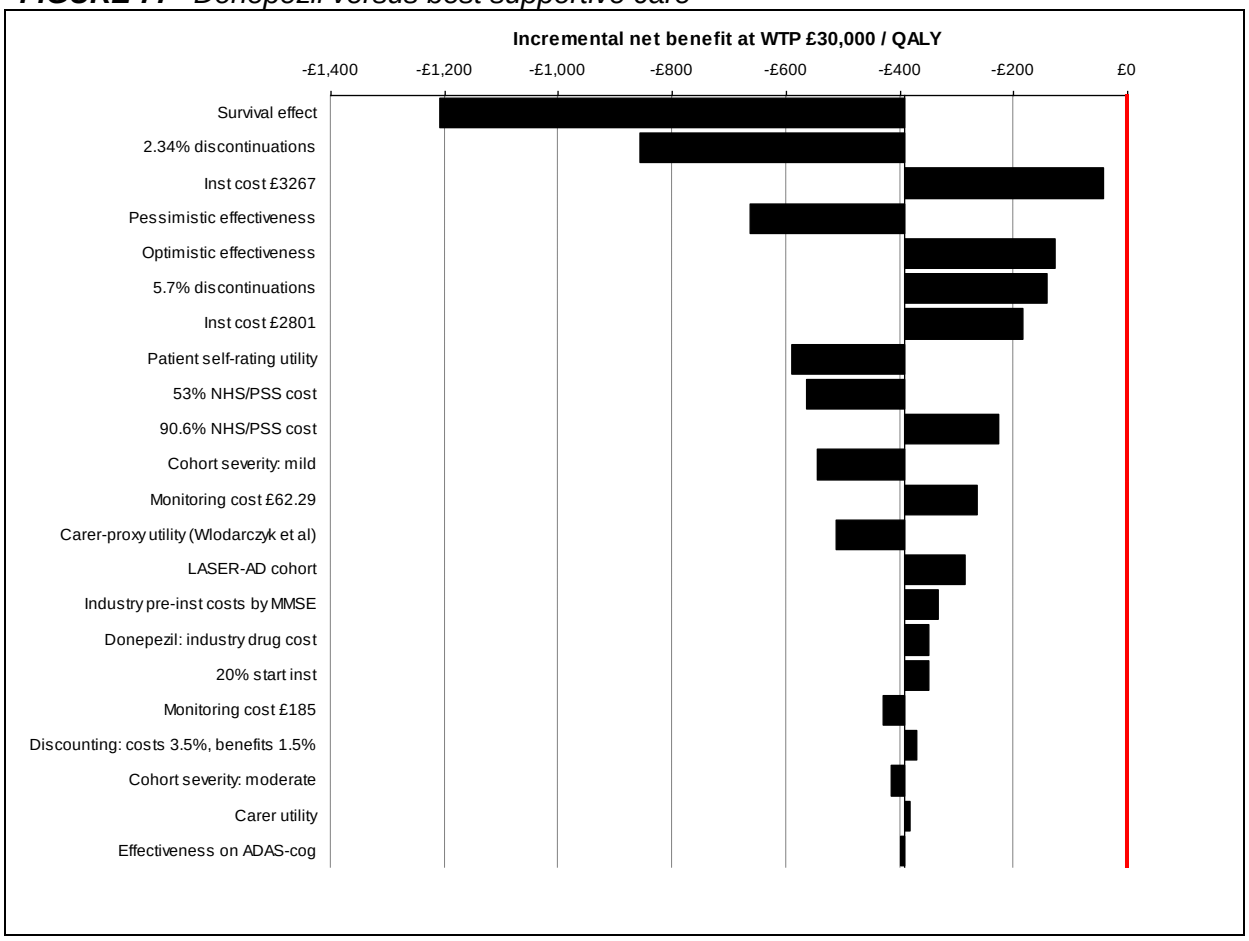


FIGURE 78 *Rivastigmine capsules versus best supportive care*

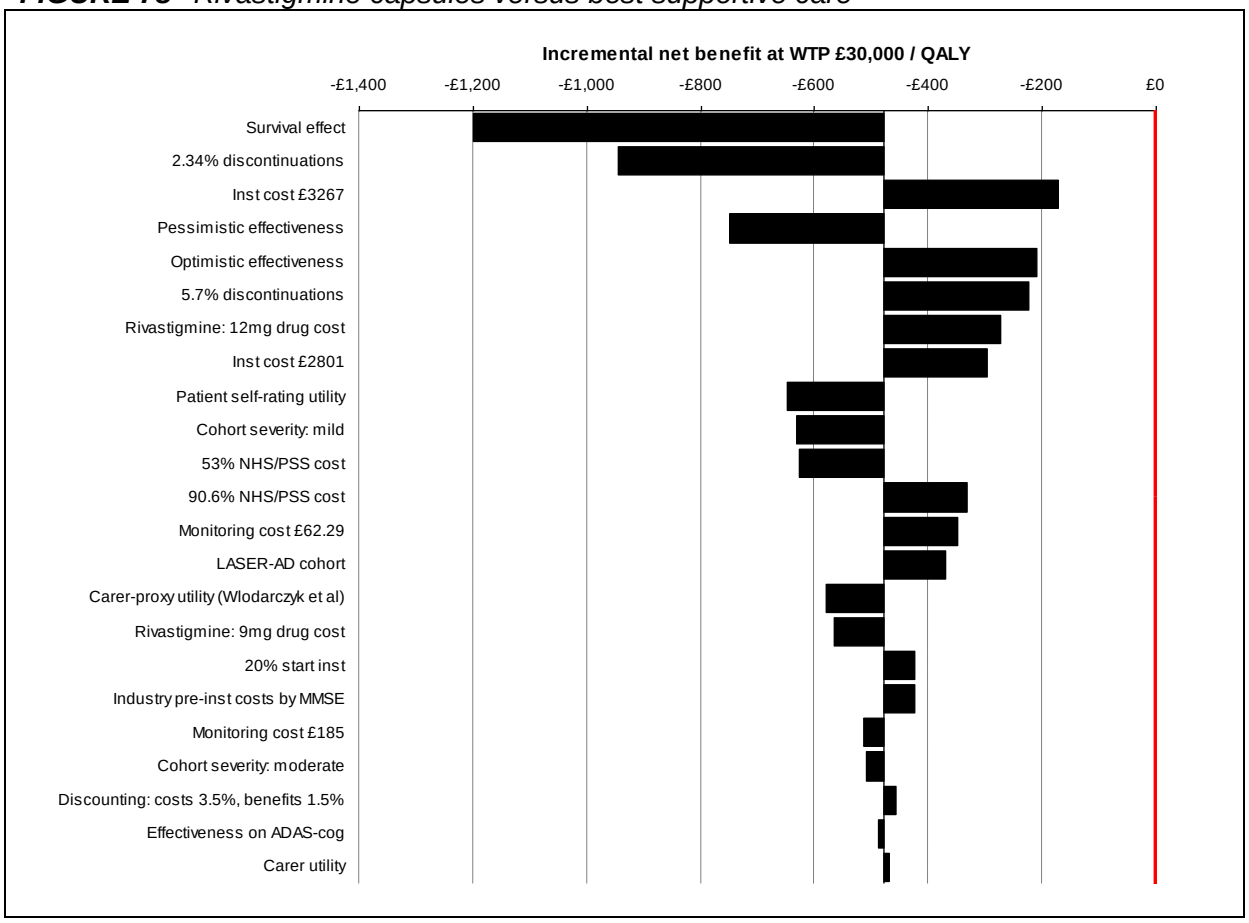
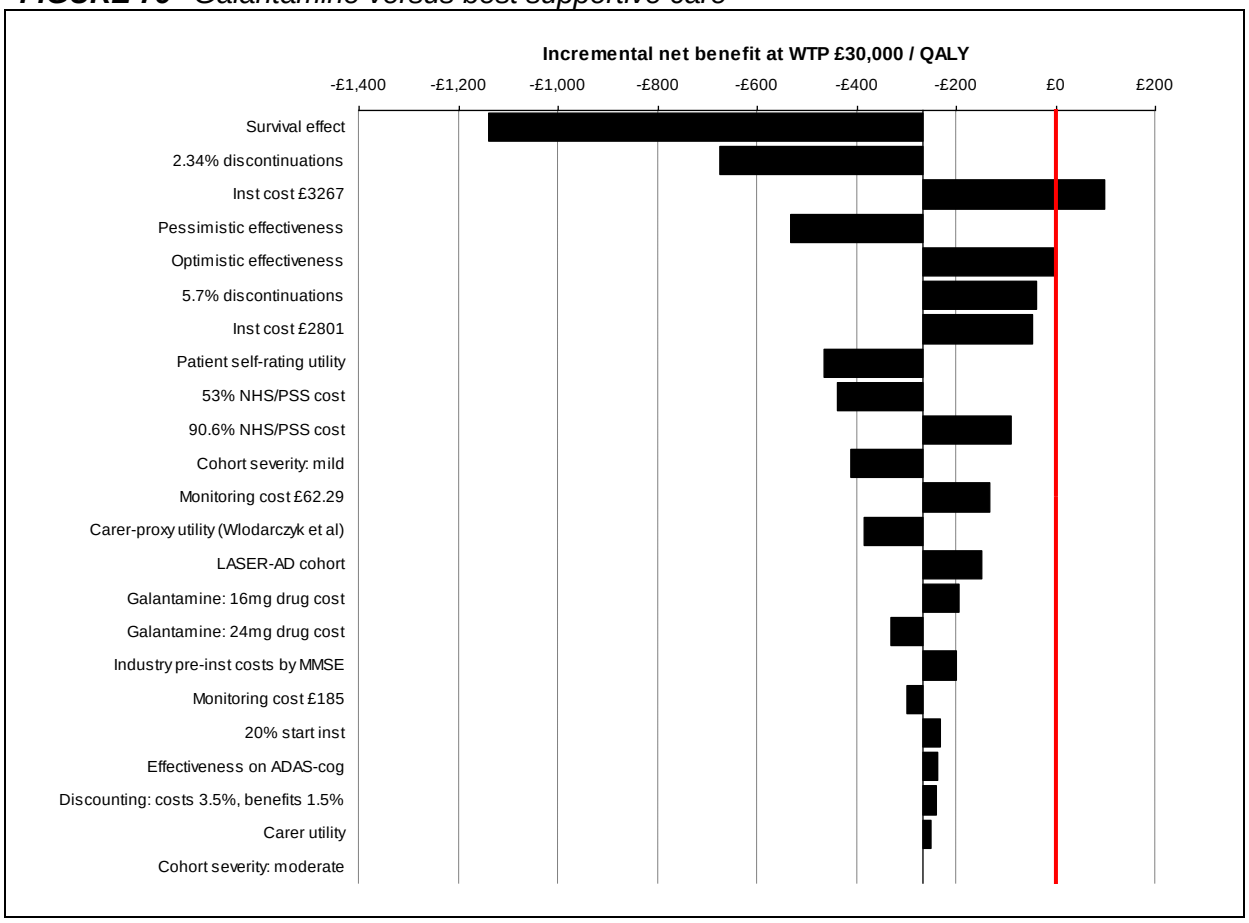


FIGURE 79 *Galantamine versus best supportive care*



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