Comparative Effectiveness Review
Number 223

Diagnosis and Treatment of Clinical Alzheimer's-Type Dementia: A Systematic Review

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Key Messages

Purpose of Review

To summarize evidence on cognitive test accuracy for clinical Alzheimer's-type dementia (CATD) in suspected cognitive impairment; biomarker accuracy for Alzheimer's disease (AD) in dementia; and effects of CATD drug treatment.

Key Messages

- Many brief cognitive tests were highly ($\geq$0.8) sensitive and specific distinguishing CATD from normal cognition, but less from mild cognitive impairment.
- Amyloid PET and MRI were highly sensitive and specific distinguishing autopsy-confirmed AD from non-AD dementia; FDG-PET was highly sensitive and moderately ($\geq$0.5 to <0.8) specific; CSF tests were moderately sensitive and specific. Data were limited on biomarkers added to clinical evaluation.
- Cholinesterase inhibitors (ChI) were slightly better than placebo for cognition and function, but increased withdrawals due to adverse effects; evidence was insufficient for supplements. In moderate to severe CATD, memantine plus ChI slightly improved cognition versus ChI, but not function.
- Donepezil and antidepressants appeared similar to placebo for agitation and depression, respectively; for other prescription drugs and all supplements, evidence was insufficient on behavioral and psychological symptoms.

This report is based on research conducted by the Minnesota Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2015-00008-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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This report may periodically be assessed for the currency of conclusions. If an assessment is done, the resulting surveillance report describing the methodology and findings will be found on the Effective Health Care Program website at www.effectivehealthcare.ahrq.gov. Search on the title of the report.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new healthcare technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the healthcare system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the website (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

If you have comments on this systematic review, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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Technical Expert Panel

In designing tudy questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Structured Abstract

Objective. To summarize evidence on: (1) the accuracy of brief cognitive tests for identifying clinical Alzheimer's-type dementia (CATD) in individuals with suspected cognitive impairment; (2) the accuracy of biomarkers for identifying Alzheimer's disease (AD) in individuals with dementia; and (3) the benefits and harms of prescription drugs and supplements for cognition, function, and behavioral and psychological symptoms of dementia (BPSD) in patients with CATD.

Data sources. Electronic bibliographic databases to March 2019, ClinicalTrials.gov, systematic review bibliographies.

Review methods. Cognitive test accuracy studies must have used explicit CATD diagnostic criteria and a non-CATD control group. Biomarker accuracy studies must have used neuropathologic criteria to define AD cases and non-AD controls. All treatment trials must have enrolled participants with CATD; those evaluating BPSD enrolled individuals with CATD and BPSD. Minimum trial duration was 2 weeks for agitation, aggression, psychosis, and disinhibited sexual behavior, and 24 weeks for other outcomes. Two reviewers rated risk of bias (ROB) and strength of evidence. One reviewer extracted data; a second checked accuracy. We analyzed English-language studies with low or medium ROB.

Results. We analyzed 56 unique studies on the accuracy of brief cognitive tests for CATD, 24 on accuracy of biomarkers for AD (15 brain imaging, nine cerebrospinal fluid [CSF] testing), and 67 trials of CATD treatment (54 reporting cognition or function, 13 reporting BPSD). Multiple brief cognitive tests were highly sensitive and specific ($\geq$0.8) for distinguishing CATD from normal cognition, but less so for distinguishing mild CATD from normal cognition or CATD from mild cognitive impairment (MCI). Based on few studies, compared with clinical evaluation alone, amyloid positron emission tomography (PET), fluorodeoxyglucose (FDG)-PET, and combinations of CSF tests added to clinical evaluation may improve accuracy for distinguishing AD from non-AD dementia. Regardless of CATD severity, cholinesterase-inhibitors produced small improvements in cognition and function compared with placebo but may increase serious adverse events and withdrawals due to adverse events. For moderate to severe CATD, memantine plus a cholinesterase inhibitor slightly improved global change and inconsistently improved cognition, but not function, compared with a cholinesterase inhibitor alone. Evidence was mostly insufficient about the effects of prescription drugs and supplements on agitation, aggression, psychosis, or disinhibited sexual behavior.

Conclusions. Brief cognitive tests accurately distinguished CATD from normal cognition, but were less accurate distinguishing smaller clinical differences. Whether biomarkers improve diagnostic accuracy when added to clinical evaluation needs further verification, but potential benefits of testing are limited by lack of effective treatments for AD and non-AD dementias. Cholinesterase-inhibitors slightly outperformed placebo for cognition and function, but evidence of whether any drug treatments improved BPSD was largely insufficient.

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Evidence Summary

Background

The ultimate reason for accurately diagnosing clinical Alzheimer's-type dementia (CATD) and whether Alzheimer's disease (AD) is the underlying neuropathological etiology is to inform decision making about drug and nondrug treatments to improve patient and caregiver outcomes.

In individuals with suspected cognitive impairment, comprehensive neuropsychological testing may help clinically diagnose dementia and distinguish between dementia subtypes. However, such testing is time consuming and access is limited in some clinical settings. Therefore, we need better understanding in this population with suspected cognitive impairment (case finding) which brief cognitive tests and test combinations most accurately distinguish patients with CATD from those with normal cognition or mild cognitive impairment (MCI), and whether patient characteristics affect test classification accuracy.

Additionally, many individuals clinically diagnosed with CATD do not meet neuropathologic (gold standard) criteria for AD on post-mortem brain autopsy. Therefore, we also need better understanding of how accurate pre-mortem brain imaging and cerebrospinal fluid (CSF) biomarkers are for distinguishing patients whose dementia is due to AD from those with non-AD dementia, and whether classification accuracy varies depending on patient characteristics.

Finally, although only a few prescription drugs are approved by the U.S. Food and Drug Administration (FDA) for CATD, many supplements are promoted for cognition and function. In addition, many prescription drugs are used off-label for CATD-associated behavioral and psychological symptoms of dementia (BPSD), including antipsychotics, despite FDA black box warnings about their increased mortality risk in this population.[1, 2] Less is understood about the beneficial and harmful effects of supplements for CATD-associated BPSD. To guide CATD treatment decisions for cognition, function, BPSD and other outcomes, we need to clarify the benefits and harms of prescription drugs and supplements in this population.

Purpose

The target audiences of this report are primary care clinicians who diagnose and treat the vast majority of older patients with cognitive disorders, psychologists who may perform additional cognitive testing in primary care settings, and dementia specialists who are most likely to have access to biomarker testing for further diagnostic clarification.

The purpose of this report is to summarize the evidence on (1) the accuracy of brief cognitive tests for distinguishing CATD from normal cognition and MCI in individuals with suspected cognitive impairment; (2) the accuracy of brain imaging and CSF biomarkers for distinguishing autopsy-confirmed AD from non-AD in individuals with dementia; (3) the benefits and harms of prescription drugs and supplements for cognition, function, and BPSD in patients with CATD; and (4) whether the accuracy of cognitive or biomarker tests for classifying patients and the efficacy of CATD drug treatments vary by patient characteristics.

Main Points

- **Accuracy of brief cognitive tests for distinguishing CATD from normal cognition and MCI:**
  - Multiple brief cognitive tests had high sensitivity and specificity (defined as $\geq$0.8) for distinguishing CATD from normal cognition, including those commonly used as

individual stand-alone tests, brief multidomain batteries, and individual memory and verbal fluency tests typically administered as part of a larger battery in clinical practice. These tests less accurately distinguished CATD from MCI, or mild CATD from normal cognition.
    - Few cognitive tests were evaluated in multiple studies which reported the same type of test score and used comparable cut points to define abnormality, and few studies compared classification accuracy between individual tests or their combinations.
    - There was minimal evidence addressing whether accuracy of brief cognitive tests for identifying CATD varied by study participant characteristics.
- **Accuracy of biomarkers for distinguishing autopsy-confirmed AD from non-AD dementia:**
    - Amyloid positron emission tomography (PET) brain imaging was highly sensitive and specific, and fluorodeoxyglucose (FDG)-PET was highly sensitive and moderately specific (latter defined as $\geq$0.5 to <0.8); based on single studies making direct comparisons, both may increase accuracy differentiating between AD and non-AD dementia when added to a clinical evaluation.
    - Magnetic resonance imaging (MRI) medial temporal atrophy was highly sensitive and specific and single-photon emission computed tomography (SPECT) cerebral blood flow had variable accuracy; SPECT plus clinical evaluation had lower sensitivity and higher specificity than clinical evaluation alone, but no studies directly compared MRI plus clinical evaluation versus clinical evaluation alone.
    - Individual CSF tests and ratios were moderately sensitive and specific; in the few direct comparisons, beta amyloid 42 (Aß42)/p-tau ratio, t-tau/Aß42 ratio and p-tau appeared more accurate and Aß42 and t-tau appeared least accurate.
    - Combinations of CSF tests may have the highest mix of sensitivity and specificity and may increase accuracy for distinguishing AD from frontotemporal lobar degeneration (FTLD) when added to clinical evaluation.
    - There was minimal evidence addressing whether the accuracy of biomarker testing for identifying AD varied by study participant characteristics.
    - No studies reported data on the accuracy of blood tests for identifying autopsy-confirmed AD.
- **Efficacy and harms of prescription drug treatment for CATD:**
    - In adults with mild to moderate CATD—
        - Cholinesterase inhibitors compared with placebo produced small improvements in cognition, function, staging, and clinical impression of change, but standard doses may increase serious adverse events and withdrawals due to adverse events.
        - In patients not receiving cholinesterase inhibitors, memantine may improve clinical impression of change, did not improve function, and evidence was insufficient about cognition, other efficacy outcomes, and harms.
        - In patients receiving cholinesterase inhibitors, memantine did not improve clinical impression of change, and evidence was insufficient for cognition, function, staging, and harms.
    - In adults with moderate to severe CATD —
        - Cholinesterase inhibitors produced small improvements in cognition, function, and clinical impression of change, but standard doses may increase serious adverse events and withdrawals due to adverse events.

        - In patients receiving cholinesterase inhibitors, memantine improved scores on brief multidomain cognitive batteries and clinical impression of change, did not improve function, and evidence was insufficient for brief cognitive tests commonly used as individual stand-alone tests, staging, and harms.
    - In adults with CATD and BPSD —
        - Evidence was insufficient to draw conclusions about the efficacy of antipsychotics, antidepressants, anticonvulsants, or memantine compared with placebo for agitation, psychosis, aggression or disinhibited sexual behavior (or of estrogen for disinhibited sexual behavior).
        - Cholinesterase inhibitors did not improve agitation more than placebo, and evidence was insufficient to draw conclusions about their effects on other BPSD or harms.
    - There was minimal evidence addressing whether efficacy of prescription drugs for CATD treatment varied by study participant characteristics.
- **Efficacy and harms of supplements for CATD:**
    - In adults with CATD —
        - Omega-3 fatty acids did not improve cognition, and the nutritional drink Souvenaid® did not improve function; evidence for both was insufficient for other outcomes.
        - Evidence was insufficient to draw conclusions about differences in efficacy and harms of gingko biloba versus donepezil, or saffron extract versus memantine, for cognition, function, or quality of life.
        - Evidence was insufficient about efficacy and harms of other supplements, including antioxidants, gingko biloba, ginseng, curcumin, and vitamin E, for cognition, function, BPSD, or other efficacy outcomes.
        - There was minimal data addressing whether efficacy of supplements for CATD treatment varied by study participant characteristics.

Methods

We used methods consistent with those outlined in the Agency for Healthcare Research and Quality Evidence-based Practice Center Program Methods Guidance (https://effectivehealthcare.ahrq.gov/topics/cer-methods-guide/overview), and we describe these in the full report. Our cognitive testing and drug treatment searches covered from database inception to March 2019, and the biomarker testing search covered from 2012 to March 2019.

Results

Brief cognitive tests for distinguishing CATD from normal cognition or MCI in adults with suspected cognitive impairment. Fifty-six unique, low or medium risk-of-bias (ROB) studies evaluated the accuracy of one or more brief cognitive tests for distinguishing CATD from normal cognition or MCI, including 26 of individual tests commonly used as stand-alone tests (n=6,953); ten of brief multidomain batteries (n=2,676); 17 of individual memory tests (n=4,061), five of individual executive function tests (n=1,167), and ten of individual language tests (n=1,676), all typically administered as part of a larger battery in clinical practice; and nine of test combinations (n=1,688). Some epidemiological cohorts were frequently used, and the extent of participant overlap across studies was unknown. Results for the most commonly evaluated brief cognitive tests are presented in Tables A and B.

Table A. Summary of findings[*] for CATD versus normal cognition for selected[†] commonly reported brief cognitive tests and metrics

Cognitive Test Category	Test Metric	Studies, N (Patients Analyzed)	CATD Prevalence, Median (Range)	SN, Median (Range)	SP, Median (Range)	TP per 1000 Patients, Median (Range)	TN per 1000 Patients, Median (Range)	FP per 1000 Patients, Median (Range)	FN per 1000 Patients, Median (Range)
Individual Stand-Alone Tests	Clock drawing totals	8 (n=1,022)	0.50 (0.15-0.64)	0.79 (0.36-0.93)	0.88 (0.42-1.00)	355 (122-581)	480 (205-612)	60 (0-314)	105 (18-320)
	MMSE total	7 (n=1,724)	0.50 (0.15-0.71)	0.88 (0.56-1.00)	0.94 (0.59-1.00)	414 (113-669)	474 (251-745)	27 (0-255)	43 (0-182)
	MoCA total	2 (n=864)	0.71 (0.60-0.71)	0.94 (0.93-0.96)	0.94 (0.91-1.00)	669 (557-683)	289 (263-378)	23 (0-26)	41 (28-43)
Brief Multidomain Batteries	DRS total	2 (n=507)	0.60 (0.50-0.71)	0.97 (0.96-0.97)	0.96 (0.92-0.99)	583 (480-686)	375 (290-460)	21 (3-40)	21 (20-21)
Memory‡	List learning, trials & totals	6 (n=1,784)	0.21 (0.11-0.50)	0.82 (0.35-0.96)	0.96 (0.73-1.00)	178 (73-480)	650 (470-837)	24 (0-240)	33 (10-295)
	List delayed recall & retention	5 (n=937)	0.50 (0.16-0.50)	0.89 (0.62-0.96)	0.94 (0.76-0.98)	430 (140-480)	480 (400-706)	30 (13-151)	35 (19-190)
	Prose recall & retention	3 (n=895)	0.40 (0.11-0.54)	0.77 (0.71-0.87)	0.87 (0.81-0.89)	334 (78-435)	524 (369-739)	78 (55-151)	65 (32-125)
Executive‡	TMT B, completion time	2 (n=457)	0.33 (0.16-0.50)	0.86 (0.85-0.87)	0.86 (0.83-0.88)	282 (138-425)	578 (415-740)	93 (85-101)	48 (21-75)
Language‡	Semantic (category) fluency	9 (n=1,586)	0.50 (0.15-0.68)	0.92 (0.35-1.0)	0.89 (0.81-1.0)	470 (142-627)	430 (307-751)	42 (0-143)	35 (0-325)
	Phonemic (letter) fluency	4 (n=830)	0.63 (0.15-0.68)	0.77 (0.72-0.89)	0.86 (0.69-0.93)	505 (111-557)	333 (236-659)	53 (28-261)	83 (38-176)
	BNT total	2 (n=479)	0.50 (0.16-0.50)	0.65 (0.53-0.84)	0.92 (0.85-0.92)	270 (119-420)	460 (460-715)	40 (40-126)	153 (40-235)
Combina-tions	WMS LM, WAIS DSy, BNT60	2 (n=302)	0.47 (0.44-0.50)	0.82 (0.68-0.95)	0.87 (0.74-1.00)	382 (342-421)	462 (368-557)	65 (0-129)	92 (22-161)

BNT=Boston Naming Test; CATD=clinical Alzheimer's-type dementia; DRS=Dementia Rating Scale; DSy=Digit Symbol; FN=false negative; FP=false positive; LM=Logical Memory; MMSE=Mini-Mental State Examination; MoCA=Montreal Cognitive Assessment; SN=sensitivity; SP=specificity; TMT B=Trail Making Test part B; TN=true negative; TP=true positive; WAIS=Wechsler Adult Intelligence Scale; WMS=Wechsler Memory Scale.

*No studies reported data on harms of brief cognitive testing for identifying CATD.

†Data presented for brief cognitive tests evaluated in two or more eligible studies and rated low or moderate risk of bias.
‡Individual tests that typically are administered as part of a larger battery in clinical practice.

Table B. Summary of findings* for CATD versus MCI for selected† commonly reported cognitive tests and metrics

Cognitive Test Category	Test Metric	Studies, N (Patients Analyzed)	CATD Prevalence, Median (Range)	SN, Median (Range)	SP, Median (Range)	TP per 1000 Patients, Median (Range)	TN per 1000 Patients, Median (Range)	FP per 1000 Patients, Median (Range)	FN per 1000 Patients, Median (Range)
Individual Stand-Alone Tests	CLOX 1 (draw)	2 (n=150)	0.58 (0.50-0.65)	0.67 (0.58-0.76)	0.86 (0.72-1.00)	393 (288-498)	374 (249-500)	48 (0-97)	185 (157-212)
	MMSE total	2 (n=604)	0.69 (0.61-0.76)	0.84 (0.79-0.88)	0.81 (0.79-0.83)	570 (542-598)	257 (192-322)	58 (51-65)	115 (71-159)
	MoCA total	3 (n=1189)	0.72 (0.25-0.76)	0.79 (0.67-0.97)	0.79 (0.78-0.88)	541 (205-655)	223 (189-659)	60 (51-90)	114 (22-250)
Memory‡	List learning, trials & totals	2 (n=139)	0.47 (0.47-0.65)	0.65 (0.35-0.91)	0.72 (0.66-0.90)	307 (165-596)	380 (238-475)	107 (53-179)	165 (59-307)
Memory‡	List delayed recall & retention	3 (n=327)	0.47 (0.47-0.62)	0.83 (0.73-0.90)	0.65 (0.52-0.83)	411 (345-564)	274 (262-438)	163 (90-253)	80 (52-128)

CATD=clinical Alzheimer's-type dementia; FN=false negative; FP=false positive; MMSE=Mini-Mental State Examination; MoCA=Montreal Cognitive Assessment; MCI=mild cognitive impairment; SN=sensitivity; SP=specificity; TN=true negative; TP=true positive.

*No studies reported data on harms of brief cognitive testing for identifying CATD.

†Data presented for brief cognitive tests evaluated in two or more eligible studies and rated low or moderate risk of bias.

‡Individual tests that typically are administered as part of a larger battery in clinical practice.

Biomarkers for distinguishing AD from non-AD in adults with CATD. Twenty-four unique, low or medium ROB studies (n=2,152) evaluated the accuracy of biomarkers for distinguishing autopsy-confirmed AD from non-AD dementia, including 15 of brain imaging (n=1,225), and nine of CSF biomarkers (n=927). No studies examined the accuracy of blood testing. Results for the most commonly evaluated biomarker tests are presented in Table C.

Table C. Summary of findings of brain imaging and CSF biomarker tests for autopsy-confirmed AD versus non-AD dementias*

Biomarker Category	Test	Studies, N (Patients Analyzed)	AD Prevalence, Median (Range)	SN, Median (Range)	SP, Median (Range)	TP per 1000 Patients, Median (Range)	TN per 1000 Patients, Median (Range)	FP per 1000 Patients, Median (Range)	FN per 1000 Patients, Median (Range)
Brain Imaging	Amyloid PET	4 (n=426)	0.64 (0.33-0.79)	0.91 (0.79-0.98)	0.92 (0.76-1.0)	599 (261-682)	324 (208-555)	28 (0-119)	65 (13-111)
	FDG PET	2 (n=182)	0.64 (0.57-0.70)	0.89 (0.84-0.94)	0.74 (0.73-0.74)	568 (477 -659)	268 (217-318)	97 (80 -114)	67 (43 -91)
	SPECT cerebral perfusion	3 (n=205)	0.56 (0.48-0.64)	0.64 (0.57-0.94)	0.83 (0.76-0.92)	437 (271-603)	390 (301-479)	48 (42-55)	125 (41-208)
	MRI MTA	2 (n=161)	0.33 (0.24-0.42)	0.91 (0.91-0.91)	0.89 (0.84-0.94)	300 (217-383)	602 (487-717)	70 (43-96)	28 (22-35)
CSF	Aß42	2 (n=362)	0.65 (0.65-0.66)	0.77 (0.74-0.79)	0.58 (0.53-0.62)	425 (373-477)	262 (220-303)	88 (41-135)	225 (168-282)
	t-tau	3 (n=449)	0.66 (0.65-0.85)	0.65 (0.62-0.72)	0.66 (0.64-0.69)	428 (401-609)	226 (103-228)	117 (46-129)	241 (228-244)
	p-tau	2 (n=362)	0.85 (0.63-0.94)	0.79 (0.78-0.80)	0.61 (0.60-0.61)	597 (451-823)	94 (59-293)	48 (0-138)	170 (81-489)
	Aß42/p-tau ratio	1 (n=217)	0.65	0.83	0.60	535	213	142	110
	Aß42/t-tau ratio	1 (n=217)	0.65	0.75	0.57	484	203	152	161

AD=Alzheimer's disease; CSF=cerebrospinal fluid FDG=fluorodeoxyglucose; FN=false negative; FP=false positive; MRI= magnetic resonance imaging; MTA=medial temporal atrophy; PET=positron emission tomography; SN=sensitivity; SP=specificity; SPECT=single-photon emission computerized tomography; TN=true negative; TP=true positive.

*Two included amyloid PET studies reported data on physical harms, with one reporting that florbetapir was well tolerated and associated with no serious adverse events,[3] and the other that five percent of participants who received flutemetamol experienced mild to moderate treatment-related adverse events and that two deaths and two nonfatal serious adverse events were considered unrelated to flutemetamol.[4] No other brain imaging studies reported data on harms.

Drugs for cognition, function, and harms in adults with CATD. Fifty-four unique, low or medium ROB trials evaluated the efficacy and harms of prescription drugs or supplements for cognition, function, and harms in CATD. These included 25 of cholinesterase inhibitors versus placebo (n=9,476), 11 that compared different cholinesterase doses with each other (n=5,893) (7 of which also included a placebo comparison), six of memantine versus placebo (n=2,227), 11 of supplements versus placebo (n=2,004), three that compared different prescription drugs (n=454), and five that compared prescription drugs with supplements (n=258). The main findings of these studies for cognition, function, and harms are summarized in Table D.

Table D. Efficacy and harms of prescription drugs versus placebo in participants with CATD*

Drug Intervention	ChEI - Co-Use†	CATD Severity	Cognition	Function	SAE
Ch-I	NA	Mild to moderate	Favors Ch-I (Low SOE) Mean Δ**: SMD 0.24-0.52 Likelihood ≥4-pt ADAS-Cog improvement: NNTB 5-11	Favors Ch-I (Low SOE) Mean Δ††: SMD -0.02 to 0.22	Ch-i may increase risk (Low SOE) 10.7% vs. 8.7%
		Moderate to severe	Favors AChEI (Low SOE) Mean Δ‡‡: SMD 0.29	Favors Ch-I (Low SOE) Mean Δ***: SMD -0.10 to 0.18	No difference (Low SOE)
Memantine	No	Mild to moderate‡	(Insufficient SOE) Mean ADAS-Cog Δ: SMD -0.13	No difference (Low SOE) Mean ADCS-ADL Δ: SMD 0.00	(Insufficient SOE) 10% vs. 10%
	Yes	Mild to moderate	(Insufficient SOE) Mean Δ**: SMD -0.11 to 0.04	No difference (Low SOE) Mean ADCS-ADL Δ: SMD 0.12	(Insufficient SOE) 12.4% vs. 13.9%
		Moderate to severe	**Brief individual stand-alone tests**: (Insufficient SOE) Mean MMSE Δ: SMD 0.47 **Brief multidomain batteries**: Favors memantine (Low SOE) Mean SIB Δ: SMD 0.27	No difference (Low SOE) Mean Δ†††: SMD -0.26 to 0.14	(Insufficient SOE) 8.2% vs. 6.3%

Δ=change; ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; BADLS=Bristol Activities of Daily Living Scale; CATD=clinical Alzheimer's-type dementia; Ch-I=cholinesterase inhibitors; DAD=Disability Assessment for Dementia; MDS-ADL=7-item Minimum Data Set Activities of Daily Living Self-Performance scale; MMSE=Mini-Mental State Examination; NA=not applicable; PDS=Progressive Deterioration Scale; SAE=serious adverse events; SIB=Severe Impairment Battery; SMD=standardized mean difference SOE=strength of evidence.

*Strength of evidence grades for a treatment comparison and outcome reflected our confidence about the direction of the treatment effect (i.e., whether or not the outcome differs between treatments). Definitions for strength of evidence grades are detailed in the Methods section of the main report.

†Indicates whether all trial participants received a cholinesterase inhibitor as a co-intervention.

‡No eligible studies compared memantine with placebo in patients with moderate to severe CATD who were not receiving a cholinesterase inhibitor.

**MMSE or ADAS-Cog

††DAD, ADCS-ADL or PDS

‡‡MMSE or SIB

***ADCS-ADL or MDS-ADL

†††ADCS-ADL or BADLS

Drugs for BPSD in adults with CATD and BPSD. Eleven unique, low or medium ROB trials evaluated the efficacy and harms of drug treatment compared with placebo on BPSD in patients with CATD, including four of antipsychotics (n=522), four of antidepressants (n=836), one of cholinesterase inhibitors (n=272), one of anticonvulsants (n=153), and one of supplements (the Japanese herbal medicine, Yokukansan) (n=145). Two trials compared different prescription drugs (n=414). The main findings of these studies for BPSD and harms are summarized in Table E.

Table E. Efficacy and harms of prescription drug treatments versus placebo for BPSD in patients with CATD and agitation and/or aggression†

Drug Treatment	Agitation	Aggression	Psychosis	SAE
Anti-psychotic	Insufficient SOE (standard- and low-dose haloperidol, pimavanserin, quetiapine)	Insufficient SOE (standard- and low-dose haloperidol, pimavanserin)	Insufficient SOE (aripiprazole, standard- and low-dose haloperidol, pimavanserin)	Insufficient SOE (aripiprazole, pimavanserin, quetiapine)
Anti-depressant	Insufficient SOE (citalopram,* sertraline)	NR	Insufficient SOE (citalopram*)	Insufficient SOE (citalopram,* mirtazapine, sertraline)
Cholinesterase inhibitor	No difference (low SOE) Likelihood 30% CMAI improvement: RR, 0.96 (0.56-1.62) for donepezil	NR	NR	NR
Anti-convulsant	Insufficient SOE (valproic acid)	NR	NR	NR

CATD=clinical Alzheimer's-type dementia; CMAI=Cohen-Mansfield Agitation Inventory; NR=not reported; NS=no statistically significant difference; RR=relative risk; SAE=serious adverse event; SOE=strength of evidence
*Citalopram was dosed up to 30 mg/day, which exceeds the currently recommended maximum dose of 20 mg/day.
†Strength of evidence grades for a treatment comparison and outcome reflected our confidence about the direction of the treatment effect (i.e., whether or not the outcome differs between treatments). Definitions for strength of evidence grades are detailed in the Methods section of the main report.

Limitations

Evidence on the accuracy of brief cognitive tests for distinguishing CATD from normal cognition and MCI in adults with suspected cognitive impairment had several limitations. We found few eligible studies for most individual cognitive tests, fewer for test combinations, none for several common tests (e.g., Mini-Cog, Saint Louis University Mental Status test [SLUMS], Telephone Interview for Cognitive Status [TICS]), and minimal data on web-based tests. Similarly, few studies evaluated the accuracy of brain imaging and CSF tests compared with autopsy-confirmed diagnoses, and none examined blood tests. Studies for both cognitive and biomarker tests were limited by small sample sizes. Cognitive test studies were heterogeneous in several ways. They varied in their definitions of normal cognition and in test scoring metrics. Further, they rarely used normative or other prespecified cut points to distinguish normal from abnormal. Rather, cut points most often were selected to maximize classification accuracy within the study cohort. Brain imaging and CSF studies were also methodologically heterogeneous. These studies varied in composition of non-AD comparison groups, interval between imaging or CSF collection and autopsy, methods of image acquisition or CSF assay and analysis, neuropathologic reference standards, and use of test cut points unique to their individual study cohorts. Biomarker studies were limited because many study participants with biomarker measures did not complete autopsy and weren't included in analyses. No studies using an autopsy-confirmed AD reference group evaluated the classification accuracy of MRI hippocampal atrophy, computed tomography (CT), tau (positron emission tomography) PET, or (functional magnetic resonance imaging) fMRI brain imaging; beta amyloid (Aβ)42/Aβ40 ratio, or neurofilament light protein CSF tests; or any blood tests. Further, few studies examined the classification accuracy of test combinations. Because cognitive test and biomarker study populations were predominately white and relatively young (mean age 73 to 74 years for cognitive studies and mean dementia symptom onset in participants' early 60s to early 70s for biomarker studies), we could not determine generalizability of results to other racial/ethnic

groups or older populations. Further, there was little evidence about whether accuracy varied by study participant characteristics and no cognitive testing studies and few brain imaging or CSF testing studies reported on harms.

Evidence on the efficacy and harms of CATD drugs had several limitations. We found few trials for individual drug treatments, especially for supplements and BPSD drugs, and most study sample sizes were small. This resulted in low statistical power for even somewhat common events and large mean differences between groups that could be clinically meaningful if real. We also found few trials that stratified results by CATD severity. Because we analyzed studies grouped by participant CATD severity and graded SOE for treatment effects within these severity categories, it is possible that SOE grades would have been different in cases when lumping studies regardless of baseline CATD severity may have been clinically reasonable (e.g., for harms). This review limited prescription drug classes evaluated for cognition and function to cholinesterase inhibitors and memantine, and prescription drug classes evaluated for BPSD to cholinesterase inhibitors, memantine, antipsychotics, antidepressants, anxiolytics, antiepileptics/mood stabilizers, hormonal agents and cannabinoids. This review required studies of cognition and function to be at least 24 weeks long, and studies of agitation, aggression, and psychosis to be at least 2 weeks long; trials reporting only on acute and shorter-term treatment effects were excluded. In addition, few included trials were longer than 26 weeks, so longer-term drug effects were unclear. Because trial populations were predominately white, we could not determine generalizability to other racial/ethnic groups. Few trials directly compared different drug treatments. Few trials reported results for CATD staging, individual cognitive domains, quality of life, or caregiver outcomes, and no eligible studies without high risk of bias reported results for disinhibited sexual behavior. Harms reporting was poor. Many eligible trials were excluded from analyses due to high risk of bias, often because of high attrition, especially trials longer than 26 weeks and those that compared two active treatments. Many trials analyzed results using methods of accounting for missing data that may overestimate treatment benefit. It was difficult to interpret the relevance of small between-group differences in continuous outcomes and most trials did not report on between-group differences for the likelihood of experiencing clinically important treatment effects (i.e., responder analyses). Lastly, few trials evaluated whether treatment efficacy and harms varied by study participant characteristics.

Implications and Conclusions

Cognitive test studies showed that among individuals with suspected cognitive impairment (case finding), selected brief cognitive tests, including those commonly used as individual stand-alone tests, brief multidomain batteries, and memory verbal fluency tests typically administered as part of a larger battery in clinical practice are accurate for distinguishing between CATD and normal cognition, but somewhat less accurate distinguishing between smaller differences in cognitive function (e.g., distinguishing mild CATD from normal cognition, or CATD from MCI). However, because few studies directly compared the accuracy of different tests, different test scoring metrics, different cut-points for defining tests as abnormal, or combinations of tests, we could not definitively determine which test or combination of tests is most accurate and which cut-point is best for each test and test metric. We found even less information about whether test accuracy varied by patient characteristics. So, brief cognitive tests may help identify which patients with suspected cognitive impairment are more likely to have CATD but are not considered sufficient alone to make the clinical diagnosis. Brief cognitive test results may help clinicians decide who warrants further diagnostic evaluation, including a detailed history of

cognitive symptoms, focused neurological exam, and possible neuropsychological testing and specialty referral. These brief cognitive test results also may be sufficient for objectively documenting cognitive impairment in more impaired patients with a recognized history of cognitive and functional decline typical for CATD.

Biomarker studies showed that several types of brain imaging and CSF tests are highly sensitive and specific for distinguishing autopsy-confirmed AD from non-AD dementia. Based on few studies, amyloid PET and FDG-PET imaging but not SPECT appear to increase classification accuracy added to a clinical evaluation when directly compared to accuracy of a clinical evaluation alone. One study (reporting data for one of two assays evaluated) suggested that a model incorporating results from multiple CSF biomarkers may improve categorization of patients between AD and FTLD when added to clinical evaluation alone. We found no analogous data for MRI or other CSF tests. One study reported that the combination of CT and amyloid PET was not more accurate than amyloid PET alone. Data were unclear for which combination of tests and which test cut points are best for distinguishing between autopsy-confirmed AD and non-AD in individuals with CATD. However, even if future research confirms that biomarkers and their combinations improve classification accuracy when added to clinical evaluation, applicability is likely to be limited as long as access to such testing is limited in many clinical settings and there are no disease-modifying drug treatments for AD and non-AD dementias.

Trials of about 6 months showed benefits for cholinesterase inhibitors compared with placebo regardless of baseline CATD severity. However, average differences for cognition and function between treatment groups were small, with standardized mean differences mostly between 0.20 to 0.40 for cognition and about 0.20 for function. Responder analyses showed that compared with placebo, for approximately every 5 to 13 participants assigned cholinesterase inhibitors, one additional individual was improved at 6 months on a cognitive battery (≥4-point improvement in Alzheimer's Disease Assessment Scale-Cognition [ADAS-Cog]) or a global change measure (Clinician's Interview-Based Impression of Change with caregiver input [CIBIC-Plus] or Clinical Global Impression of Improvement [CGIC]). Whether these 6 month improvements are clinically meaningful is unclear. Data on moderate or marked improvement for cognition or function were not reported and moderate or marked improvement on the global change measures was rare and no more likely with cholinesterase inhibitor treatment than placebo. We could not determine the likelihood of longer-term benefits, because no eligible cholinesterase inhibitor trials with low or medium risk of bias reported efficacy outcomes beyond 6 months. For memantine, one trial suggested that for every 6 additional participants assigned memantine compared with placebo, one additional individual was improved on the CIBIC-Plus global change measure, but other eligible memantine trials did not report responder analyses and mean differences between memantine and placebo for measures of cognition and function were not statistically significant or small, particularly in patients with mild to moderate CATD.

On the whole, evidence to guide treatment decisions about prescription drugs for BPSD in patients with CATD was lacking. Few eligible trials with low or medium risk of bias examined treatment efficacy and harms of prescription drugs in patients with CATD and BPSD and were at least 2 weeks in duration. While a few trials reported some findings suggesting possible treatment benefit, the evidence was insufficient to draw conclusions. This was largely due to small sample sizes and inconsistent results within and between trials. For example, one trial of aripiprazole showed statistically significant improvement compared with placebo in two of three psychosis scores, a small trial of standard-dose haloperidol versus placebo showed numerically

higher likelihood of improvement in agitation and psychosis (likelihood of absolute risk differences ≥25% and/or standardized mean differences (SMDs) >0.4 that were not statistically significant), and a trial of quetiapine showed no difference in mean change for agitation compared with placebo. No eligible trials of antipsychotics reported data on stroke and just three (n=451) reported data on deaths (4.4% for the antipsychotic group vs. 1.8% for placebo), too few to draw conclusions but not inconsistent with FDA warnings.[1, 2] For antidepressants, one trial of citalopram up to 30 mg/day reported statistically significant improvement compared with placebo for a minority of agitation and psychosis outcomes. However, this dose exceeds the current maximum recommended dose of 20 mg/day. A trial of sertraline showed no statistically significant difference in agitation compared with placebo. Strength of evidence for all efficacy outcomes for both these antidepressant trials was considered insufficient to draw conclusions and insufficient to guide treatment decisions. We found no evidence from qualifying trials for other antidepressants, low-strength evidence that donepezil and placebo did not differ for agitation in one trial, and only insufficient evidence about the efficacy of antiseizure drugs, memantine, and estrogen. Only one trial compared different prescription drugs for agitation and evidence was insufficient to draw conclusions about differences in BPSD or harms for continued antipsychotics compared with switching to memantine. No trials compared antipsychotics with antidepressants.

Few eligible trials with low or medium risk of bias examined efficacy and harms of supplements on the outcomes of cognition, function, and BPSD in patients with CATD. Two trials each for the nutritional drink Souvenaid® and omega-3 fatty acids showed no benefit compared with placebo for function and cognition, respectively. Several other trials showed statistically significant benefits compared with placebo for one or more outcomes. However, due to small sample sizes, few trials for each intervention, and study limitations, evidence was insufficient to draw conclusions about the efficacy and safety of these supplements for CATD treatment for all these outcomes.

Future Research Recommendations

Future research about the accuracy of brief cognitive testing for CATD should continue to define CATD and MCI based on standard clinical criteria and should define normal cognition based on a formal cognitive evaluation rather than self-report or brief testing. Studies should evaluate the accuracy of commonly used or promoted brief cognitive tests for which we identified no eligible studies. Studies should prespecify test cut points or the methodology for defining them to enable external validation beyond single study populations. Studies should compare the accuracy of different individual and combined brief cognitive tests in the same study population and evaluate whether cognitive test accuracy varies by study participant characteristics (e.g., age, sex, race, education). Studies should systematically collect data on potential harms of cognitive testing. Directly or through modeling, studies should evaluate whether brief cognitive testing of patients with suspected cognitive impairment modifies subsequent drug and nondrug treatment decisions and, more importantly, alters patient and caregiver outcomes.

Future research about the accuracy of biomarkers for distinguishing AD from non-AD dementias in patients with CATD should compare the accuracy of brain imaging, CSF and blood biomarkers with autopsy-confirmed AD pathology. Among participants with collected biomarkers, studies should compare characteristics between participants with and without available autopsy data to better identify potential attrition biases in studies using autopsy

neuropathology as a reference standard. Research should better clarify how biomarker accuracy varies as a function of the time between biomarker collection and autopsy, to inform how changes in biomarkers and brain neuropathology over time affect test accuracy, and the strengths and limitations of using biomarkers as a surrogate for brain neuropathology. Future studies should evaluate the accuracy of biomarkers for which we identified no eligible studies (e.g., MRI hippocampal atrophy, CT, tau PET, and fMRI for brain imaging; Aß42/Aß40 ratio and neurofilament light protein for CSF; and blood biomarkers). Studies should report information about participant clinical diagnosis to make it clear how often clinical diagnoses are reclassified based on biomarker testing. Studies should standardize imaging and assay analytic methods and rating criteria that are feasible to implement in typical clinical settings. Studies should externally validate cut points for optimally distinguishing AD from non-AD dementias across populations, including in typical clinical populations. Studies should compare different individual and combined brain imaging and CSF tests in the same study population and evaluate whether test accuracy varies by study participant characteristics (e.g., age, sex, race, education). Studies should systematically collect data on potential psychological and physical harms of biomarker testing. Lastly, directly or through modeling, studies should evaluate whether biomarker testing affects drug and nondrug treatment decisions and, more importantly, alters patient and caregiver outcomes.

Future trials investigating drug treatment for CATD should be large enough to detect the likelihood of treatment response as defined for clinically important cognitive, functional, and global outcome measures. Trials should routinely report on patient quality of life and caregiver outcomes. Future trials should investigate treatment efficacy and harms beyond 6 months to increase applicability to clinic populations who may be treated for years. Trials should enroll more diverse participants, including nonwhites and older patients, and pre-specify analyses with sufficient statistical power to examine whether treatment effects are modified by patient characteristics, including age, sex, race/ethnicity, baseline CATD severity, baseline BPSD severity, and living setting. Additional trials should examine drug treatments and doses for which data suggest signals of possible benefits, but for which the strength of evidence is insufficient, such as antipsychotics and antidepressants for agitation and psychosis. Antipsychotics and antidepressants should be directly compared for treatment of BPSD. Future BPSD trials also should directly compare drug and nondrug treatment strategies, and drug trials should specify whether participants receive a concomitant psychosocial intervention. Future BPSD drug trials should be longer to better establish the evidence for long-term efficacy and safety. Supplements should be subjected to rigorous trial examination, both for efficacy and safety compared with placebo, and for comparative effectiveness and safety compared with FDA approved prescription drugs. Future drug trials for BPSD, which likely will continue to target agitation, aggression, and psychosis, should also prespecify disinhibited sexual behavior, depression, and anxiety as secondary efficacy outcomes.

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Chapter 1. Introduction

Background

Dementia is a clinical syndrome in which an acquired cognitive deficit interferes with independence in daily activities.[5] It affects about 10 percent of older adults in the United States.[6, 7] Dementia lowers patients' quality of life (QOL), burdens caregivers, increases institutionalization, and is costly to families and society.[8] Agitation, aggression, and other behavioral and psychological symptoms in dementia (BPSD) are common,[9] especially late in the disease course. These symptoms may threaten the safety of patients and others and are often highly distressing to caregivers.

The ultimate reason for accurately diagnosing clinical Alzheimer's-type dementia (CATD) and for determining whether Alzheimer's disease (AD) is the underlying neuropathological etiology is to inform decision making about drug and nondrug treatments to improve patient and caregiver outcomes. In most individuals with a clinical dementia syndrome, AD is the primary underlying cause or at least is a contributing factor.[10, 11] Historically, patients with suspected AD have been diagnosed clinically, including by criteria set by the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA),[5] the Diagnostic and Statistical Manual of Mental Disorders (DSM),[12-14] and the National Institute on Aging-Alzheimer's Association (NIA-AA) workgroup.[15] NINCDS-ADRDA and DSM criteria prior to DSM-V require acquired, persistent impairment in memory and at least one other cognitive domain, along with associated functional disability not attributable to another disorder. Though DSM-V and NIA-AA criteria for major neurocognitive disorder and probable AD dementia, respectively, also require acquired deficits in at least two cognitive domains and functional disability not attributable to another disorder, memory need not be the initial or most prominently impaired cognitive domain. According to NIA-AA criteria, a diagnosis of possible AD dementia applies when either the clinical course has been atypical for AD or the clinical presentation suggests contribution from a non-AD etiology. In this report, we refer to patients with a dementia syndrome clinically suggestive of AD as having CATD.

Whereas these clinical criteria dichotomously frame AD as present or absent, AD is an insidious disease in which neuropathologic changes begin and progress for many years before symptoms are detectable and multiple neuropathologies may contribute. In clinical settings, even when the etiology of CATD is thought to be AD, it may be impossible to differentiate between CATD attributable to isolated AD, to a combination of AD plus another etiology (e.g., cerebrovascular disease), or to a non-AD neurodegenerative disease. Many individuals with CATD do not meet neuropathological AD criteria at autopsy. In patients followed in research centers, sometimes for extended durations, sensitivity and specificity of a clinical diagnosis of probable AD for autopsy-confirmed AD are approximately 80 percent and 70 percent, respectively.[16] Accuracy of clinical diagnoses earlier in the disease course and in primary care settings are likely to be lower.[17] Many patients with clinical AD and neuropathological AD changes also have other neuropathologic changes (e.g., microinfarcts or Lewy bodies).[18]

Neuropsychological testing may quantify the severity of cognitive impairment and the pattern of cognitive performance across multiple domains, helping to diagnose dementia and distinguish between different dementia subtypes. However, comprehensive neuropsychological testing is time consuming and access is limited in some healthcare settings. This has heightened interest in identifying which brief cognitive tests or their combinations are most accurate for

distinguishing CATD from mild cognitive impairment (MCI) or normal cognition in patients in whom CATD is suspected (case finding) (Appendix Table K.1). Currently, no evidence-based guidelines address the merits of brief cognitive testing in patients suspected to have CATD. Though brief cognitive tests are not by themselves sufficient for diagnosing CATD, identifying brief tests that are sensitive and specific for distinguishing CATD from MCI and normal cognition in patients with suspected cognitive impairment could increase the efficiency of recognizing CATD in clinical settings, especially in primary care.

Limitations in the accuracy of clinical diagnosis of AD as the underlying cause of CATD, even after a full clinical evaluation with or without neuropsychological testing, have spurred efforts to identify specific biological markers of AD (i.e., biomarkers) that may be present across preclinical, MCI and dementia clinical stages. Existing brain imaging and cerebrospinal fluid (CSF) biomarkers may reflect specific manifestations of AD pathology, including localized neuronal hypometabolism, localized neuronal loss, abnormal ß-amyloid metabolism, cortical amyloid deposition, and accumulation of tau pathology.[19] Blood tests are earlier in development.[20, 21] Because of the promise of these biomarkers, NIA-AA proposed research diagnostic criteria that combine clinical and biomarker information—probable or possible AD dementia with evidence of the AD pathophysiological process.[15] More recently, NIA-AA proposed a research framework classifying individuals as cognitively unimpaired, or having either MCI or dementia, based only on cognitive symptom severity and without inference about an underlying etiology.[22] This framework then defines and stages AD in living persons based only on biomarkers that reflect ß amyloid deposition, pathologic tau, and neurodegeneration (AT[N]), but suggests using variable cut points to categorize biomarker levels as abnormal versus normal based on the particular research question being addressed. No cut points for specific biomarker levels or pattern of biomarker abnormalities have been proposed for clinical decision making.[18]

Many interventions are used to treat CATD or have been proposed for treatment, with the goal of improving, stabilizing or slowing decline in cognition, function, quality of life, and BPSD. These include nondrug interventions (e.g., exercise and cognitive training for patients, social support for caregivers), prescription drug interventions, and nonprescription drug interventions (e.g., over-the-counter drugs, supplements).

A recent Agency for Healthcare Research and Quality (AHRQ) report examined the effects of nondrug interventions for preventing or slowing cognitive decline in adults with normal cognition or MCI.[23] Moderate-strength evidence showed that in patients with normal cognition, cognitive training could improve the cognitive domain trained, but did not improve untrained cognitive domains. In contrast, effects of cognitive training in patients with MCI appeared mixed and there was minimal data about whether cognitive training could delay clinical progression to MCI or CATD. This report also found no cognitive benefit from most physical activity interventions in individuals with normal cognition or MCI and that evidence was insufficient to draw conclusions about the benefits and harms of dietary interventions. We are not aware of a recent review on the effect of nondrug interventions for treating cognition, function, and QOL in patients with established CATD. Though nondrug interventions are recommended as first line treatments for BPSD,[24] a recent AHRQ report found that patient-level and care delivery-level interventions were not superior to usual care for managing agitation and aggression, and that evidence was insufficient to draw conclusions about the efficacy of most caregiver-level interventions.[25] While these interventions generally are presumed safe, very few trials have reported information about harms.

A 2008 American Academy of Family Physicians (AAFP)/American College of Physicians (ACP) guideline focused on drug treatment of CATD (Appendix Table K.2).[26] It reported that evidence from mostly short-term randomized controlled trials (RCTs) showed that cholinesterase inhibitors and memantine statistically significantly improve cognition, but that the mean differences in cognitive scores between active treatment and control groups were not clinically important. Some studies reported that more patients assigned cholinesterase inhibitors than placebo had clinically important improvements in cognition, suggesting a possible subpopulation benefit. However, these studies did not report formal test results for whether the proportions with clinically important improvements significantly differed between treatment groups. Data reported on function was limited, and these treatments did not improve behavioral symptoms. The guideline stated that evidence was insufficient to compare the effectiveness of different drugs for treatment of dementia. The guideline recommended that decisions to initiate one of these therapies should be individualized to the patient and should consider issues of adverse effects, ease of use, and cost, and that further research on the clinical effectiveness of drug treatments for dementia was urgently needed. Supplements were included in the evidence review but not addressed in the guideline. Though no new medications have been approved for treatment of CATD by the U.S. Food and Drug Administration (FDA) since before the 2008 AAFP/ACP guideline, many new trials of existing agents have been published. A recent nonsystematic review reported that antipsychotics and mood stabilizers for treating BPSD in patients with dementia did not improve behavioral symptoms more than placebo, but had a substantially increased risk of harms.[27] Results for selective serotonin reuptake inhibitor (SSRI) antidepressants were mixed. Treatment with supplements was not addressed.

Notably, claims abound on the internet and elsewhere about the benefits of various supplements for cognition, function, and BPSD in patients with CATD. In addition, 13 states currently include AD as a qualifying condition for their medical marijuana program, with use specified for severe or end-stage AD in one of the states and for individuals with AD-related BPSD in eight of the States.[28] Anecdotally, patient and caregiver questions to primary care providers about the potential benefits of supplements for CATD are common. The efficacy of some older supplements has been evaluated in RCTs and systematic reviews. For many of these, it is not likely that new trials have been conducted, and thus fresh reviews are not warranted. However, for old agents with new trials, new agents, or agents with increased public interest (e.g., cannabinoids, ginseng, omega 3, gingko, huperzine A), a new comprehensive systematic review examining the effects of these agents on cognition, function, QOL, BPSD, and harms is needed.

Primary care providers routinely provide dementia care and need current, evidence-based guidance to optimize diagnosis and treatment. To address this need, the AAFP nominated this topic to update their 2008 AAFP/ACP guideline on prescription drugs and supplements for treatment of CATD.[26] The AAFP also sought to broaden the guideline by adding questions about the efficacy and harms of nondrug CATD treatment, and the accuracy and harms of cognitive and biomarker testing of adults with suspected cognitive impairment. Separate ongoing AHRQ reviews are focused on screening asymptomatic older adults for dementia (https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/cognitive-impairment-in-older-adults-screening?ds=1&s=cognitive)[29] and on the efficacy and harms of care interventions (including nondrug treatments) for patients with CATD and care interventions for their caregivers (https://effectivehealthcare.ahrq.gov/products/care-interventions-pwd/protocol).[30] These topics are not addressed by the present review except when a nondrug

treatment is included as the control group for drug treatment. Therefore, the scope of the present review is limited to brief cognitive testing for CATD in patients in whom there is suspicion for CATD, biomarker testing for AD in patients with dementia, and prescription drug and supplement treatment of CATD.

Because primary care providers must make clinical decisions for individual patients, group-level results for the accuracy of brief cognitive and biomarker tests and treatment efficacy and harms may have limited utility. Identification of the patient characteristics associated with cognitive and biomarker test accuracy and harms, and with drug treatment efficacy and harms, may help physicians, patients, and caregivers make more individualized decisions about how to test, whether to treat, with what to treat and when, and when to stop treatment. Therefore, this review also examines whether factors such as age, sex, race/ethnicity, education, depression, pre-treatment cognitive or functional level/CATD stage, pre-treatment BPSD severity, and living setting modify the accuracy and comparative accuracy of cognitive and biomarker tests or the efficacy and comparative effectiveness of drug treatments.

The main target audiences of this report are primary care clinicians who diagnose and treat the vast majority of older patients with cognitive disorders, psychologists who may perform diagnostic cognitive testing in primary care settings, and dementia specialists who may be most likely to consider biomarker testing for further disease classification.

Scope and Key Questions

Key Questions

Key Question (KQ) 1: In adults with suspected cognitive impairment, what are the accuracy, comparative accuracy, and harms of brief cognitive tests and their combinations for identifying CATD as defined by full clinical evaluation or neuropsychological testing with explicit diagnostic criteria?

KQ 1a: Do the accuracy and comparative accuracy of brief cognitive tests for identifying CATD vary as a function of patient characteristics (i.e., age, sex, race/ethnicity, depression, education, pre-testing cognitive or functional level/CATD stage)?

KQ 2: In adults with a clinical diagnosis of CATD, what are the accuracy, comparative accuracy, and harms of brain imaging, CSF, and blood tests for identifying pathologically confirmed AD as the underlying etiology?

KQ 2a: Do the accuracy and comparative accuracy of brain imaging, CSF, and blood tests for identifying pathologically confirmed AD vary as a function of patient characteristics (i.e., age, sex, race/ethnicity, depression, education, pre-testing cognitive or functional level/CATD stage)?

KQ 3: In adults with CATD, what are the efficacy and harms of prescription drug interventions versus placebo/inactive control for treatment of cognition, function, and quality of life?

KQ 3a: Does the efficacy of prescription drug interventions versus placebo/inactive control vary as a function of patient characteristics (i.e., age, sex, race/ethnicity, depression, pre-treatment cognitive or functional level/CATD stage, living setting)?

KQ 4: In adults with CATD, what are the efficacy and harms of supplements versus placebo/inactive control for treatment of cognition, function, and quality of life?

KQ 4a: Does the efficacy of supplements versus placebo/inactive control vary as a function of patient characteristics (i.e., age, sex, race/ethnicity, depression, pre-treatment cognitive or functional level/CATD stage, living setting)?

KQ 5: In adults with CATD, what is the comparative effectiveness for cognition, function, and quality of life, and what are the comparative harms for the following interventions:

KQ 5a: Prescription drugs versus other prescription drugs?

KQ 5b: Prescription drugs versus supplements?

KQ 5c: Prescription drugs versus nondrug interventions (e.g., exercise, cognitive training, caregiver social support)?

KQ 5d: Does comparative effectiveness of prescription drugs versus other prescription drugs, supplements, or nondrug interventions for cognition, function, and quality of life vary by patient characteristics (i.e., age, sex, race/ethnicity, depression, pre-treatment cognitive or functional level/CATD stage, living setting)?

KQ 6: In adults with CATD and behavioral and psychological symptoms of dementia (BPSD), what are the efficacy and harms of prescription drug interventions versus placebo/inactive control for:

KQ 6a: Acute treatment of BPSD?

KQ 6b: Reducing frequency and severity of future BPSD?

KQ 6c: Does efficacy of prescription drugs versus placebo/inactive control for acute treatment and reducing frequency and severity of future BPSD vary by patient characteristics (i.e., age, sex, race/ethnicity, depression, pre-treatment cognitive or functional level/CATD stage, pre-treatment BPSD severity, living setting)?

KQ 7: In adults with CATD and BPSD, what are the efficacy and harms of supplements versus placebo/inactive control for:

KQ 7a: Acute treatment of BPSD?

KQ 7b: Reducing frequency and severity of future BPSD?

KQ 7c: Does efficacy of supplements versus placebo/inactive control for acute treatment and reducing frequency and severity of future BPSD vary by patient characteristics (i.e., age, sex, race/ethnicity, depression, pre-treatment cognitive or functional level/CATD stage, pre-treatment BPSD severity, living setting)?

KQ 8: In adults with CATD and BPSD, what is the comparative effectiveness for BPSD, and what are the comparative harms for the following interventions:

KQ 8a: Prescription drugs versus other prescription drugs?

KQ 8b: Prescription drugs versus supplements?

KQ 8c: Prescription drugs versus nondrug interventions (e.g., exercise, cognitive training, caregiver social support)?

KQ 8d: Does comparative effectiveness of prescription drugs versus other prescription drugs, supplements, or nondrug interventions for BPSD vary by patient characteristics (i.e., age, sex, race/ethnicity, depression, pre-treatment cognitive or functional level/CATD stage, living setting)?

PICOTS

Table 1.1 outlines the populations, interventions, comparisons, outcomes, timing, and settings (PICOTS) eligible for the present review.

Table 1.1. PICOTS

KQ	Population	Intervention	Treatment Comparator or Diagnostic Reference Standard	Health Outcomes and Harms	Timing	Setting	Study Design
KQ 1-2: Test accuracy for identifying CATD or AD & test harms	Cognitive tests Adults ≥50 years of age with suspected cognitive impairment Biomarker tests only Adults ≥50 years of age with clinical syndrome of CATD Patient characteristics assessed as possible effect modifiers of test accuracy Age Sex Race/ethnicity Education Depression Pre-test cognitive or functional level/ CATD stage	Brief, validated cognitive tests Individual stand-alone tests, brief multidomain batteries, individual domain level tests typically administered as part of a larger battery in clinical practice (memory, executive, language) Biomarker tests *Brain imaging* CT/MRI (e.g., medial temporal atrophy, hippocampal volume) PET (Amyloid, FDG, Tau) fMRI: resting state and task specific activation SPECT: cerebral perfusion *CSF tests* Aß42 Aß42/Aß40 ratio t-tau p-tau t-tau/Aß42 ratio p-tau/Aß42 ratio neurofilament light protein *Blood tests* Aß42 Aß42/Aß40 ratio APP *Combinations*	Cognitive tests Full clinical evaluation or neuropsychological testing with explicit diagnostic criteria Biomarker tests Postmortem neuropathological confirmation of AD	Accuracy and comparative accuracy (e.g., sensitivity, specificity, TP, FP, TN, FN, PPV, NPV)* Cognitive tests for distinguishing CATD from normal cognition or MCI Biomarker tests for distinguishing AD from non-AD Harms *True positive* Labeling stigma *False positive* Incorrect diagnosis Labeling stigma Side effects of unneeded interventions (e.g., restrictions on independence, medication adverse effects) *False negative* Unexplained symptoms Failure to make appropriate interventions (e.g., safety precautions, future planning) *Physical (directly from diagnostic tests)* Pain Infection Headache Radiation	Cognitive tests ≤6 months between cognitive test and CATD diagnosis Biomarker tests Any	Community-dwelling Assisted living	Accuracy and comparative accuracy Controlled observational studies Systematic review of controlled observational studies Harms Controlled observational studies Systematic review of controlled observational studies

KQ	Population	Intervention	Treatment Comparator or Diagnostic Reference Standard	Health Outcomes and Harms	Timing	Setting	Study Design
KQ 3-5: Drug treatment efficacy, comparative effectiveness & harms on cognition, function & QOL	Adults with CATD ≥50 years of age Patient characteristics assessed as possible treatment effect modifiers Age Sex Race/ethnicity Depression Pretreatment cognitive or functional level/CATD stage Living setting	Prescription drug treatment Cholinesterase inhibitors NMDA antagonists Supplements	Efficacy comparisons Placebo Other inactive control Comparative effectiveness comparisons Prescription drug treatment Supplements Nondrug treatment	Efficacy and comparative effectiveness Change in patient cognition (individual stand-alone tests, brief multidomain batteries, individual domain level tests typically administered as part of a larger battery in clinical practice [memory, executive, language, attention], function, or QOL on validated test) Change in Alzheimer's disease stage Change in patient "at home" IADL or ADL function Change in patient residence to different level of independence Harms *General* FDA defined SAE Withdrawals due to AE *Psychiatric* Somnolence Confusion/Delirium *Nonpsychiatric* Falls Extrapyramidal symptoms Stroke Mortality	≥24 weeks	Cognitive outcomes Community-dwelling Assisted living Functional & QOL outcomes Community-dwelling Assisted living Nursing home	Efficacy and comparative effectiveness RCT CCT Systematic review of RCTs or CCTs Harms RCT CCT Controlled prospective cohort studies >1000 Systematic review of these study designs

KQ	Population	Intervention	Treatment Comparator or Diagnostic Reference Standard	Health Outcomes and Harms	Timing	Setting	Study Design
KQ 6-8: Drug treatment efficacy, comparative effectiveness, & harms on BPSD	Adults with CATD ≥50 years of age with BPSD (studies specified BPSD inclusion criterion) Patient characteristics assessed as possible treatment effect modifiers Age Sex Race/ethnicity Pre-treatment cognitive or functional level/CATD stage Pre-treatment BPSD severity Living setting	Prescription drug treatment Cholinesterase inhibitors NMDA antagonists Antipsychotics, second generation (any) and first (only haloperidol) Antidepressants Anti-seizure/mood stabilizers Anxiolytics, benzodiazepine Anxiolytics, other Hormonal agents (Disinhibited sexual behavior only) Cannabinoids Combinations Supplements	Efficacy comparisons Placebo Other inactive control Comparative effectiveness comparisons Prescription drug treatment Supplements Nondrug treatment	Efficacy and comparative effectiveness *Primary* Change in frequency or severity of BPSD† on validated test (agitation/aggression, psychosis, depression, anxiety, disinhibited sexual behavior) Change in patient QOL on validated test Change in validated general behavior scale *Secondary* Change in caregiver/staff outcomes on validated test (depression, global stress/distress, QOL, burden) Harms: *General* FDA defined SAE Withdrawals due to AE *Psychiatric* Somnolence Confusion/Delirium *Nonpsychiatric* Falls Extrapyramidal symptoms Stroke Mortality	Agitation, aggression, psychosis or Disinhibited sexual behavior outcomes ≥2 weeks Depression or anxiety outcomes ≥24 weeks	Community-dwelling Assisted living Nursing home	Efficacy and comparative effectiveness RCT CCT Systematic review of RCTs or CCTs Harms RCT CCT Controlled prospective cohort studies ≥1000 Systematic review of these study designs

Aß=beta amyloid; AD=Alzheimer's dementia; ADL=activities of daily living; AE=adverse events; APP=amyloid precursor protein; BPSD=behavioral and psychological symptoms of dementia; CATD=clinical Alzheimer's-type dementia; CCT=controlled clinical trial; CSF=cerebrospinal fluid; CT=computed tomography; DTI=diffusion tensor imaging; FDA=U.S. Food and Drug Administration; FDG=fluorodeoxyglucose; fMRI=functional magnetic resonance imaging; FN=false negative; FP=false positive; IADL=instrumental activities of daily living; KQ=Key Question; MCI=mild cognitive impairment; MRI=magnetic resonance imaging; NMDA=N-methyl-D-aspartate; NPV=negative predictive value; PET=positron emission tomography; p-tau=abnormally phosphorylated tau; PICOTS= populations, interventions, comparators, outcomes, timing, and settings; PPV=positive predictive value; QOL=quality of life; RCT=randomized clinical trial; SAE=serious adverse events; SPECT=single-photon emission computed tomography; TN=true negative; TP=true positive; t-tau=total tau

*PPV and NPV results were reported only in appendix tables.

†This report did not address apathy and sleep disturbances to focus scope and because they were addressed in recent, high quality systematic reviews.[31, 32] Wandering was not reviewed because this symptom is usually treated with nonpharmacologic interventions, which are not covered in the scope of this review.

Analytic Framework

The analytic framework for this review is illustrated in Figure 1.1 (KQs 1–2), Figure 1.2 (KQs 3–5), and Figure 1.3 (KQs 6–8).

Figure 1.1. Analytic framework for Key Questions 1–2

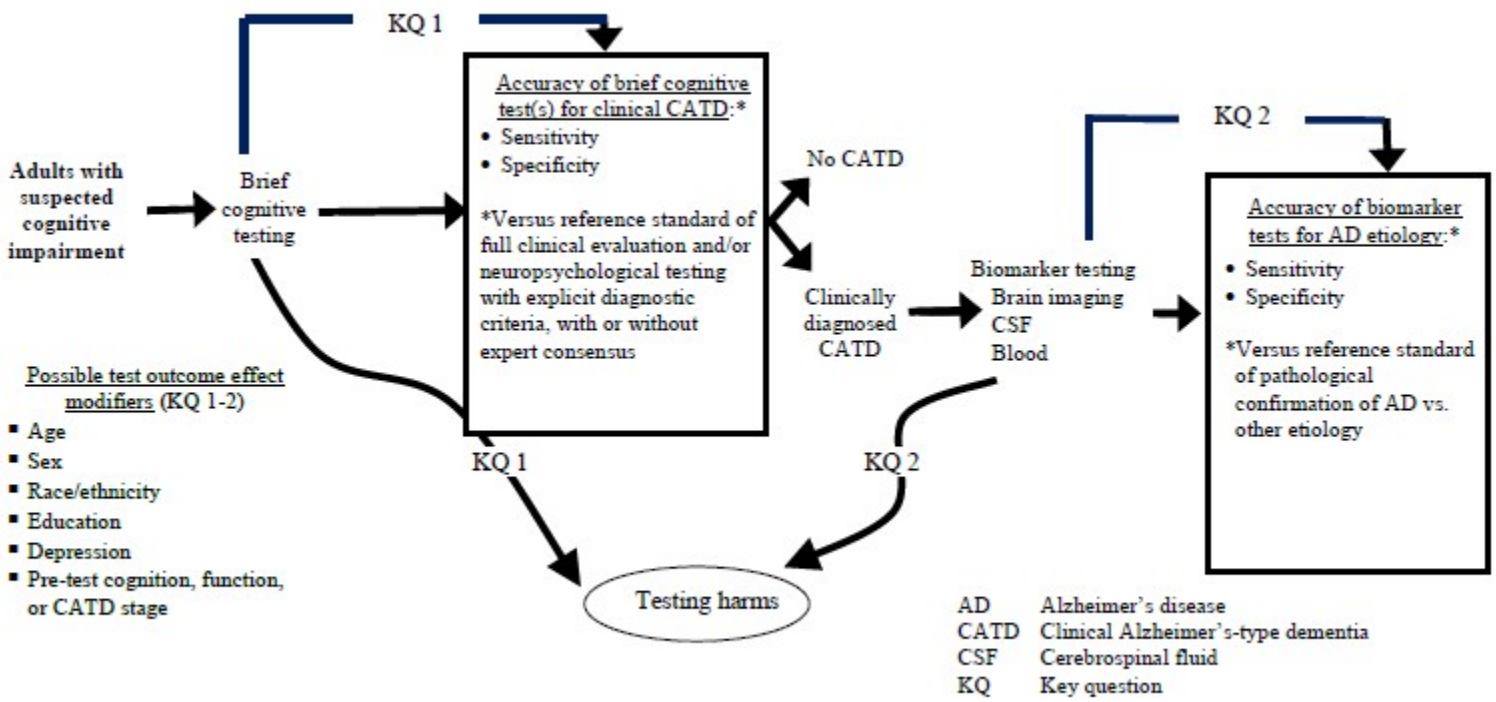


Figure 1.2. Analytic framework for Key Questions 3–5

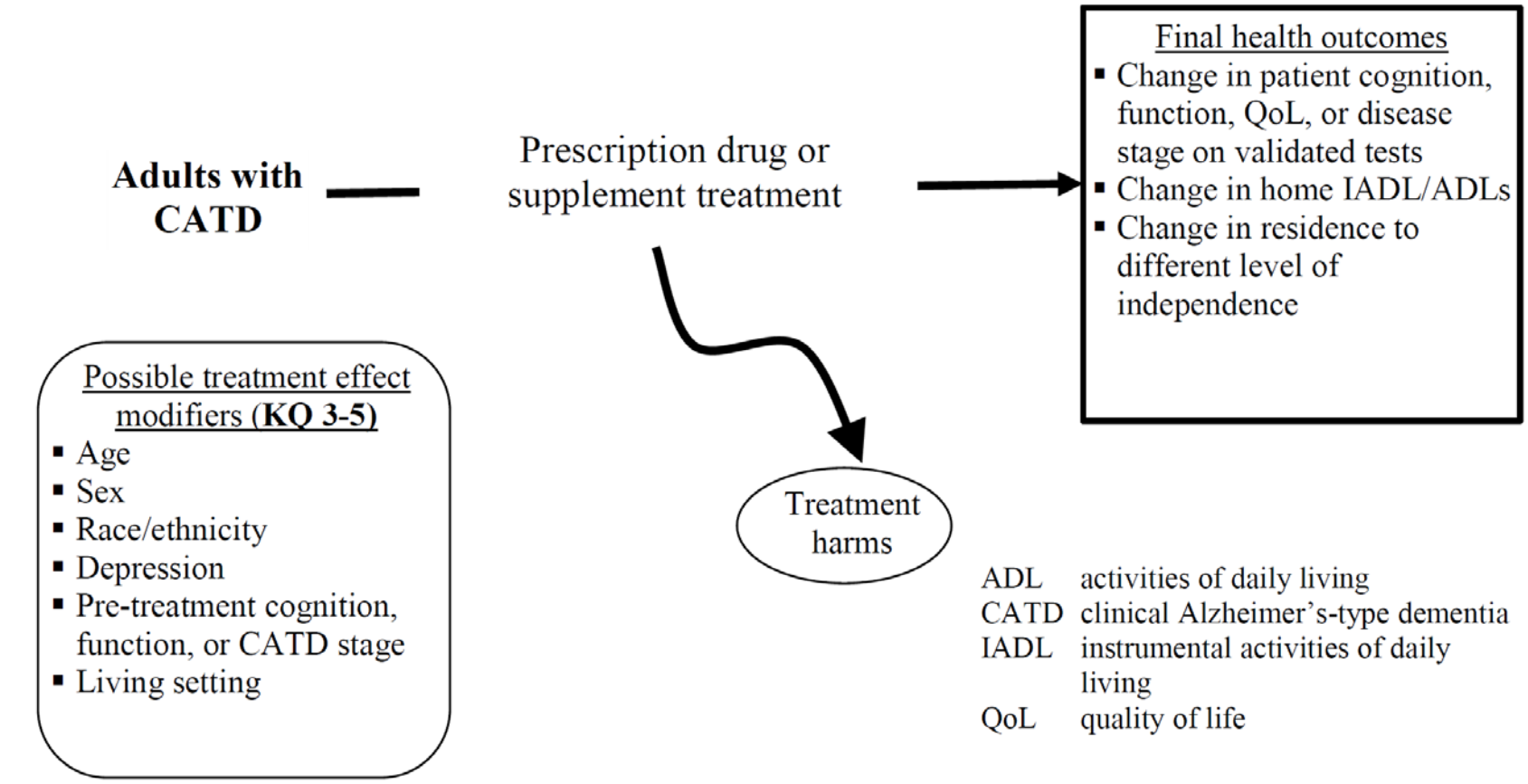
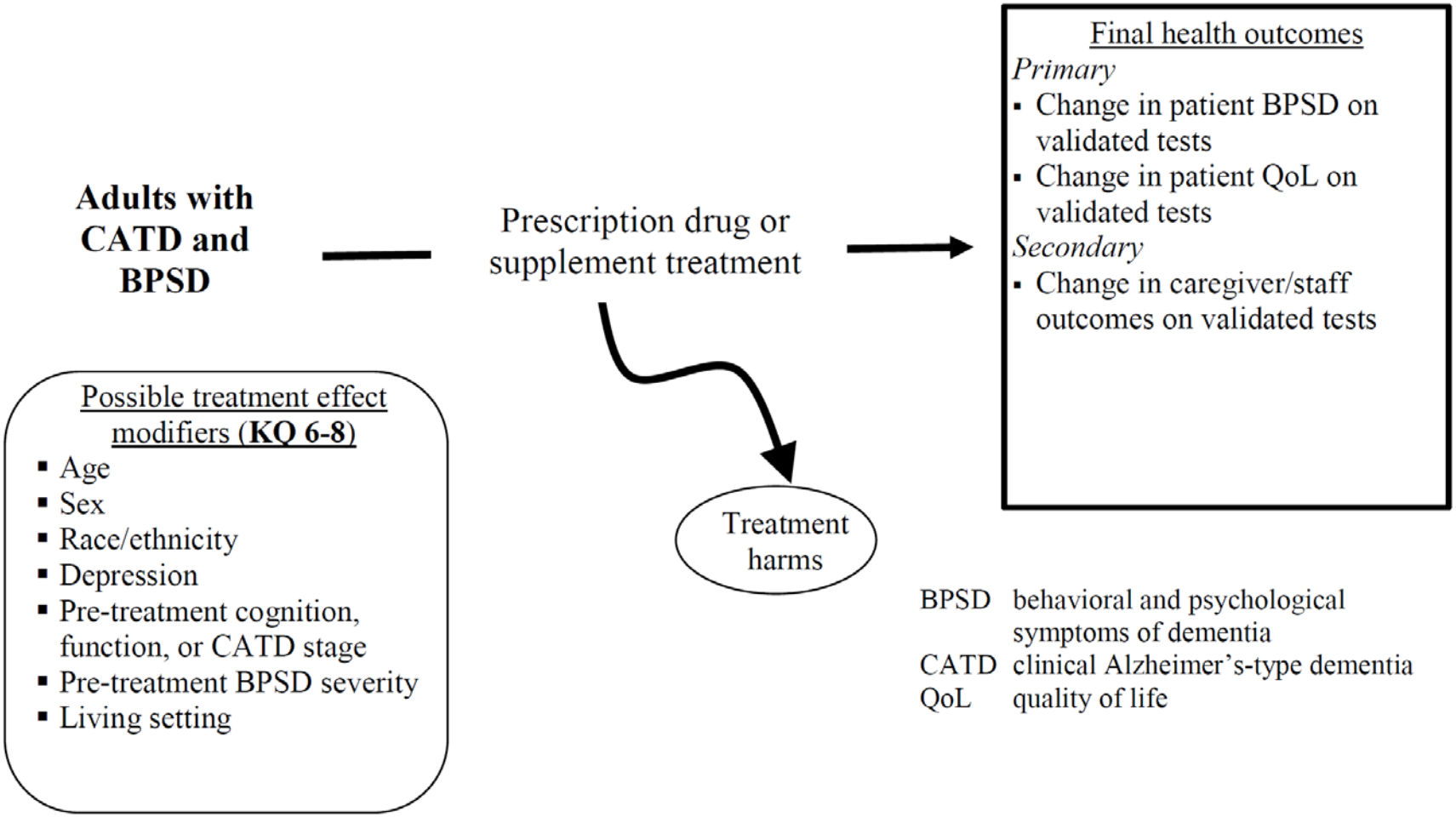


Figure 1.3. Analytic framework for Key Questions 6–8



Chapter 2. Methods

This Comparative Effectiveness Review follows methods suggested in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews (http://www.effectivehealthcare.ahrq.gov/methodsguide.cfm); certain methods map to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[33]

Topic Refinement and Review Protocol

The American Academy of Family Physicians (AAFP) developed the original Key Questions. We refined the Key Questions in collaboration with a Key Informant Panel and AHRQ staff. The resulting Key Questions were incorporated into the final protocol, which is registered in PROSPERO (CRD42018117897) and available at https://effectivehealthcare.ahrq.gov/topics/alzheimers-type-dementia/protocol.

Literature Search Strategy

Electronic Database Search

We searched Ovid Medline®, Ovid Embase®, PsycINFO®, and the Cochrane Central Register of Controlled Trials (CENTRAL) to identify randomized controlled trials (RCTs), nonrandomized controlled clinical trials, observational studies, and systematic reviews published and indexed in these bibliographic databases. We conducted separate searches on the accuracy of brief cognitive testing for distinguishing clinical Alzheimer's-type dementia (CATD) from mild cognitive impairment (MCI) or normal cognition, the accuracy of biomarker testing for distinguishing neuropathologically-confirmed Alzheimer's disease (AD) from non-AD, and the efficacy and harms of CATD drug treatment. The cognitive testing and drug treatment searches covered from database inception to March 2019. The biomarker testing search covered from 2012 to March 2019 and relied on systematic reviews to identify biomarker studies published before 2012. Our search strategy, detailed in Appendix A, included relevant medical subject headings and natural language terms for the concepts of AD, MCI, dementia, drug treatment, cognitive tests, biomarkers, and diagnostic accuracy. These terms were combined with validated filters for study designs.

Grey Literature Search

We searched ClinicalTrials.gov to identify additional relevant completed and ongoing studies. AHRQ also opened a Supplemental Evidence and Data for Systematic Reviews (SEADs) portal for 30 days to solicit pharmaceutical manufacturer protocols with additional information about published or unpublished drug studies. These search results were used to identify studies, outcomes, and analyses not reported in the published literature to assess publication and reporting bias and to inform future research needs.

Study Selection and Risk of Bias Assessment

We reviewed studies relevant to inclusion criteria based on our population, intervention, comparators, timing, and settings (PICOTS) framework outlined in Table 2.1.

Table 2.1. Study inclusion criteria

Category	Inclusion Criteria
Study Population	Adults aged ≥50 years KQ 1: Suspected cognitive impairment (note that "suspected" cognitive impairment applied to prospective studies, but that cognitive diagnoses were already known in retrospective studies) KQ 2: Clinically diagnosed CATD KQ 3-5: CATD KQ 6-8: CATD with BPSD (study must have specified BPSD inclusion criterion) Exclude: Normal cognition, MCI, or dementia known to be secondary solely to TBI, FTD, PD, LBD, stroke, or another non-AD etiology (inclusion was limited to participants with CATD to focus on the most common subgroup of patients with dementia in typical clinical settings)
Study Objectives	KQ 1: Evaluate accuracy, comparative accuracy and harms of brief cognitive tests for distinguishing between clinically diagnosed CATD and either normal cognition or MCI KQ 2: Evaluate accuracy, comparative accuracy and harms of biomarker tests for distinguishing between neuropathologically confirmed AD and non-AD in individuals with clinically diagnosed CATD KQ 3-5: Evaluate efficacy, comparative effectiveness, and harms of drug treatment for CATD for symptoms of cognition, function, and quality of life KQ 6-8: Evaluate efficacy, comparative effectiveness, and harms of drug treatment for CATD for symptoms of BPSD KQ 1a, 2a, 3d, 4a, 5a, 6d, 7a, 8a: Evaluate possible effect modifiers of CATD drug treatment efficacy and comparative efficacy; and of brief cognitive test and biomarker classification accuracy
Study Design	KQ 1-2: Controlled observational studies (i.e., cross-sectional, retrospective cohort, case control) with ≥25 participants,* systematic review of these study designs that assessed ROB of included studies using validated tools. KQ 3-8: Treatment efficacy and comparative effectiveness: RCT or CCT, systematic review of RCTs or CCTs that assessed ROB of included studies using validated tools. Treatment harms: RCT, CCT, controlled prospective cohort studies of ≥1000 participants (will consider smaller cohort studies if evidence from larger cohort studies is insufficient); systematic review of RCTs, CCTs, or large, controlled prospective cohort studies that assesses ROB of included studies using validated tools.
Interventions	KQ 1: Brief cognitive tests: tests that generally take ≤30 minutes to administer, are English-language and are available in the U.S. (individual stand-alone tests, multidomain batteries, and individual domain level tests typically administered as part of a larger battery in clinical practice (all memory tests, selected prespecified executive and language tests). We included these types of brief cognitive tests to evaluate their potential applicability for CATD case finding in typical primary care clinical settings, whether administered by primary care providers or psychologists or others embedded in primary care clinic practices. KQ 2: Brain imaging tests in contemporary use (CT, MRI, PET, fMRI, SPECT), CSF or blood tests KQ 3-5: For targeting cognitive, functional, and quality of life outcomes: cholinesterase inhibitors, NMDA antagonists, supplements (orally ingested over-the-counter supplements, vitamins, or herbal medications) KQ 6-8: For targeting BPSD and quality of life outcomes: prescription drugs (cholinesterase inhibitors, NMDA antagonists, antipsychotics, antidepressants, anxiolytics, antiseizure/mood stabilizers, hormones [disinhibited sexual behavior only], cannabinoids, combinations), supplements
Comparisons	KQ 1: Diagnosis group is CATD based on full clinical evaluation and/or neuropsychological testing with explicit diagnostic criteria (e.g., DSM, ICD, NINCDS-ADRDA, NIA-AA), with or without expert consensus; comparison groups included "normal" cognition or mild cognitive impairment based on brief cognitive test, full clinical evaluation and/or neuropsychological testing. KQ 2: "Normal level" on biomarker test, other biomarker tests; reference diagnosis group is neuropathologically-defined AD. KQ 3-8: Placebo, other inactive control, prescription drug treatment, supplement treatment, nondrug treatment
Outcomes	KQ 1-2: Sensitivity, specificity of specific brief cognitive or biomarker test cut-off values, or data which enable their calculation KQ 3-5: Patient-related outcomes: Change in cognition (global, memory, executive function, language, attention), function, quality of life, and disease stage on validated tests; harms (FDA defined SAE, withdrawals due to AE, somnolence, confusion/delirium, falls, extrapyramidal symptoms, stroke, mortality) KQ 6-8: Patient-related outcomes: Change in BPSD and quality of life on validated tests; harms per KQ 3-5 Caregiver/staff outcomes: depression, QOL, global stress/distress/burnout, burden

Category	Inclusion Criteria
Possible Treatment/ Test Outcome Modifiers	KQ 1-8: pretest/pretreatment age, race/ethnicity, sex, depression, pretest/treatment cognitive or functional level/CATD stage KQ 1-2 only: education KQ 3-8: living setting KQ 6-8 only: pre-treatment BPSD severity Indicate whether reported subgroup analyses or tests of interaction were planned *a priori* versus post hoc, as post hoc analyses are at greater risk for false positive findings.
Timing	KQ 1: ≤6 months between brief cognitive testing and clinical diagnosis of CATD (to focus on cross-sectional accuracy rather than predictions of clinical progression) KQ 2: Any, including pre- or post-mortem, and any interval between biomarker collection and neuropathological assessment. KQ 3-5: Cognitive, functional, quality of life, and harms outcomes: ≥24 weeks (to focus on longer than very short term effects) KQ 6-8: BPSD and harms outcomes: ≥24 weeks (but ≥2 weeks for agitation/aggression, psychosis, or disinhibited sexual behavior) (focused on effects longer than the very short term; for more severe symptoms, included shorter follow-up) KQ 6-8: Quality of life and harms outcomes: ≥24 weeks (to focus on effects beyond the very short term)
Setting	KQ 1-2: For brief cognitive or biomarker testing: community-dwelling, assisted living KQ 3-5: For cognitive outcomes: community-dwelling, assisted living KQ 6-8: For functional, quality of life, and BPSD outcomes: community-dwelling, assisted living, nursing home
Publication Type	Published in full text in peer reviewed journals
Language of Publication	English only, due to resource limitations

AD=Alzheimer's disease; BPSD=behavioral and psychological symptoms of dementia; CATD=clinical Alzheimer's-type dementia; CCT=controlled clinical trial; CT=computed tomography; DSM=Diagnostic and Statistical Manual of Mental Disorders; fMRI=functional magnetic resonance imaging; FTD=frontotemporal dementia; ICD=International Classification of Disease; KQ=Key Question; LBD=Lewy body dementia; MCI=mild cognitive impairment; MRI=magnetic resonance imaging; NINDCS-ADRDA=National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders; NMDA=N-methyl-D-aspartate; PD=Parkinson's disease; PET=positron emission tomography; QOL=quality of life; RCT=randomized controlled trial; SAE=serious adverse events; SPECT=single-photon emission computed tomography; TBI=traumatic brain injury.

*We excluded controlled observational studies with N <25 since these small studies are often lower in quality, inadequately powered on their own, and inappropriate to pool. The quality of the evidence from such small observational studies often is low since statistical adjustment is not possible because models become unstable when the number of cases is not much larger than the number of covariates (e.g. 10 to 15-fold). Without pooling, studies of this size (i.e., with 12 or fewer participants per arm) cannot reject null hypotheses even when true associations are large (i.e. Cohen's D = 1.2 for N=24 at 80% power). Also, small studies are prone to overestimate the magnitude of an association, potentially exaggerating the accuracy and harms of diagnostic testing, and biasing the pooled estimates.[34]

We screened titles and abstracts of all references identified from our bibliographic database search (Appendix A), references from relevant systematic reviews published since 2013, and grey literature. Studies considered possibly eligible (Table 2.1) by at least one of two independent reviewers were flagged for full text screening. Then, two independent reviewers screened the full text articles to determine if inclusion criteria were met. Differences in screening decisions were resolved by consultation between investigators, and, if necessary, consultation with a third investigator or team consensus. For studies excluded at the full text review stage, reasons for ineligibility were documented. Reviewers regularly met to discuss inclusion criteria and ensure consistency between reviewers.

Based on AHRQ guidance, two investigators assessed risk of bias (ROB) of eligible studies in their design, analysis, and reporting.[35] For individual CATD treatment studies, ROB was rated using a tool (Appendix B) as high, medium, or low for each of the following domains: (1) Selection bias (adequacy of randomization method [RCTs], accounting for imbalance in prognostic variables [observational studies]); (2) attrition bias (loss to followup); (3) detection

bias (outcome measurement quality, outcome assessor masking); (4) performance bias (intention to treat or test analysis, adjustment for potential confounding variables, participant masking to treatment assignment); (5) reporting bias (selective outcome reporting).

For studies on the classification accuracy of brief cognitive and biomarker tests, for each test of interest, two independent investigators assessed risk of bias using the Quality Assessment tool for Diagnostic Accuracy Studies (QUADAS)-2 tool[36] for each of the following domains as high, low, or unclear: (1) Patient selection (consecutive or random sample enrolled, avoided case-control design, avoided improper exclusions); (2) index test (index test interpreted without knowledge of the reference standard, any index test threshold prespecified); (3) reference standard (reference standard likely to correctly classify target condition [i.e., AD], reference standard results interpreted without knowledge of index test results); (4) flow and timing (appropriate interval between index test and reference standard, all patients received same reference standard, all patients included in analysis).

Considering the domain risk of bias ratings, each investigator independently rated overall ROB for each individual study as high, medium, or low. Investigators then consulted to reconcile any discrepancies in ROB ratings for individual domains and overall. More details are reported in the appendices for each section.

Systematic reviews that directly addressed a question in our review and assessed ROB for included individual studies using appropriate validated tools were assessed for quality. We used A Measurement Tool to Assess Systematic Reviews (AMSTAR) 2 criteria for systematic reviews of CATD treatment studies,[37] and modified AMSTAR 2 criteria for systematic reviews of diagnostic test studies.

Data Extraction

For all eligible studies, one investigator extracted selected data and a second reviewer checked the data for accuracy.

Studies determined to be high ROB had only limited data extracted. Information extracted from both treatment and diagnostic studies included author, year of publication, population description and number enrolled, study design, and funding source. Information extracted only from treatment studies included intervention, comparator, and types of efficacy and harms outcomes. Information extracted only from studies that examined the accuracy of brief cognitive and biomarker tests included the test name/description, reference test or gold standard diagnosis, and the measures of classification accuracy assessed.

Additional data was extracted from studies determined to be low to moderate ROB. Information included participant eligibility criteria, setting, and participant baseline characteristics (age, race/ethnicity, sex, depression, stroke), pretreatment/pretesting cognitive and functional level/CATD stage, and living setting.

For studies on the accuracy of brief cognitive and biomarker tests, additional information extracted included prevalence of the reference condition in the tested population, index test (e.g., specific cognitive test, brain imaging, CSF or blood test), metric, and cut-off values used to categorize participants, specific diagnosis reference standard (e.g., National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders [NINCDS-ADRDA] for clinical CATD or Alzheimer's Disease Neuropathological Criteria [ADNC] for neuropathological AD), full clinical evaluation with pathologic confirmation, methods of participant sampling and recruitment, time interval between measurements of index

test and reference diagnosis, and sensitivity and specificity at each combination of index test and reference diagnosis threshold.

For treatment studies, additional information extracted included intervention details (drug class, name, dose, and delivery route), control intervention details, followup duration, and results of treatment efficacy and harms, including how efficacy and harms outcomes were defined.

In addition, pretreatment severity of behavioral and psychological symptoms of dementia (BPSD) was extracted for BPSD treatment studies, and education was extracted from studies on brief cognitive test or biomarker test accuracy.

Systematic reviews determined to be high quality were used to replace *de novo* data extraction processes for specific population, treatment, or outcome comparisons deemed sufficiently relevant. Individual studies from included systematic reviews were tracked for contribution to unique population, treatment, or outcome comparisons to avoid double-counting study results.

Data Synthesis

Results were organized by Key Question (KQ). Within KQs 1-2, results were organized by test category (brief cognitive test, brain imaging, CSF, blood), then by specific test. Data on brief cognitive test classification accuracy was stratified into analyses distinguishing CATD from normal cognition and CATD from MCI. Data on biomarker classification accuracy was stratified into analyses distinguishing neuropathologically-confirmed AD from non-AD dementia and AD from specific individual types of non-AD dementia. Within KQs 3-5, results were organized first by treatment comparison, then by targeted treatment outcome (disease stage, cognition [individual stand-alone tests, brief multidomain battery, individual domain level tests typically administered as part of a larger battery in clinical practice [memory, executive function, language, attention], function, quality of life) and harms. Within outcomes, results were organized by baseline CATD severity. Baseline CATD severity for a study's participants was determined either from the descriptor used by study authors or, if no descriptor was used, by study participants' baseline Mini-Mental State Exam (MMSE) range (i.e., 20-30 considered mild, 10-19 considered moderate, and <10 considered severe). Within KQs 6-8, results were organized by treatment comparison, then by targeted treatment outcome (global BPSD, agitation/aggression, psychosis, depression, anxiety, disinhibited sexual behavior) and harms, and then by baseline BPSD.

When comparisons were adequately addressed by a previous systematic review of acceptable quality and no new studies were available, we extracted data from and reiterated the conclusions drawn from that review. When new trials were available, previous systematic review data was synthesized with data from the additional trials.

For studies of brief cognitive test or biomarker test accuracy, we reported median and range for sensitivity, specificity, true positive, true negative, false positive, and false negative for each population and combination of index and reference test thresholds. These calculations were derived from the studies analyzed and the CATD, normal cognition, MCI, AD and non-AD prevalences they reported and not for standardized prevalences across all studies. For treatment studies, we prioritized analyses of outcomes framed as responders, or as improved versus stable versus declined, or those using previously established thresholds for clinically meaningful improvement. For binary outcomes, we calculated risk ratios (RR) and absolute risk differences (ARD) with corresponding 95 percent confidence intervals (CI). When strength of evidence for a result was considered low, moderate or high, but not insufficient, we also calculated number needed to treat for benefit (NNTB) and number needed to treat for harm (NNTH) with

corresponding 95 percent CI. For continuous outcomes we calculated weighted mean differences and/or standardized mean differences (SMD) with corresponding 95 percent CI.

We assessed clinical and methodological heterogeneity of individual studies to determine appropriateness of pooling data.[38] For studies on test accuracy, we evaluated clinical heterogeneity by whether the populations, index and reference test thresholds, and measures of test performance were comparable. For treatment studies, we evaluated clinical heterogeneity by whether the populations, interventions, controls, and outcomes were comparable.

When we judged that data were appropriate for pooling (i.e., minimal clinical heterogeneity of patient populations, interventions, and outcomes), we synthesized data with Comprehensive Meta-Analysis version 3 (Biostat). We used random-effects models to calculate RRs, ARDs, and corresponding 95-percent CIs for binary outcomes and SMDs and corresponding 95-percent CIs for continuous outcomes.

We measured the magnitude of statistical heterogeneity with the I^2 statistic. [39] When results suggested substantial heterogeneity (i.e., $I^2 \geq 70\%$), we stratified the results by patient or study characteristics and/or explored sensitivity analyses.

When data allowed, we stratified analyses to evaluate possible effect modifiers of brief cognitive test and biomarker test accuracy and comparative accuracy, and CATD treatment efficacy and comparative effectiveness. For all KQs, we examined age, sex, race/ethnicity, depression, and pretreatment cognitive or functional status/CATD stage. For KQs 1-2 only, we examined education. For KQs 3-8, we also examined living setting. For KQs 6-8, we also examined pretreatment BPSD severity. We recorded whether possible effect modifiers were identified *a priori*. We examined whether treatment efficacy differed as a function of drug dose, treatment duration, and followup duration. We also examined whether biomarker test accuracy differed as a function of the time between test measurement and the determination of the reference diagnosis.

Strength of Evidence for Major Comparisons and Outcomes

We graded strength of evidence for an intervention comparison and outcome when there were at least two eligible studies or one eligible study of ≥100 participants. For KQs on benefits and harms of CATD treatment, we graded strength of evidence for the direction of the treatment effect (i.e., whether benefits or harms are greater or are not different between one treatment and another).[40] In general, we evaluated strength of evidence for the one or two most commonly reported validated treatment efficacy outcomes for each of the following test categories: stage, brief stand-alone tests, brief multidomain batteries, brief domain level tests typically administered as part of a larger battery in clinical practice (memory, executive functioning, language, attention), function, quality of life, BPSD agitation/aggression, serious adverse events, and withdrawals due to adverse events.

Two investigators independently assessed five required domains (listed below) and other possible factors to grade strength of evidence within each treatment comparison. Differences in individual domain ratings and overall strength of evidence grades were resolved by consultation between investigators, and, if necessary, consultation with a third investigator. The five required strength of evidence domains were: (1) study limitations; (2) directness; (3) consistency; (4) precision; and (5) reporting bias. When considered appropriate for a body of evidence, we also considered dose-response association across or within studies, unmeasured confounders that would decrease an effect, and strength of association.[41]

Study limitations were rated as low, medium, or high based on the design and ROB of the aggregated individual studies within an evidence base. Directness was rated as either direct or indirect based on whether the evidence directly linked the intervention to the primary outcome of interest for the review. Because patients with suspected or confirmed CATD may not be able to reliably self-report outcomes, results reported by caregivers were not downgraded for indirectness. Consistency within an evidence base was rated as consistent or inconsistent based on whether treatment effects from multiple studies were similar. For treatment effects, we assessed consistency in direction (effect estimates on the same side of no effect or of a minimally important difference, if one was available). An evidence base was rated inconsistent if differences in results could not have been accounted for by heterogeneity in study characteristics. When evidence was based on a single study, regardless of its size or the number of participating study centers, consistency was rated as unknown. Precision was the degree of certainty around an outcome effect estimate based on the sufficiency of the total sample size and/or number of events. Precision was rated as precise or imprecise based on the degree of certainty surrounding each effect estimate. An imprecise estimate was one for which the confidence interval was wide enough to include clinically distinct conclusions regarding the direction of the effect (for treatment benefits or harms) or magnitude of the effect (for measures of diagnostic test performance) based on established minimal detectable differences when available.

For treatment comparisons, the starting grade for an evidence base derived from RCTs was high, while the starting grade for an evidence based derived from observational studies was low.

Based on these elements, we assessed the overall strength of evidence for each comparison and outcome as follows—

High: Very confident that the estimate of effect lies close to the true effect. Few or no deficiencies in the body of evidence, and findings are believed to be stable.

Moderate: Moderately confident that the estimate of effect lies close to the true effect. Some deficiencies in the body of evidence, and findings are likely to be stable, but there is some doubt.

Low: Limited confidence that the estimate of effect lies close to the true effect; major or numerous deficiencies in the body of evidence. Additional evidence is necessary before concluding that findings are stable or that the estimate of effect is close to the true effect.

Insufficient: No evidence, unable to estimate an effect, or no confidence in the estimate of effect. No evidence is available or the body of evidence precludes judgment.

An overall rating of high strength of evidence was assigned when included studies were RCTs with low risk of bias, and the results were consistent, direct, and precise. If strength of evidence for a treatment-outcome or testing-outcome comparison was rated insufficient based on assessment of only low to moderate ROB studies, we considered evaluating eligible high ROB studies that addressed the same treatment-outcome or testing-outcome comparison. More details are reported in the appendices for each section.

Our original plan was to grade strength of evidence for the sensitivity and specificity of selected diagnostic test-outcome comparisons following AHRQ criteria. However, we could not estimate thresholds of sensitivity and specificity that would lead to different clinical decisions. Thus, we were uncertain how to reliably rate the precision domain and consequently of how to grade overall strength of evidence for each diagnostic comparison. Instead, when sensitivity or specificity, respectively, was $\geq$0.8, we referred to them as high, when they were $\geq$0.5 to <0.8 we referred to them as moderate, and when they were <0.5 we referred to them as low. In summary results tables, when strength of evidence for treatment interventions was high, moderate or low, we accompanied the numerical results with a qualitative summary phrase such as “increased risk” or

"no difference." However, when we judged strength of an evidence base insufficient, we reported only the numerical results with no phrasing to suggest a direction of effect.

Applicability

Applicability of studies was determined according to the PICOTS framework. Factors that affected applicability included when studies had narrow eligibility criteria or when study population characteristics (e.g., age, race/ethnicity, sex, presence or lack of comorbidities, living setting, country of residence) differed from those in population studies of individuals with undiagnosed cognitive impairment or with clinically diagnosed CATD or AD. This limitation in applicability may have been magnified if these population characteristics were associated with test accuracy or treatment response. In addition, applicability of study findings may have been limited if the studied brief cognitive tests, biomarker tests or treatments were not easily available in typical clinical settings.[42]

Peer Review and Public Commentary

AHRQ staff and an AHRQ associate editor reviewed the draft report. After we revised the report based on this review, the revised draft review was posted on the AHRQ website for four weeks to solicit public comment. At the same time, experts in primary care, geriatrics, geropsychiatry, psychology, neurology, pharmacological treatment of CATD, neuropsychology, use of brain imaging, CSF and blood biomarkers in diagnosis of AD, epidemiology, systematic reviews, clinical guidelines, and complex medical patients/multimorbidity were invited to provide external peer review. After we addressed all public and peer reviewer comments, revised the text as appropriate, and documented all comments, responses and revisions in a Disposition of Comments report, we submitted the final report and the Disposition of Comments report for posting on the Effective Health Care website. The Disposition of Comments will be posted about 3 months after the final report is posted.

Chapter 3. Search Results

We conducted separate searches for brief cognitive tests for identifying clinical Alzheimer's-type dementia (CATD) (Key Question [KQ]1), biomarker testing for identifying neuropathologically-confirmed Alzheimer's disease (AD) (KQ2), and CATD drug treatment (KQ 3-8).

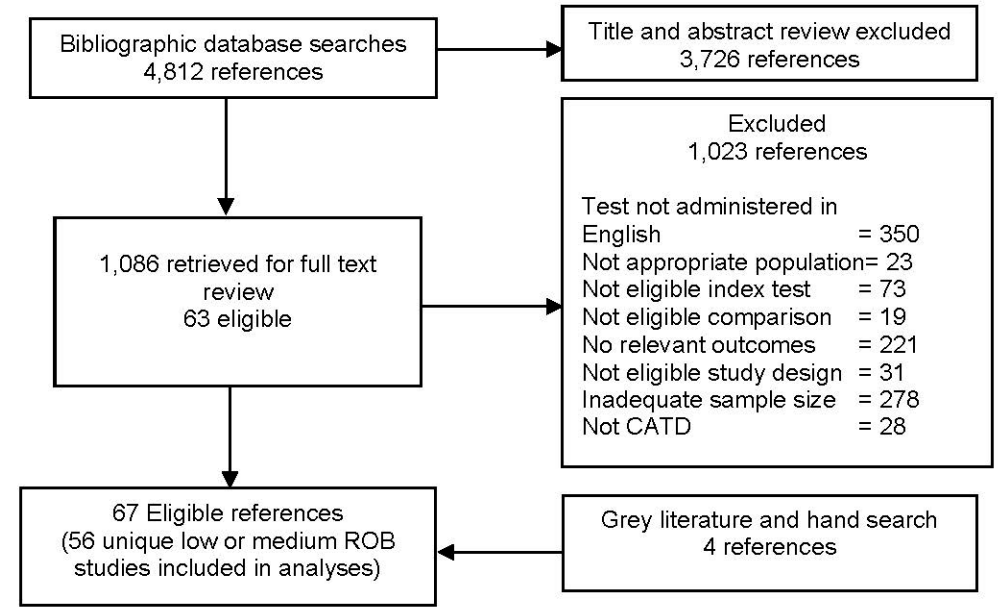
In bibliographic database searches from database inception to March 2019, we identified 4812 unique references addressing cognitive testing for CATD diagnosis (Figure 3.1). Based on title and abstract review, we excluded 3726 as not relevant to KQ1. Of the remaining references, 65 were considered eligible after full text review. An additional four references were identified from ClinicalTrials.gov and hand search. Of these 67 eligible references, 4 were duplicates and 7 were rated high risk of bias and excluded from analyses, leaving 56 unique studies with low or medium risk of bias included in analyses.

In bibliographic database searches from 2012 to March 2019 for brain imaging and cerebrospinal fluid CSF biomarkers and from inception to March 2019 for blood tests, we identified 649 unique references addressing biomarker testing for Alzheimer's disease (AD) diagnosis (Figure 3.2). Based on title and abstract review, we excluded 385 references as not relevant to the KQ2. Of remaining references, 21 were considered eligible after full text review. To identify references published prior to 2012, we hand searched six systematic reviews[17, 18, 43-46] a report from the Consensus of the Task Force on Biological Markers in Psychiatry of the World Federation of Societies of Biological Psychiatry,[47] and ClinicalTrials.gov. From these sources, we identified an additional 19 eligible references. Of the 40 total eligible references, 11 were duplicates and five were rated high risk of bias and excluded from analyses, leaving 24 unique studies with low or medium risk of bias that were included in analyses.

In bibliographic database searches from database inception to March 2019, we identified 6217 unique references that addressed CATD drug treatment (Figure 3.3). Based on title and abstract review, we excluded 5381 as not relevant to KQ3-8. Of remaining references, 244 were considered eligible after full text review. An additional seven references were identified from ClinicalTrials.gov and hand search, resulting in a total of 251 references eligible for the review. Of these eligible references, 67 unique studies had low or medium risk of bias and were included in analyses.

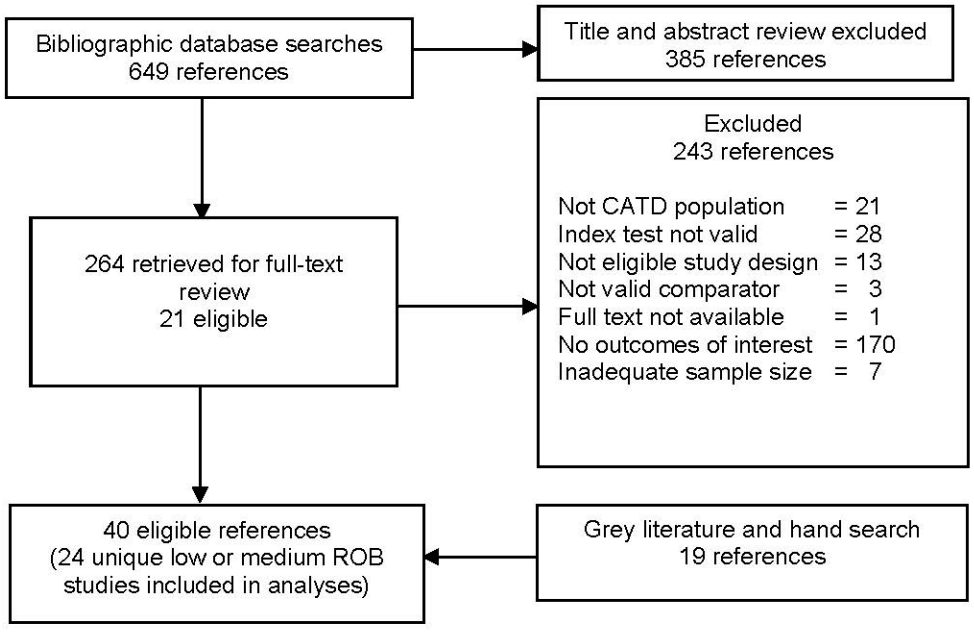
Appendix L provides a list of articles excluded after full text review. Appendix M provides a list of articles included after full text review.

Figure 3.1. Literature flow diagram for brief cognitive test identification of CATD



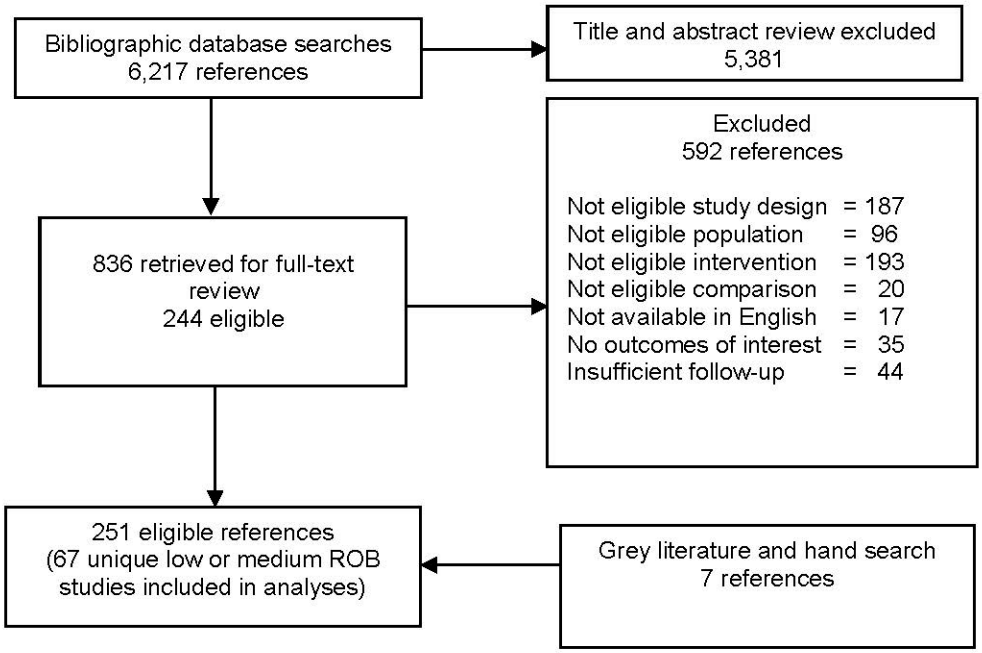
CATD=clinical Alzheimer's-type dementia; ROB=risk of bias

Figure 3.2. Literature flow diagram for biomarker identification of AD



AD=Alzheimer's disease; CATD=clinical Alzheimer's-type dementia; ROB=risk of bias

Figure 3.3. Literature flow diagram for CATD drug treatment



CATD=clinical Alzheimer's-type dementia; ROB=risk of bias

Chapter 4. Key Question 1: Brief Cognitive Tests for Identifying CATD

Key Messages

- Many brief cognitive tests had high (≥0.8) sensitivity and specificity for distinguishing between clinical Alzheimer's-type dementia (CATD) and normal cognition in older adults. Of these, clock drawing, Mini-Mental State Exam (MMSE), list learning, and semantic [category] fluency were most frequently studied.
    - Cognitive tests were reported as more accurate distinguishing CATD or moderate CATD from normal cognition than they were for distinguishing CATD from mild cognitive impairment (MCI) or distinguishing mild CATD from normal cognition.
- Most studies did not evaluate the accuracy of cut points suggested by prior work; this prevented validation of cut points, direct comparisons between studies, and pooling of data across studies.
- Most studies that examined the accuracy of combinations of cognitive tests had high specificity for identifying CATD.
- Few studies directly tested the effects of participant characteristics on the accuracy of brief cognitive tests for CATD, including whether accuracy varies by age, sex, race/ethnicity, education, or history of depression.
- We found no data from eligible studies in older adults on the accuracy of several commonly used stand-alone tests and brief multidomain batteries for distinguishing CATD from MCI or normal cognition (e.g., Mini-Cog, Saint Louis University Mental Status [SLUMS], Telephone Interview for Cognitive Status [TICS]).

Eligible Studies

We identified 69 eligible publications reporting 65 unique studies that evaluated the accuracy of cognitive tests for identifying CATD. Nine studies were assessed as high risk of bias (ROB) and not used in our analyses. These excluded studies all had multiple concerns contributing to an overall rating of high ROB, commonly including patient selection, test not administered in English, index test definition or interpretation, interval between cognitive testing and CATD diagnosis, and participant attrition. The 56 remaining studies with low or medium ROB were analyzed.

Few studies evaluated the sensitivity or specificity of previously recommended brief cognitive test cut points, though these are not established for many tests. Instead, most calculated "optimal" cut points using data from their own samples to maximally separate diagnostic groups. Some reported cut points such as 1.5 or 2.0 standard deviations below their own cognitively normal comparison samples, to simulate the clinical practice of referencing an individual's test performance to normative data. When available, we reported the classification accuracy of brief cognitive tests separately for clinically recommended and optimal cut points.

Characteristics of the participants with CATD, MCI, and normal cognition enrolled in the 56 analyzed studies are shown in Tables 4.1a-c. Most participants were diagnosed with mild to moderate CATD. Mean age was 74 years and approximately 41 percent of participants were male. Among the few studies that reported race or ethnicity data, most participants were white. Appendix C provides evidence tables, plots, and summary ROB assessments. For brief cognitive

tests included in this review, scoring metrics, scoring range, direction indicating better performance and administration times are detailed in Appendix Table C.9.

Table 4.1a. Characteristics of participants with CATD in studies evaluating classification accuracy of brief cognitive tests for CATD versus MCI or normal cognition*

Characteristic	N, Mean, % (Study Range)	Studies Reporting, N
Participants, N	5,062 (26-674)	56
Age, years	74 (63-84)	54
Men, %	43 (12-67)	48
Race – white, %	88 (43-100)	18
Education, years	13.0 (6.0-15.8)	46
Global CDR	0.90 (0.5-1.3)	13
MMSE	21.2 (12.8-26.2)	37
DRS	110 (103-120)	8

CATD = Clinical Alzheimer's Type Dementia; CDR = Clinical Dementia Rating; DRS = Dementia Rating Scale; MCI = Mild Cognitive Impairment; MMSE = Mini-Mental State Exam

*Total subject characteristic data are replicated across clinical diagnostic groups for any studies that did not report individual group data; subject characteristics reported as median values or qualitative data are not included. Calculations assume each participant was unique across studies excluding those publications citing common study samples.[48-50] There was likely unknown additional overlap from frequently used epidemiological cohorts.

Table 4.1b. Characteristics of participants with MCI in studies evaluating classification accuracy of brief cognitive tests for CATD versus MCI*

Characteristic	N, Mean, % (Study Range)	Studies Reporting, N
Participants, N	1,229 (29-299)	13
Age, years	73 (66-77)	12
Men, %	48 (34-61)	12
Race – white, %	83 (65-100)	8
Education, years	14.5 (10.9-16.2)	11
Global CDR	0.5 (0.3-0.5)	6
MMSE	27.4 (26.0-28.1)	10
DRS	131	1

CATD = Clinical Alzheimer's Type Dementia; CDR = Clinical Dementia Rating; DRS = Dementia Rating Scale; MCI = Mild Cognitive Impairment; MMSE = Mini-Mental State Exam

*Total subject characteristic data are replicated across clinical diagnostic groups for any studies that did not report individual group data; subject characteristics reported as median values or qualitative data are not included. Calculations assume each participant was unique across studies excluding those publications citing common study samples.[48-50] There was likely unknown additional overlap from frequently used epidemiological cohorts.

Table 4.1c. Characteristics of participants with normal cognition in studies evaluating classification accuracy of brief cognitive tests for CATD versus normal cognition*

Characteristic	N, Mean, % (Study Range)	Studies Reporting, N
Participants, N	7,631 (26-860)	49
Age, years	74 (62-80)	45
Men, %	38 (18-67)	40
Race – white, %	83 (50-100)	14
Education, years	14.0 (11.3-17.0)	38
Global CDR	0.1 (0.0-0.3)	12
MMSE	28.4 (26.1-30.0)	28
DRS	137 (135-140)	7

CATD = Clinical Alzheimer's Type Dementia; CDR = Clinical Dementia Rating; DRS = Dementia Rating Scale; MMSE = Mini-Mental State Exam

*Total subject characteristic data are replicated across clinical diagnostic groups for any studies that did not report individual group data; subject characteristics reported as median values or qualitative data are not included. Calculations assume each participant was unique across studies excluding those publications citing common study samples.[48-50] There was likely unknown additional overlap from frequently used epidemiological cohorts.

Harms of Cognitive Testing

No studies reported data on harms of brief cognitive testing for identifying CATD. Further, among 30 identified systematic reviews of cognitive testing for dementia published since 2013, none reported data on harms of this cognitive testing.

Brief Cognitive Tests Commonly Used as Individual Stand-Alone Tests

Baseline Study Characteristics

Twenty-six unique studies (n=6,953) evaluated brief cognitive tests commonly used as individual stand-alone tests for the identification of CATD (Table 4.2). Ten of these evaluated clock drawing tests, seven evaluated the MMSE, three evaluated the Montreal Cognitive Assessment (MoCA), two evaluated the Memory Impairment Screen (MIS), one evaluated the 7 Minute Screen (7MS), one evaluated the Minnesota Cognitive Acuity Screen (MCAS), and one evaluated the Test Your Memory (TYM) test.

Study participants included 2,652 with CATD, 740 with MCI, and 3,561 healthy control older adults. Many studies reported using Diagnostic and Statistical Manual of Mental Disorders (DSM)-III-R or DSM-IV criteria for defining dementia. Most reported using National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders (NINCDS-ADRDA) criteria for diagnosis of CATD, except for one that used only DSM-IV[51] and one that used DSM-IV and International Classification of Disease (ICD)-10.[52] None used National Institute on Aging-Alzheimer's Association (NIA-AA) criteria. Participants with MCI were diagnosed using Petersen criteria,[53] and/or by specifying a Clinical Dementia Rating (CDR) score of 0.5. Normal older adult control participants were most commonly defined as cognitively normal based on a diagnostic workup, though two studies defined it by patient self-report,[54, 55] and two did not provide clear definitions.[56, 57]

Participant mean age was 74 years, 40 percent were male, and mean years of education was 14. From eight studies reporting race or ethnicity, 87 percent of participants were white.[51, 54, 57-63]

Table 4.2. Summary of reported results for primary outcomes:* brief cognitive tests commonly used as individual stand-alone tests†

Diagnostic Question	Test Metric	Studies, N (Patients Analyzed)	CATD Prevalence, Median (Range)	Cut Points	SN, Median (Range)	SP, Median (Range)	TP per 1,000 Patients, Median (Range)	TN per 1,000 Patients, Median (Range)	FP per 1,000 Patients, Median (Range)	FN per 1,000 Patients, Median (Range)
CATD vs. Normal Cognition	Clock drawing totals	8 (n=1022)	0.50 (0.15-0.64)	‡	0.79 (0.36-0.93)	0.88 (0.42-1.00)	355 (122-581)	480 (205-612)	60 (0-314)	105 (18-320)
	Clock element scores	2 (n=200)	0.51 (0.48-0.51)	‡	0.83 (0.12-0.97)	0.90 (0.21-1.00)	413 (62-477)	461 (102-488)	54 (0-385)	85 (15-451)
	MMSE total	7 (n=1724)	0.50 (0.15-0.71)	21, 23-27**	0.88 (0.56-1.00)	0.94 (0.59-1.00)	414 (113-669)	474 (251-745)	27 (0-255)	43 (0-182)
	MIS total	2 (n=712)	0.10 (0.08-0.12)	4	0.87 (0.86-0.87)	0.97 (0.96-0.97)	86 (72-100)	869 (857-881)	32 (27-37)	14 (11-16)
	MoCA total	2 (n=864)	0.71 (0.60-0.71)	22, 23 10 (short)	0.94 (0.93-0.96)	0.94 (0.91-1.00)	669 (557-683)	289 (263-378)	23 (0-26)	41 (28-43)
	BAS total	1 (n=1534)	0.46 (0.43-0.46)	22, 23, 26	0.92 (0.90-0.98)	0.97 (0.96-0.99)	421 (411-425)	537 (526-544)	16 (5-23)	37 (9-46)
	TYM total	1 (n=376)	0.25	42	0.93	0.86	233	645	105	18
CATD vs. MCI	CLOX 1 (draw) total	2 (n=150)	0.58 (0.50-0.65)	11	0.67 (0.58-0.76)	0.86 (0.72-1.00)	393 (288-498)	374 (249-500)	48 (0-97)	185 (157-212)
	MoCA total	3 (n=1189)	0.72 (0.25-0.76)	19, 24 6 (short)	0.79 (0.67-0.97)	0.79 (0.78-0.88)	541 (205-655)	223 (189-659)	60 (51-90)	114 (22-250)
	MMSE total	2 (n=604)	0.69 (0.61-0.76)	18, 25	0.84 (0.79-0.88)	0.81 (0.79-0.83)	570 (542-598)	257 (192-322)	58 (51-65)	115 (71-159)

BAS=Brief Alzheimer Screen; CATD=Clinical Alzheimer's-type dementia; FN=false negative; FP=false positive; MCI=mild cognitive impairment; MIS=Memory Impairment Screen; MMSE=Mini Mental State Exam; MoCA=Montreal Cognitive Assessment; ROB=risk of bias; SN=sensitivity; SP=specificity; TYM=Test Your Memory; TN=true negative; TP=true positive

*Data shown for tests evaluated in ≥2 or more low or moderate ROB studies or in 1 such study with 300 or more participants. Calculations assume each participant was unique across studies, excluding from reports citing common study samples.[48, 49] There was likely additional overlap from frequently used epidemiological cohorts.

†No studies reported data on harms of brief cognitive tests for identifying CATD.

‡Cut points varied by scoring methods. Two studies evaluating the MMSE did not report cut points.[64, 65]

Clock Drawing Tests

Eleven publications of 10 unique studies (n=1,177 participants) evaluated clock drawing tasks for identifying CATD.[48, 49, 55, 56, 66-72] Several methods are available for administration and scoring of clock drawing tests, most requiring five minutes or less. While all eligible studies evaluated tasks that required the subject to draw the numbers and hands of a clock, two provided a pre-drawn circle[71, 72] and others provided only a blank sheet. Some scoring methods used a holistic scale requiring raters to score the clock on multiple features considered together.[56, 72] Many scoring rubrics assigned points for specific elements of overall clock appearance as well as accuracy of both number and hand placement,[48, 67-71] and others used both types of scoring.[49, 55, 66]Some scoring rubrics were newly generated, while others were based on or adapted from existing literature.[69, 72-77]

Classification Accuracy

CATD Versus Normal Cognition

Nine studies evaluated clock drawing tests for distinguishing patients with CATD as defined by NINCDS-ADRDA criteria (n=419) from demographically similar or matched older adults with normal cognition (n=603).[48, 49, 55, 56, 66, 68, 69, 71, 72] To define cognitively normal controls, four studies reported completion of a diagnostic workup [48, 49, 66, 72] and the remainder reported brief cognitive testing or a medical history interview.

The most commonly evaluated clock drawing scoring scale (n=136 CATD, n=327 normal controls)[48, 49, 66, 68] was the 10-point Rouleau scale,[74] which assigns 2 points for clock face, 4 points for numbers, and 4 points for hands. The best-performing Rouleau cut point for sensitivity (by Bayesian algorithm) was <10 (sensitivity 0.93, specificity 0.42). The best-performing Rouleau cut point for specificity (by regression analysis or receiver operating characteristic [ROC] analyses with or without Youden Index) was <8 (sensitivity 0.74 to 0.88, specificity 0.63 to 0.88). Two studies (n=58 CATD, n=58 normal controls)[55, 56] evaluated the Sunderland scale, a 10-point holistic scale with a qualitative description provided for each point on the scale. Sensitivity and specificity ranged from 0.57 and 1.00, respectively, for a cut point of 5 to 0.79 and 0.93, respectively, for a cut point of 8. Several studies reported indices derived from Mendez scoring,[55, 68, 69] with the best performing total score of 18 (sensitivity 0.91 and specificity 1.00). Single studies each evaluated the Shulman,[56, 78#435#435] Tuokko,[71] and Watson[66, 73] scoring methods, with sensitivities ranging from 0.52 to 0.97 and specificities ranging from 0.80 to 0.96. Finally, three studies evaluated the Wolf-Klein[72] scoring method,[56, 66, 72] with cut points ranging from 5 to 8 and a cut point of 5 producing the highest overall classification, with sensitivity and specificity of 0.87 and 0.93, respectively.

CATD Versus MCI

Two studies evaluated clock drawing tests for distinguishing CATD (n=93) from MCI (n=62).[67, 70] Both used the CLOX, an executive clock drawing task,[75] and scores evaluated included CLOX 1 (free drawn), CLOX 2 (copy), and a modified Rouleau error scoring method.[74] Both derived post hoc optimal cut scores that best distinguished the CATD and MCI groups from each other using ROC analyses. The optimal cut scores and corresponding sensitivity and specificity were: CLOX 1: 11.5 (0.76 and 0.72), [67] CLOX 2: 13.5 (0.67 and 0.62)[67] and Rouleau error scoring: 11 (0.58 and 1.00).[70]

Variation in Classification Accuracy by Participant Characteristics

Three studies stratified CATD subjects by disease severity (i.e., very mild, mild, moderate) and separately evaluated clock drawing tests in distinguishing these three CATD subgroups from cognitively normal adults.[55, 56, 66] In one of these studies, sensitivity distinguishing from normal controls was 0.33 to 0.44 for participants with very mild CATD, 0.77 to 0.82 for mild CATD, and 1.00 for moderate CATD.[55] In a second study, sensitivity distinguishing from normal controls mostly ranged between 0.5 to 0.6 in participants with mild CATD and 0.8 to 1.0 in those with moderate CATD.[66] In a third study, sensitivity of clock drawing was 0.13 to 0.88 in participants with MMSE $\geq$24 and 0.75 to 0.85 in participants with MMSE <24.[56] Specificity for distinguishing from cognitively normal controls did not appear to vary by baseline CATD severity in any of these studies. No studies reported testing for an interaction. Further, no studies reported whether participant characteristics affected accuracy of clock drawing tests for distinguishing CATD from MCI.

Mini-Mental State Examination (MMSE)

Seven studies (n=1,892 participants) evaluated the performance of the MMSE[79] total score for identifying CATD.[51, 54, 57, 61, 64, 80, 81] The MMSE assesses orientation, attention, memory, language, and visual-spatial skills (maximum score 30, higher score is better, approximately 10 minutes administration time).

Classification Accuracy

CATD Versus Normal Cognition

Seven studies evaluated MMSE scores for distinguishing patients with mild-to-moderate CATD (n=818) from older adults with normal cognition (n=906). Studies evaluated total score cut points from 21 to 27. Most often, cut points were determined post hoc to maximize separation of participants with CATD from those with normal cognition in the study sample (using ROC curves or logistic regression). Less often, studies examined cut points commonly used in clinical settings (e.g., 24). Sensitivity ranged from 0.56 to 1.00 and specificity ranged from 0.59 to 1.00, with most >0.75. No clear pattern suggested an optimal MMSE cut point within the studied range.

CATD Versus MCI

Two studies evaluated optimal post hoc MMSE cut points for distinguishing patients with mild-to-moderate CATD (n=435) from demographically similar older adults with MCI (n=169).[51, 61] For one, the cut point of 25.5 had a sensitivity of 0.88 and specificity of 0.83,[61] whereas for the other, the cut point of 18 had a sensitivity of 0.79 and specificity of 0.79.[51]

Variation in Classification Accuracy by Participant Characteristics

Three studies reported evaluating whether the accuracy of MMSE performance for distinguishing CATD from normal cognition varied by participant characteristics. In one study, optimal cut points for distinguishing CATD from normal cognition did not differ significantly as a function of age, gender, or education.[54] A second study examined MMSE accuracy distinguishing CATD from normal cognition within separate strata of educational attainment.[57] For an MMSE cut point of 24, sensitivity and specificity, respectively, were 1.0 and 0.59 for participants with a middle school education, 0.88 and 0.79 in those with a high school education,

and 0.83 and 1.0 in those with a college education. A third study stratified CATD subjects by severity (i.e. mild vs. moderate) and reported that MMSE sensitivity for distinguishing CATD from normal cognition was 0.79 for mild CATD (MMSE cut point not reported) and 1.0 for moderate CATD (MMSE cut point 23).[80] None of these studies tested whether differences in MMSE classification rates by CATD severity were statistically significant.

No studies reported examining whether MMSE performance in distinguishing between CATD and MCI varied by participant characteristics.

Montreal Cognitive Assessment (MoCA)

Three studies (n=1,482 participants) evaluated MoCA[82] scores for identifying CATD.[51, 60, 83] The MoCA is designed for the assessment of somewhat higher functioning patients than many other individual stand-alone tests (higher ceiling). It assesses attention and concentration, executive function, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation (maximum score 30, higher score is better, approximately 10 minutes administration time).

Classification Accuracy

CATD Versus Normal Cognition

Two studies[51, 60] evaluated the MoCA for distinguishing patients with CATD (n=571) from those with normal cognition (n=293), with normal cognition confirmed by diagnostic evaluation. Both studies evaluated the traditional total score. One study reported results of MoCA classification using a combination of directly measured MoCA scores and MoCA scores estimated from MMSE.[60] However, results reported here are based only on directly measured MoCA scores obtained by direct communication from the study authors. Post hoc optimal cut points of 22 and 23 produced sensitivity of 0.93 to 0.94 and specificity of 0.94 to 1.0. One study also evaluated a shortened version of the MoCA (maximum score 16) and reported that an optimal cut point of 10 had a sensitivity of 0.96 and specificity of 0.91.[51]

CATD Versus MCI

Three studies[51, 60, 83] evaluated the MoCA for distinguishing CATD (n=671) from MCI defined in a manner consistent with the Petersen criteria[53] (n=518). For post hoc optimal cut points of 19 to 24, sensitivities were 0.76 to 0.97 and specificities were 0.78 to 0.88. The one of these studies that evaluated a 16-point version of the MoCA reported a sensitivity of 0.67 and specificity of 0.79 for an optimal cut point of 6.[51]

Variation in Classification Accuracy by Participant Characteristics

No studies reported on whether MoCA test performance for distinguishing CATD from normal cognition or MCI varied by participant characteristics.

Memory Impairment Screen (MIS)

Two studies (n=712 participants) evaluated the performance of the MIS total score for identifying CATD.[58, 59] The MIS consists of four items that evaluate memory with both free and cued recall (maximum score 8, higher score is better, less than five minutes administration time).

Classification Accuracy

CATD Versus Normal Cognition

Two studies evaluated MIS test performance for distinguishing patients with mild-to-moderate CATD (n=67) from older adults defined with normal cognition based on a diagnostic work-up (n=645). Studies evaluated both post hoc cut scores to maximize CATD prediction in the study sample (ROC analysis) and a priori cut points with suspected clinical relevance (e.g. Alzheimer's Association recommendations). MIS total score cut points evaluated ranged from 0 to 8, with the best performing scores ranging from 2 to 4 depending on the severity of the CATD sample. At these cut points, sensitivity ranged from 0.75 to 1.0 and specificity ranged from 0.85 to 1.0.

CATD Versus MCI

No studies reported data on MIS test performance for distinguishing between CATD and MCI.

Variation in Classification Accuracy by Participant Characteristics

Both studies reported on whether MIS test performance for distinguishing CATD from normal cognition varied by different participant characteristics. In each case, age, gender, education, and depression were tested but found to be non-significant.[58, 59] No study reported statistical tests to evaluate variation in cognitive test accuracy by participant race/ethnicity, but one study reported that the frequency of false positive CATD classification with MIS did not differ between African American and white participants.[58] Both studies also stratified CATD subjects by dementia severity, then separately evaluated the MIS for distinguishing each of these CATD subgroups from cognitively normal adults. In the first study, for an MIS cut point of 4, sensitivity and specificity, respectively, were 0.79 and 0.96 in participants with mild CATD and 0.95 and 0.96 in those with moderate CATD.[58] In the second study, for an MIS cut point of 4, sensitivity was 0.75 in participants with very mild dementia (CDR 0.5), 0.81 in those with mild dementia (CDR 1.0), and 1.0 in those with moderate dementia (CDR 2.0), whereas specificity appeared similar regardless of dementia severity.[59] Neither study tested whether differences in MIS classification rates by CATD severity were statistically significant.

Brief Alzheimer's Screen (BAS)

One study (n=1,534 participants) evaluated the BAS weighted total score for identifying CATD.[62] The BAS was developed from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological evaluation data set and consists of items taken from the MMSE (date, 3-word recall, spelling 'WORLD' backwards) along with a 30-second semantic (animals) fluency evaluation (no maximum score, higher score is better, less than 5 minutes administration time).

Classification Accuracy

CATD Versus Normal Cognition

The BAS was evaluated for distinguishing patients with mild CATD (n=674) from healthy older adults evaluated with diagnostic workup (n=860). Weighted sum score cut points ranging from 22 to 26 resulted in sensitivities from 0.90 to 0.98 and specificities from 0.96 to 0.99.

CATD Versus MCI

No studies reported data on the BAS for distinguishing between CATD and MCI.

Variation in Classification Accuracy by Participant Characteristics

No studies reported on whether BAS test performance for distinguishing CATD from normal cognition varied by participant characteristics.

Test Your Memory (TYM)

One study (n=376 participants) evaluated the TYM total score for identifying CATD.[84] TYM is a self-administered and performance-based test consisting of 10 common cognitive testing tasks. The ability to independently complete the test is also a performance item and added to the total score (maximum of 50, higher score is better, no provider administration time, approximately 2 minutes to score).

Classification Accuracy

CATD Versus Normal Cognition

The TYM total score was evaluated for distinguishing patients with mild-moderate CATD (n=94) from healthy older adults (n=282). For the post hoc optimal cut point of 42, sensitivity was 0.93 and specificity was 0.86.

CATD Versus MCI

No studies reported data on the TYM for distinguishing between CATD and MCI.

Variation in Classification Accuracy by Participant Characteristics

No studies reported on whether TYM diagnostic test performance for distinguishing CATD from normal cognition varied by participant characteristics.

Minnesota Cognitive Acuity Screen (MCAS)

One study (n=150 participants) evaluated the MCAS[85] total score[63] for identifying CATD. The MCAS is telephone-administered and assesses orientation, attention, delayed recall, comprehension, repetition, naming, computation, judgment, and verbal fluency (no maximum score, higher score is better, approximately 15 minutes administration time).

Classification Accuracy

CATD Versus Normal Cognition

No studies reported data on the MCAS test for distinguishing CATD from normal cognition.

CATD Versus MCI

This study evaluated the MCAS test for distinguishing patients with possible or probable mild CATD (n=50) from amnestic MCI defined by a diagnostic workup aligned with Petersen criteria[53] (n=100). At the post hoc optimal cut point of 42.5, sensitivity was 0.86 and specificity was 0.77.

Variation in Classification Accuracy by Participant Characteristics

Analyses testing whether MCAS test performance for distinguishing CATD from MCI varied by participant age and education reported little improvement over base models and authors presented cut point data without adjustment.

7 Minute Screen (7MS)

One study (n=120 participants) evaluated the 7MS[86] total score[87] for identifying CATD. The 7MS assesses orientation, memory (cued recall), clock drawing, and verbal fluency (no maximum score, higher score is better, less than 10 minutes administration time).

Classification Accuracy

CATD Versus Normal Cognition

This study evaluated the 7MS for distinguishing patients with mild to moderate CATD (n=60) from healthy older adults evaluated by medical history and self-reported as functionally independent (n=60). 7MS cut points for the total score were identified by maximizing CATD prediction in the study sample using logistic regression including weighted terms for each subtest score. Using model estimated probability of CATD of <0.1 as a cut point for controls and >0.9 as a cut point for CATD, sensitivity ranged from 0.92 to 1.0 and specificity ranged from 0.96 to 1.0 in initial and repeated random subsamples for validation.

CATD Versus MCI

No studies reported data on the 7MS for distinguishing CATD from MCI.

Variation in Classification Accuracy by Participant Characteristics

In a subset of AD patients with MMSE scores of ≥21 (n=95), using model probabilities of <0.1 and >0.9 as cut points, both sensitivity and specificity values were 0.98. In a subset of CATD patients with MMSE scores of ≥24 (n=13), sensitivity was 0.98 and specificity was 1.0. The study also evaluated participant age, gender, and education in the logistic regression predicting classification of CATD versus healthy older adults, but all were non-significant.

Brief Memory and Executive Test (BMET)

One study (n=102 participants) evaluated the BMET total score for identifying CATD.[52] The BMET was developed to distinguish CATD from vascular cognitive impairment and consists of executive and memory tasks (maximum score 16, higher score is better, approximately 10 minutes administration time).

Classification Accuracy

CATD Versus Normal Cognition

The BMET was evaluated for distinguishing patients with mild to moderate CATD (n=51) from healthy older adults (n=51). At the post hoc optimal cut point of 13, sensitivity was 0.86 and specificity was 1.00.

CATD Versus MCI

No studies reported data on the BMET for distinguishing between CATD and MCI.

Variation in Classification Accuracy by Participant Characteristics

No studies reported on whether BMET diagnostic test performance for distinguishing CATD from normal cognition varied by participant characteristics.

Brief Multidomain Batteries

Baseline Study Characteristics

Ten unique studies evaluated the performance of summary metrics from established brief multidomain batteries of cognitive tests for identifying CATD (Table 4.3). Three of these studies evaluated the Dementia Rating Scale (DRS), one evaluated Addenbrooke's Cognitive Examination (ACE), one evaluated the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), one evaluated the CogState Brief Battery (CBB), one evaluated the CERAD Neuropsychological Battery, one evaluated the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), one evaluated the Wechsler Adult Intelligence Scale (WAIS), and one evaluated Wechsler Memory Scales (WMS).

Study participants included 864 patients with CATD, 276 with MCI, and 1,536 healthy control older adults. All studies reported using NINCDS-ADRDA criteria for diagnosis of CATD and none used NIA-AA criteria. Participants with MCI were diagnosed consistent with Petersen criteria.[53] Normal older adult control participants were most commonly evaluated with a diagnostic workup and/or assessment sufficient to assign a CDR score of 0. One study defined participants as cognitively unimpaired through self-report.[88]

Participant mean age was 72 years, 44 percent were male, and mean years of education was 13. Six studies reported race or ethnicity, with five describing predominantly white samples[61, 88-91] and one reporting an all Asian (predominantly Chinese) sample.[92]

Table 4.3. Summary of reported results for primary outcomes: brief multidomain battery summary scores for distinguishing CATD from normal cognition*†

Test Metric	Studies, N (Patients Analyzed)	CATD Prevalence, Median (Range)	Cut Points	SN, Median (Range)	SP, Median (Range)	TP per 1000 Patients, Median (Range)	TN per 1000 Patients, Median (Range)	FP per 1000 Patients, Median (Range)	FN per 1000 Patients, Median (Range)
DRS total‡	2 (n=507)	0.60 (0.50-0.71)	129, 132	0.97 (0.96-0.97)	0.96 (0.92-0.99)	583 (480-686)	375 (290-460)	21 (3-40)	21 (20-21)
DRS construction	1 (n=359)	0.71	5	0.73	0.70	516	205	88	191
DRS memory	1 (n=359)	0.71	21	0.93	0.98	658	287	6	50
DRS attention	1 (n=359)	0.71	35	0.71	0.84	502	246	47	205
DRS initiation/ perseveration	1 (n=359)	0.71	33	0.93	0.94	658	275	18	50
DRS conceptualization	1 (n=359)	0.71	30	0.69	0.91	488	266	26	219
DRS memory & initiation/ perseveration	1 (n=641)	0.43 (0.16-0.71)	†	0.95 (0.91-0.98)	0.96 (0.93-0.98)	418 (142-693)	536 (287-785)	32 (6-59)	14 (14-14)
CBB learning & working memory	1 (n=684)	0.06	89	1.00	0.85	61	795	144	0
CBB attention & psychomotor	1 (n=710)	0.07	89	0.53	0.86	38	795	133	34

CATD=Clinical Alzheimer's-type dementia; CBB=CogState Brief Battery; CERAD=Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Battery; DRS=Dementia Rating Scale; FN=false negative; FP=false positive; MCI=mild cognitive impairment; SN=sensitivity; SP=specificity; TN=true negative; TP=true positive Scale; MCI=mild cognitive impairment; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status

*Data shown for tests evaluated in ≥2 low or moderate ROB studies or in 1 such study with ≥300 participants (data evaluating brief multidomain cognitive batteries for distinguishing CATD from MCI were only from single studies with <300 participants). Calculations assume participants were unique across studies. There was likely additional overlap from frequently used study cohorts.

†No studies reported data on harms of brief multidomain cognitive batteries for identifying CATD.

‡One study[89] evaluated a logistic regression to combine DRS scores and did not cite raw cut points.

Dementia Rating Scale (DRS)

Three studies (n=936 participants) evaluated the DRS (also known as the Mattis DRS)[93] for identifying CATD.[89, 90, 94] The DRS is a brief battery of commonly used tasks designed to evaluate CATD in five domains: attention, initiation and perseveration, construction, conceptual ability, and memory (higher scores are better, approximately 30 minutes administration time).

Classification Accuracy

CATD Versus Normal Cognition

Two studies evaluated DRS performance for distinguishing patients with mild to moderate CATD (n=372) from demographically similar older adults with normal cognition defined by a diagnostic workup (n=417).[89, 94] Studies evaluated the DRS total score, subscale scores, and subscale combinations. All cut points were identified by maximizing CATD prediction from normal cognition in the study samples (logistic regression, ROC analysis). Optimal DRS total score cut points ranged from 129 to 132, with sensitivity ranging from 0.96 to 0.97 and specificity from 0.92 to 0.99.[89, 94] In further analyses, one study reported optimal cutpoints with corresponding sensitivity and specificity for DRS subscales as follows: Attention (sensitivity 0.71 and specificity 0.84 for a cut point of 35), Conceptualization (sensitivity 0.69 and specificity 0.91 for a cut point of 33), Construction (sensitivity 0.73 and specificity 0.70 for a cut point of 6), Memory (sensitivity 0.93 and specificity 0.98 for a cut point of 22), and Initiation/Preservation (sensitivity 0.93 and specificity 0.94 for a cut point of 33).[89] In data from two cohorts (n=641), a combined Memory and Initiation/Perseveration index (adjusted for age and education) was associated with sensitivity ranging from 0.91 to 0.98 and specificity from 0.93 to 0.98, respectively.[89]

CATD Versus MCI

One study[90] evaluated the DRS for distinguishing between patients with CATD (n=49) and MCI determined by a diagnostic workup (n=98).[90] At a post hoc optimal DRS total score cut point of 123, sensitivity was 0.78 and specificity was 0.83.

Variation in Classification Accuracy by Participant Characteristics

No studies reported on whether DRS diagnostic test performance for distinguishing CATD from normal cognition or MCI varied by participant characteristics.[90]

Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog)

One study (n=269) evaluated ADAS-Cog[95] total score[92] for distinguishing CATD from normal cognition or MCI. Designed to emphasize memory evaluation in CATD, the original ADAS-Cog includes 11 tasks assessing memory, language, and praxis, and the ADAS-Cog-12 adds a delayed recall task intended to increase sensitivity for earlier stages of AD[96] (lower scores are better, approximately 30 minutes administration time).

Participants' CATD was defined as mild (CDR scores 0.5 to 1.0) and those with normal cognition and MCI had CDR scores of 0 and 0.5, respectively. Unique compared with other studies that examined brief multidomain batteries, 83 percent of participants in this study self-reported as Chinese, and 13 percent self-reported as Malay, Indian, Eurasian, or other. Testing was administered in English for 75 percent of participants, the minimum for study eligibility in

the current review, and in Mandarin for 25 percent. Participants with CATD were approximately 6 to 10 years older than those with MCI or normal cognition.

Classification Accuracy

CATD Versus Normal Cognition

ADAS-Cog 11 and ADAS-Cog 12 total scores were evaluated for distinguishing individuals with CATD (n=64) from those with normal cognition (n=125). A post hoc optimal ADAS-Cog 11 cut point of 14 had a sensitivity of 0.81 and specificity of 1.0, and a post hoc optimal ADAS-Cog 12 cut point of 21 had a sensitivity of 0.73 and specificity of 1.0.

CATD Versus MCI

ADAS-Cog 11 and ADAS-Cog 12 total scores also were evaluated for distinguishing individuals with CATD (n=64) from those with MCI (n=80). A post hoc optimal ADAS-Cog 11 cut point of 12 had a sensitivity of 0.86 and specificity of 0.89, and a post hoc optimal ADAS-Cog 12 cut point of 21 had a sensitivity of 0.79 and a specificity of 0.89.

Variation in Classification Accuracy by Participant Characteristics

No studies reported on whether ADAS-Cog test performance for distinguishing between CATD and either normal cognition or MCI varied by participant characteristics.

Cogstate Brief Battery (CBB)

The CBB is a computer-administered battery of four tasks assessing attention, processing speed, visual learning, and working memory (scoring characteristics are task and score dependent, higher summary scores are better, approximately 12 to 15 minutes administration time).

Classification Accuracy

CATD Versus Normal Cognition

One study (n=710) evaluated two CBB composite summary scores for distinguishing mild to moderate CATD (n=51) from normal cognition (n=659).[97] Optimal cut scores were identified by maximizing CATD prediction in the study sample using ROC analysis. A post hoc optimal cut point for the Attention/Psychomotor composite summary score of <90 had a sensitivity of 0.53 and specificity of 0.86. A post hoc optimal cut point for the CBB Learning/Working Memory composite summary score of <90, evaluated in a subset of 684 participants, had a sensitivity of 1.0 and specificity of 0.85.

CATD Versus MCI

No studies reported data on the CBB for distinguishing between CATD and MCI.

Variation in Classification Accuracy by Participant Characteristics

No studies reported on whether CBB test performance for distinguishing CATD from normal cognition varied by participant characteristics.

Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Neuropsychological Battery

One study (n=250 participants) evaluated a total score derived from the CERAD Neuropsychological Battery[98] for identifying CATD.[61] The CERAD was developed with National Institute on Aging (NIA) support to standardize assessment procedures in AD. The CERAD Battery includes assessment of mental status, language ability, constructional praxis, and memory. The CERAD total score evaluated included all tasks in the original CERAD battery (verbal fluency, list-learning, constructional praxis, a brief Boston Naming Test [BNT]) except object naming, and the MMSE (maximum score 100, higher score is better, approximately 20 minutes administration time). Patients with mild CATD were compared with demographically similar patients with MCI,[53] and healthy normal controls defined by a CDR score of 0.

Classification Accuracy

CATD Versus Normal Cognition

For distinguishing individuals with CATD (n=95) from those with normal cognition (n=95), a post hoc optimal cut point of 77 for this CERAD total score had a sensitivity of 0.94 and specificity of 0.93.

CATD Versus MCI

For distinguishing individuals with CATD (n=95) from those with MCI (n=60), a post hoc optimal cut point of 68 for this CERAD total score had a sensitivity of 0.80 and specificity of 0.81.

Variation in Classification Accuracy by Participant Characteristics

No studies reported data on whether CERAD Neuropsychological Battery test performance for distinguishing CATD from either normal cognition or MCI varied by participant characteristics.

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

One study (n=238) evaluated performance of the RBANS for identifying CATD.[88, 99] The RBANS is a brief battery assessing attention, language visuospatial/construction, and memory, designed with multiple forms to be used in repeated assessment (higher scores are better, administration time approximately 30 minutes). The RBANS scores evaluated included a Verbal Index, Visual Index, and a combined Verbal plus Visual Index score (index scores have a mean of 100 and SD of 15). Patients with mild CATD, as defined by cognitive testing and clinical records, were compared with patients with MCI,[53] and older adults who self-reported normal cognition.

Classification Accuracy

CATD Versus Normal Cognition

For distinguishing individuals with CATD (n=100) from those with normal cognition (n=100), unspecified post hoc optimal RBANS cut points had sensitivities and specificities,

respectively, of 0.88 and 0.82 for the Verbal Index, of 0.86 and 0.77 for the Visual Index, and 0.92 and 0.79 for the combined Verbal plus Visual Index.

CATD Versus MCI

For distinguishing individuals with CATD (n=100) from those with MCI (n=38), unspecified post hoc optimal RBANS cut points had sensitivities and specificities, respectively, of 0.61 and 0.71 for the Verbal Index, 0.68 and 0.76 for the Visual Index, and 0.66 and 0.75 for the combined Verbal plus Visual Index.

Variation in Classification Accuracy by Participant Characteristics

No studies reported data on whether RBANS test performance for distinguishing CATD from either normal cognition or MCI varied by participant characteristics.

Wechsler Adult Intelligence Scale (WAIS)

One study (n=98 participants) evaluated a WAIS-derived summary score for identifying CATD.[100] The WAIS is a battery of tests designed to evaluate general intellectual ability that also provides domain summary indices. The WAIS battery administration time is not brief cognitive testing, but abbreviated summary metrics may be administered in 30 minutes or less.

Classification Accuracy

CATD Versus Normal Cognition

This study evaluated the "Fuld profile," a seven subtest index found to be associated with cholinergic deficiency and CATD (profile scored as yes/no, approximately 30 minutes administration time for included subtests).[101] Test performance consistent with the Fuld profile (yes or no) using the WAIS-R was used to distinguish between mild to moderate CATD (n=44) and normal cognition (n=54) and had a sensitivity of 0.07 and specificity of 0.93.[100]

CATD Versus MCI

No studies reported data on the WAIS for distinguishing between CATD and MCI.

Variation in Classification Accuracy by Participant Characteristics

No studies reported on whether WAIS diagnostic test performance for distinguishing between CATD and normal cognition varied by participant characteristics.

Wechsler Memory Scales (WMS)

One study (n=68) evaluated WMS-derived scores for identifying CATD.[91] The WMS is a battery of tests producing various index scores to characterize memory ability/dysfunction (auditory versus visual, immediate versus delayed, etc.). The full WMS battery administration time is not brief cognitive testing, but abbreviated summary metrics may be administered in 30 minutes or less.

Classification Accuracy

CATD Versus Normal Cognition

This study evaluated WMS-III derived index scores for distinguishing mild to moderate CATD (n=34) from normal cognition (n=34) and asked whether classification ability is better using the index alone versus when compared with a measure of general intellectual ability (the WAIS-III General Ability Index; GAI). The WMS-III index scores evaluated were the General Memory Index (GMI), Immediate Memory Index (IMI), and the Delayed Memory Index (DMI) (index scores have a mean of 100 and SD of 15, higher scores are better). For each WMS-III memory index score, classification was tested 1) using the index alone, 2) using a simple difference score between the memory index and the GAI, 3) using a memory index-GAI difference score stratified by GAI, and 4) using a memory index difference score that took into account the participant's predicted memory ability from the GAI. Each of the four classification methods was assessed using a 5^{th} and 10^{th} age-based normative percentile cut point. Most resulting scores produced classification with sensitivity and specificity values at 0.70 or above with many much higher. In each case, optimal classification was achieved using only the WMS-III index score and not including the WAIS-III GAI. GMI classification resulted in sensitivities of 0.94 and 0.97 and specificities of 0.97 and 0.91, respectively, for the 5^{th} and 10^{th} percentiles. IMI classification resulted in sensitivities of 0.85 and 0.94 and specificities of 1.00 and 0.94, respectively, for the 5^{th} and 10^{th} percentiles. DMI classification resulted in sensitivities of 0.88 and 0.97 and specificities of 0.97 and 0.97, respectively, for the 5^{th} and 10^{th} percentiles.

CATD Versus MCI

No studies reported data on the WMS for distinguishing between CATD and MCI.

Variation in Classification Accuracy by Participant Characteristics

No studies reported on whether WMS test performance for distinguishing CATD from normal cognition varied by participant characteristics.

Addenbrooke's Cognitive Exam (ACE)

One study (n=59 participants) evaluated the ACE[102, 103] for identifying CATD.[104] The ACE is a very brief battery consisting of several brief tasks to assess attention, memory, fluency, language, and visuospatial abilities (maximum score 100, higher score is better, approximately 15-20 minutes administration time).

Classification Accuracy

CATD Versus Normal Cognition

This study evaluated the ACE-III total score for distinguishing individuals with early onset CATD (age $\leq$65 years; n=31) from otherwise undefined healthy controls (n=28).[104] A post hoc optimal cut score of 88 had a sensitivity of 0.97 and specificity of 0.96.

CATD Versus MCI

No studies reported data on the ACE for distinguishing CATD from MCI.

Variation in Classification Accuracy by Participant Characteristics

No studies reported on whether ACE diagnostic test performance for distinguishing CATD from normal cognition varied by participant characteristics.

Memory Tests

Baseline Study Characteristics

Seventeen unique studies evaluated the performance of eligible memory tests for identifying CATD, including memory for word lists, prose, figure drawings, and common objects (Table 4.4). These included 13 studies that evaluated performance on list-learning tasks, four that evaluated prose recall, two that evaluated figure recall, and four that evaluated other memory tests.

Study participants included 1,341 with CATD, 242 with MCI, and 2,478 healthy control older adults. All studies reported using NINCDS-ADRDA criteria for diagnosis of CATD with the exception of one study which described DSM-IV dementia criteria and a neurologist assigned subtype.[105] Participants with MCI were diagnosed consistent with Petersen criteria.[53] Normal older adult control participants were most commonly evaluated with a diagnostic workup and/or assessment sufficient to assign a CDR score of 0. Two studies described control participants as self-reporting that they were cognitively unimpaired.[54, 85]

Participant mean age was 74 years, 43 percent were male, and mean years of education was 13. Five studies reported race or ethnicity data, with four describing predominantly white samples[54, 61, 106 107] and one reporting an all Asian (predominantly Chinese) sample.[92]

Table 4.4. Summary of reported results for primary outcomes: memory*†

Diagnostic Question	Test Metric	Studies, N (Patients Analyzed)	CATD Prevalence, Median (Range)	Cut Points	SN, Median (Range)	SP, Median (Range)	TP per 1000 Patients, Median (Range)	TN per 1000 Patients, Median (Range)	FP per 1000 Patients, Median (Range)	FN per 1000 Patients, Median (Range)
CATD vs. Normal Cognition	List learning, trials & totals	6 (n=1784)	0.21 (0.11-0.50)	‡	0.82 (0.35-0.96)	0.96 (0.73-1.00)	178 (73-480)	650 (470-837)	24 (0-240)	33 (10-295)
	List learning, delayed recall & retention	5 (n=937)	0.50 (0.16-0.50)	‡	0.89 (0.62-0.96)	0.94 (0.76-0.98)	430 (140-480)	480 (400-706)	30 (13-151)	35 (19-190)
	List learning, recognition	2 (n=479)	0.50 (0.16-0.50)	‡	0.48 (0.25-0.73)	0.96 (0.91-0.98)	195 (95-365)	490 (480-765)	20 (10-76)	260 (64-375)
	List learning, intrusion errors	2 (n=470)	0.50 (0.14-0.50)	‡	0.30 (0.14-0.62)	0.94 (0.78-0.96)	135 (51-310)	470 (390-732)	30 (20-129)	350 (87-430)
	List learning, combined scores	2 (n=287)	0.42 (0.34-0.50)	‡	0.83 (0.77-0.89)	0.95 (0.92-0.98)	353 (261-445)	554 (460-648)	27 (13-40)	66 (55-78)
	Prose recall & retention	3 (n=895)	0.40 (0.11-0.54)	‡	0.77 (0.71-0.87)	0.87 (0.81-0.89)	334 (78-435)	524 (369-739)	78 (55-151)	65 (32-125)
	Figure recall & retention	2 (n=447)	0.16 (0.16-0.50)	‡	0.87 (0.74-0.90)	0.86 (0.79-0.93)	141 (118-435)	698 (430-782)	90 (59-177)	31 (16-65)
	Process dissociation, recollection	1 (n=583)	0.11	NR	0.77	0.86	85	766	125	25
	Fuld OME	1 (n=412)	0.65	17-19	0.94 (0.93-0.95)	1.00 (0.94-1.00)	**	**	**	**
CATD vs. MCI	List learning, trials & totals	2 (n=139)	0.47 (0.47-0.65)	‡	0.65 (0.35-0.91)	0.72 (0.66-0.90)	307 (165-596)	380 (238-475)	107 (53-179)	165 (59-307)
	List learning, delayed recall & retention	3 (n=327)	0.47 (0.47-0.62)	‡	0.83 (0.73-0.90)	0.65 (0.52-0.83)	411 (345-564)	274 (262-438)	163 (90-253)	80 (52-128)

CATD=Clinical Alzheimer's type dementia; FN=false negative; FP=false positive; MCI=Mild Cognitive Impairment; OME=Object Memory Evaluation; SN=sensitivity; SP=specificity; TN=true negative; TP=true positive

*Data shown for tests evaluated in ≥2 low or moderate ROB studies or in 1 such study with ≥300 participants. Calculations assume participants were unique across studies excluding publications citing common study samples.[48, 50, 108, 109] There was likely additional overlap from frequently used study cohorts.

†No studies reported data on harms of brief cognitive testing for identifying CATD.

‡Cut point varied by the specific test or metric.

**TP, TN, FP, and FN per 1000 patients could not be calculated based on data reported.[110]

List Learning

Fifteen publications of 13 studies (n=3,084)[48, 50, 54, 61, 67, 81, 85, 92, 105-109, 111, 112] evaluated list-learning verbal memory tests for distinguishing CATD from normal cognition or MCI. Most list-learning procedures include four broad categories of performance: initial efforts to learn a list of words during multiple presentations (immediate recall trials), recall of the list at some later time often with alternate tasks in between (delayed recall), the ability to identify words on the list from distractors (recognition), and evaluation of errors made during the prior tasks.

Classification Accuracy

CATD Versus Normal Cognition

Thirteen publications of 11 studies evaluated list-learning performance for distinguishing patients with CATD (n=676) from demographically similar or matched older adults with normal cognition (n=2,038).[48, 50, 54, 61, 81, 85, 92, 105, 107-109, 111, 112] Three studies evaluated various scores for the CERAD word list,[98] including delayed recall, percent retention (savings), and recognition metrics. Cut scores were identified by maximizing diagnosis group separation within the study sample using ROC analysis or by comparing performance to control group norms (most commonly 2 standard deviations [SD] below the control group mean). CERAD list delayed recall scores, using cut points at 4, 4.5 and 2 SD below control performance, respectively, had sensitivity ranging from 0.86 to 0.93 and specificity ranging from 0.84 to 0.94.[48, 61, 108, 109] One study reported that CERAD list delayed recall percent retention (savings) scores at a cut point of 66 percent had a sensitivity of 0.88 and specificity of 0.82.[48] Three studies reported various CERAD list recognition scores, with sensitivity ranging from 0.25 to 0.60 and specificity ranging from 0.91 to 0.98.[48, 108, 109] Finally, two studies reported group discrimination for CERAD intrusion error scores, with sensitivity ranging from 0.14 to 0.62 and specificity ranging from 0.78 to 0.96.[50, 109]

Two studies evaluated the Free and Cued Selective Reminding test (FCSR) for distinguishing CATD from normal cognition.[105, 112, 113] Both reported results for free recall, one reporting that an unspecified post hoc optimal cut point had a sensitivity of 0.91 and specificity of 0.73,[112] and the other that a cut point of 24 cited from prior work[114] also reported that an FCSR total recall cut point of 44 cited from prior work had a sensitivity of 0.71 and specificity of 0.94.

The other five studies each evaluated scores for different word lists. Three studies reported immediate list recall and learning trial totals, including the CogState International Shopping List Test (ISLT),[111] Hopkins Verbal Learning Test (HVLT),[54] and Neuropsychological Assessment Battery (NAB) word list.[107] The best-performing post hoc optimal cut scores for these measures had sensitivity ranging from 0.78 to 0.92 and specificity ranging from 0.75 to 0.95.

Three studies reported delayed recall scores, including the DemTect[81] Delayed Word Recall (DWR) test[85] and NAB word list.[107] The best-performing post hoc cut scores for these measures had sensitivity ranging from 0.89 to 0.93 and specificity ranging from 0.76 to 0.98. One study reported on performance of a combined metric from the ADAS-Cog (immediate recall, delayed recall, and recognition) in which a cut point of >14 had a sensitivity and specificity of 0.77 and 0.98, respectively.[92]

CATD Versus MCI

Five studies[61, 67, 92, 106, 107] evaluated list-learning performance for distinguishing individuals with CATD (n=313) from similar or matched older adults with MCI (n=242). No two studies evaluated the same list learning test or scores, but four of the five included traditional measures of recall or retention.[61, 67, 106, 107] One reported that an optimal performing cut point of 2 on the CERAD list delayed free recall score had a sensitivity of 0.68 and specificity of 0.81.[61] A second study reported that an optimal performing cut point of 15 on the HVLT three trials total score had a sensitivity of 0.69 and specificity of 0.91.[67] A third study reported both best-performing and conventional cut points for several scores from the NAB list.[107] Optimal performing cut points, as determined by ROC analysis, and associated sensitivity and specificity, respectively, were as follows: 30 for list A immediate recall (0.58 and 0.86), 41 for list B immediate recall (0.65 and 0.72), 30 for list A short delay (0.73 and 0.83), and 36 for list A long delay (0.89 and 0.52). Another study reported that <30 percent retention scores for the RBANS list had a sensitivity of 0.90 and specificity of 0.72.[106] Last, one study reported on performance of a combined metric from the ADAS-Cog (immediate recall, delayed recall, and recognition), and reported that the cut point of 14 had a sensitivity and specificity of 0.76 and 0.85, respectively.[92, 106]

Variation in Classification Accuracy by Participant Characteristics

In one study, optimal HVLT cut points for distinguishing between CATD and normal cognition did not differ significantly as a function of age, gender, or education.[54] A second study stratified CATD subjects by severity (i.e. mild, moderate, or severe CATD), then separately evaluated CERAD list recognition scores for distinguishing each of these CATD subgroups from cognitively normal adults; however, this study did not statistically test for different classification rates.[108, 109] For most scores reported, specificity was consistently high across severity groups, while sensitivity was generally higher in more severely impaired participants.

No studies reported on whether list learning test performance for distinguishing CATD from MCI varied by participant characteristics.

Prose Recall

Four studies (n=1,012) evaluated the performance of prose recall tasks (repeating short stories or paragraphs from memory) for identifying CATD. Three studies compared individuals with mild to moderate CATD to older adults with normal cognition[94, 112, 115] and one compared individuals with CATD to those with amnestic MCI.[106, 94, 106, 115]All cut points evaluated were post hoc and no two studies evaluated the same score.

Classification Accuracy

CATD Versus Normal Cognition

Three studies[94, 112, 115] evaluated prose recall for distinguishing individuals with CATD (n=220) from those with normal cognition (n=675) using the WMS Logical Memory (LM) subtest.[116, 117] The first study evaluated several scores based on propositional content (breaking down text into small units of meaning) with sensitivities and specificities ranging from 0.75 to 0.84 and 0.81 to 0.89, respectively.[115] The other two studies both evaluated the delayed recall score from the WMS-Revised LM subtest. In one, a post hoc optimal cut point of <10 had a

sensitivity of 0.87 and specificity of 0.89,[94] and in the other, an unspecified cut point had a sensitivity of 0.71 and specificity of 0.87.[112]

CATD Versus MCI

One study[106] evaluated prose recall for distinguishing CATD (n=73) from amnestic MCI (n=44) using the RBANS Story Memory subtest.[99] At a cut score of below 60 percent retention (savings), sensitivity was 0.85 and specificity was 0.55.

Variation in Classification Accuracy by Participant Characteristics

No studies reported data on whether prose recall test performance for distinguishing CATD from either normal cognition or MCI varied by participant characteristics.

Figure Recall

Three publications of two studies (n=447)[48, 50, 94] evaluated the performance of figure recall tasks (most commonly reproducing designs from memory by drawing them on paper) for identifying CATD.

Classification Accuracy

CATD Versus Normal Cognition

Two studies evaluated the WMS[116, 117] Visual Reproduction (VR) subtest for distinguishing individuals with CATD (n=127) from those with normal cognition (n=320). Best-performing cut points were identified by maximizing CATD prediction in the study samples (ROC, discriminant function). In one study, an optimal immediate recall cut point of <9 had a sensitivity of 0.90 and specificity of 0.79; an optimal savings score of <30 percent had a sensitivity of 0.74 and specificity of 0.93, and an optimal figural intrusions score of >0 had sensitivity of 0.27 and specificity of 0.82.[48, 50] For delayed figure recall, this study reported sensitivity of 0.87 and specificity of 0.87 for an optimal cut point of 2,[48, 50] while another study reported sensitivity of 0.87 and specificity of 0.86 for an optimal cut point of 3.[94]

CATD Versus MCI

No studies reported data on figure recall test performance for distinguishing CATD from MCI.

Variation in Classification Accuracy by Participant Characteristics

No studies reported on whether figure recall test performance for distinguishing CATD from either normal cognition or MCI varied by participant characteristics.

Other Memory Tests

Four studies (n=1,206) evaluated the performance of other eligible memory tasks for identifying CATD,[67, 110, 112, 118] although no two studies reported data for the same test.

Classification Accuracy

CATD Versus Normal Cognition

One study (n=127) evaluated combined verbal (prose recall) and visuospatial (figure recall) memory tasks for distinguishing participants with mild to moderate CATD (n=58) from healthy older adults defined with normal cognition by medical history (n=69).[118] A post hoc optimal cut point for combined percent retention (savings) scores for delayed recall performance on the WMS-Revised LM and VR subtests had a sensitivity of 0.88 and specificity of 0.99. A second study (n=583) evaluated a recollection estimate (as opposed to familiarity) from a dual process dissociation procedure for distinguishing mild CATD (n=64) from CDR-defined normal control participants (n=519).[112] An unreported post hoc optimal cut point had a sensitivity of 0.77 and specificity of 0.86.

CATD Versus MCI

One study (n=68) evaluated the Placing Test, a visuospatial memory test, for distinguishing between CATD (n=40) and MCI (n=28).[67] A post hoc optimal cut point for total score of 10.5 had a sensitivity of 0.90 and specificity of 0.50, a cut point for objects of 6.5 had a sensitivity of 0.80 and specificity of 0.71, and a cut point for faces of 5.5 had a sensitivity of 0.68 and specificity of 0.68.

Variation in Classification Accuracy by Participant Characteristics

One study (n=412 participants) reported age-stratified results for distinguishing between mild-moderate CATD (n=268) and normal cognition (n=144) with the Fuld Object Memory Evaluation (FOME),[119, 120] a test of memory and tactile recognition.[110] Total recall scores were evaluated for age groups 59 to 68, 69 to 78, and 79 to 90. Cut scores of 17, 18, and 19 had sensitivity ranging from 0.93 to 0.95 and specificity ranging from 0.94 to 1.00. Best-performing cut scores were 19 in the youngest group and 18 in the 79 to 90 age group. Cut scores of 17 and 18 performed equally well for the 69 through 78 age group. The study did not report on whether differences in FOME classification between CATD and normal cognition by participant age were statistically significant.

Tests of Executive Function

Baseline Study Characteristics

Five unique studies evaluated the performance of eligible tests of executive function, including complex trail and coding tasks, design fluency, and conceptual rule attainment (rule learning and switching) tasks, for identifying CATD (Table 4.5). These included three studies that evaluated part B of the Trail Making Test (TMT), one that evaluated the Wisconsin Card Sorting Test (WCST), one that evaluated the Digit Symbol substitution task, and one that evaluated the Graphic Pattern Generation Test (GPGT) performance.

Study participants included 394 patients with CATD, 200 with MCI, and 573 healthy control older adults. All studies reported using NINCDS-ADRDA criteria for the diagnosis of CATD and none used NIA-AA criteria. Participants with MCI were diagnosed consistent with Petersen criteria.[53] Normal older adult control participants were most commonly evaluated with a diagnostic workup or some combination of history and brief cognitive assessment. One study described control participants as self-reporting they were cognitively unimpaired.[121]

Participant mean age was 76 years, 43 percent were male, and mean years of education was 15 years. Only one study reported race or ethnicity data, in which 69 percent of participants were white and 31 percent were black.[122]

Table 4.5. Summary of reported results for primary outcomes: executive function*

Diagnostic Question	Test Metric	Studies, N (Patients Analyzed)	CATD Prevalence, Median (Range)	Cut Points	SN, Median (Range)	SP, Median (Range)	TP per 1,000 Patients, Median (Range)	TN per 1,000 Patients, Median (Range)	FP per 1,000 Patients, Median (Range)	FN per 1,000 Patients, Median (Range)
CATD vs. Normal Cognition	TMT B time	2 (n=457)	0.33 (0.16-0.50)	131 and 173 sec	0.86 (0.85-0.87)	0.86 (0.83-0.88)	282 (138-425)	578 (415-740)	93 (85-101)	48 (21-75)

CATD=Clinical Alzheimer's-type dementia; FN=false negative; FP=false positive; MCI=mild cognitive impairment; Sec=seconds; SN=sensitivity; SP=specificity; TMT B=Trail Making Test part B; TN=true negative; TP=true positive

*Data only shown for tests evaluated in 2 or more studies rated low or moderate risk of bias or in 1 study with 300 or more participants rated low or moderate risk of bias; no studies that compared CATD versus MCI met this threshold. Calculations assume each participant was unique across study samples.

†No studies reported data on harms of brief cognitive testing for identifying CATD.

Trail Making Test (TMT) Part B

Three studies (n=736) evaluated the TMT part B[123, 124] for distinguishing mild to moderate CATD from either normal cognition or MCI.[48, 94, 122] In the TMT part B, mental flexibility is assessed by asking participants to quickly draw lines between circles with ascending numbers and letters, alternating between the two.

Classification Accuracy

CATD Versus Normal Cognition

Two studies evaluated TMT part B time to completion in seconds for distinguishing individuals with CATD (n=143) from those with workup confirmed normal cognition (n=336).[48, 94] Each identified an optimal cut point by maximizing CATD prediction in the study sample using ROC analysis. For the first study, for an optimal cut point of >172 seconds, sensitivity was 0.87 and specificity was 0.88.[48] For the second study, for an optimal cut point of >130 seconds, sensitivity was 0.85 and specificity was 0.83.[94]

CATD Versus MCI

One study also evaluated TMT part B for distinguishing individuals with CATD (n=57) from those with MCI defined by Petersen criteria[53] (n=200).[122] ROC analysis was used to determine optimal cut points for several combinations of performance time and errors. These included completion time in seconds (cut point z score -1.0 compared with normative data had sensitivity 0.53 and specificity 0.57), number of errors (cut point >1 had sensitivity 0.72 and specificity 0.41), a combination of time and errors (sensitivity 0.44 and specificity 0.67), and a combination of time or errors (sensitivity 0.81 and specificity 0.31).

Variation in Classification Accuracy by Participant Characteristics

No studies reported on whether TMT part B test performance for distinguishing between CATD and either normal cognition or MCI varied by participant characteristics.

Digit Symbol Substitution

One study (n=283) evaluated a test of digit symbol substitution for distinguishing CATD from normal cognition.[48] The Wechsler Adult Intelligence Scale Revised (WAIS-R)[117] Digit Symbol subtest was analyzed for distinguishing individuals with mild to moderate CATD (n=45) from older adults with normal cognition (n=238). In the Digit Symbol task, processing speed and divided attention are assessed by asking participants to quickly re-code a sheet of numbers into abstract symbols based upon a provided key of digit/symbol pairs.

Classification Accuracy

CATD Versus Normal Cognition

This study defined an optimal cut point for the WAIS-R Digit Symbol subtest total score by maximizing CATD prediction in the study sample using ROC analysis. For an optimal cut point of <34, sensitivity was 0.95 and specificity was 0.67.

CATD Versus MCI

No studies reported data on digit symbol substitution test performance for distinguishing CATD from MCI.

Variation in Classification Accuracy by Participant Characteristics

No studies reported on whether digit symbol substitution test performance for distinguishing CATD from either normal cognition or MCI varied by participant characteristics.

Tests of Design/Figure Fluency

One study (n=277) evaluated the performance of a test of figural fluency for distinguishing CATD from normal cognition.[125] This study evaluated the GPGT,[126, 127] a test of design fluency in which participants must draw as many different designs as possible within a set of parameters, but without time limits. Patients with mild to moderate CATD (n=110) were compared with demographically similar older adults with normal cognition (n=167; defined by MMSE ≥27).

Classification Accuracy

CATD Versus Normal Cognition

This study evaluated GPGT scores for row 1 perseverations (repeated figure design errors) and row 1 unique figure designs. Optimal cut points were identified by maximizing CATD prediction in the study sample using ROC analysis. A cut point of 4 on perseverations in row 1 was associated with a sensitivity of 0.76 and specificity of 0.37, and a cut point of 15 unique designs in row 1 was associated with a sensitivity of 0.81 and a specificity of 0.36.

CATD Versus MCI

No studies reported data on figure fluency test performance for distinguishing CATD from MCI.

Variation in Classification Accuracy by Participant Characteristics

No studies reported on whether GPGT diagnostic test performance for distinguishing CATD from either normal cognition or MCI varied by different participant characteristics.

Wisconsin Card Sorting Test (WCST)

One study (n=162) evaluated the performance of the WCST,[128, 129] a test of abstraction and mental flexibility for distinguishing between CATD and normal cognition.[121] Participants completing the WCST are asked to sort cards by color, shape, or number according to rules that change once a pattern has been established, requiring them to identify implicit rules and infer when they have changed. In this study, the performance of a modified version of the WCST was evaluated for distinguishing between mild to moderate CATD (n=87) and self-reported normal cognition (n=75) in older adults.

Classification Accuracy

CATD Versus Normal Cognition

Optimal cut points for WCST non-perseverative errors, perseverative errors, and the number of categories achieved were identified by maximizing CATD prediction in the study sample using ROC analysis. A cut point of >15 non-perseverative errors had a sensitivity of 0.58 and specificity of 0.84. A cut point of >5 perseverative errors had a sensitivity of 0.76 and specificity of 0.93. A cut point of <5 categories had a sensitivity of 0.93 and specificity of 0.82.

CATD Versus MCI

No studies reported on WCST performance for distinguishing CATD from MCI.

Variation in Classification Accuracy by Participant Characteristics

In a subgroup analysis evaluating the WCST for distinguishing between mild CATD (defined by DRS >120; n=27) and normal cognition, results appeared similar to those for the comparison between participants with mild to moderate severity and those with normal cognition. In this subgroup, >15 non-perseverative errors had a sensitivity of 0.48 and specificity of 0.84, >5 perseverative errors had a sensitivity of 0.74 and specificity of 0.93, and <5 categories had a sensitivity of 0.83 and specificity of 0.81. However, no statistical tests for interaction by CATD severity were reported.

Language Tests

Baseline Study Characteristics

Twelve publications of 10 unique studies evaluated eligible language tests, including tests of verbal fluency and confrontation naming, for distinguishing CATD from normal cognition (Table 4.6).[48, 50, 66, 67, 81, 94, 106, 108, 109, 130-132] These included 3 studies that evaluated the BNT and 10 that evaluated various types of verbal fluency tasks.

Study participants included 751 patients with CATD, 29 with MCI, and 896 healthy control older adults. All studies reported using NINCDS-ADRDA criteria for diagnosis of CATD and none used NIA-AA criteria. Participants with MCI were diagnosed consistent with Petersen criteria.[53] Normal older adult control participants were evaluated with a diagnostic workup, except one study that described control participants as defined by medical history.[132]

Mean participant age was 74 years, 44 percent were male, and mean years of education was 13. The only study that reported race or ethnicity data was 98 percent white.[132]

Table 4.6. Summary of reported results for primary outcomes: language*

Diagnostic Question	Test Metric	Studies, N (Patients Analyzed)	CATD Prevalence, Median (Range)	Cut Points	SN, Median (Range)	SP, Median (Range)	TP per 1000 Patients, Median (Range)	TN per 1000 Patients, Median (Range)	FP per 1000 Patients, Median (Range)	FN per 1000 Patients, Median (Range)
CATD vs. Normal Cognition	Semantic fluency, animals	4 (n=582)	0.50 (0.50-0.68)	9, 12-14	0.88 (0.35-0.94)	0.98 (0.86-1.00)	455 (175-592)	465 (307-500)	6 (0-70)	74 (30-325)
	Semantic fluency, other categories	2 (n=327)	0.63 (0.48-0.63)	†‡	0.94 (0.92-0.96)	0.87 (0.81-0.96)	592 (438-599)	331 (324-425)	49 (14-100)	35 (28-50)
	Semantic fluency, category combinations	4 (n=876)	0.33 (0.15-0.63)	†	0.94 (0.90-1.00)	0.88 (0.83-0.93)	312 (142-627)	569 (345-751)	78 (28-143)	14 (0-20)
	Phonemic fluency, single letter scores	3 (n=286)	0.63 (0.63-0.68)	†	0.77 (0.72-0.87)	0.87 (0.74-0.93)	505 (451-542)	324 (236-345)	49 (28-83)	148 (85-176)
	Phonemic fluency, letter combinations	3 (n=686)	0.39 (0.15-0.63)	†	0.82 (0.73-0.89)	0.81 (0.69-0.92)	333 (111-557)	461 (317-659)	122 (31-261)	56 (38-81)
	Mixed semantic & phonemic fluency	2 (n=418)	0.14 (0.14-0.68)	†	0.53 (0.39-0.67)	0.87 (0.52-0.96)	93 (54-361)	448 (307-749)	112 (13-413)	85 (46-320)
	BNT, total score	2 (n=479)	0.50 (0.16-0.50)	BNT15: 13 BNT30: 22	0.65 (0.53-0.84)	0.92 (0.85-0.92)	270 (119-420)	460 (460-715)	40 (40-126)	153 (40-235)

BNT15=15-item Boston Naming Test; BNT30=30-item Boston Naming Test; CATD=Clinical Alzheimer's type dementia; FN=false negative; FP=false positive; MCI=Mild Cognitive Impairment; SN=sensitivity; SP=specificity; TN=true negative; TP=true positive

*Data only shown for tests evaluated in 2 or more studies rated low or moderate risk of bias or in 1 study with 300 or more participants rated low or moderate risk of bias. Calculations assume each participant was unique across studies excluding those publications citing common study samples.[48, 50, 108, 109] There was likely unknown additional overlap from frequently used study cohorts.

†Cut point varied by the specific test or metric.

‡One study evaluating "semantic verbal fluency, other categories" did not a report cut point.[81]

**No studies reported data on harms of brief cognitive testing for identifying CATD.

Tests of Verbal Fluency

Ten publications of nine unique studies (n=1,586[48, 50, 66, 81, 94, 109, 130-133] evaluated tests of verbal fluency for distinguishing between individuals with mild to moderate CATD and older adults with normal cognition. Verbal fluency tests assess both language and executive functions. Most commonly, participants are asked to provide as many words as possible within one minute that fall into a known category (semantic fluency) or begin with a specific letter (phonemic fluency).

Classification Accuracy

CATD Versus Normal Cognition

Semantic (Category) Fluency

All nine studies evaluated semantic (category) fluency tasks. Four studies evaluated classification metrics specifically for the naming of animals.[66, 109, 130, 132] Most reported data for cut points identified by maximizing CATD prediction in the study sample using either logistic regression or ROC analyses.

For optimal cut points ranging from 12 to 16, sensitivity ranged from 0.73 to 0.92 and specificity ranged from 0.87 to 1.00. Only one study identified a cut point based upon the commonly used clinical threshold of 2 SD below the control group performance mean, for which sensitivity ranged from 0.35 to 0.94, with lower values for groups with less severe cognitive impairment, and specificity was 1.0.[109] Three studies evaluated classification metrics for the combined total of animals, fruit, and vegetable naming,[94, 131, 132] with each reporting cut points identified by maximizing CATD prediction in the study sample. For optimal cut points ranging from 28 to 38, sensitivity ranged from 0.93 to 1.00 and specificity ranged from 0.88 to 1.00. Two studies evaluating the naming of items found in a supermarket[81, 132] reported that sensitivity and specificity for unspecified best-performing cut points ranged between 0.92 to 0.93 and 0.81 to 0.97, respectively. One of these studies also reported that sensitivity and specificity, respectively, for unspecified optimal cut points was 0.96 and 0.89 for naming fruits, 0.96 and 0.87 for naming vegetables, and 0.94 to 0.96 and 0.87 to 0.92 for first names.[132] Finally, one study reported classification with modeling of combined semantic fluency scores (including correct responses, perseveration errors, intrusion errors, response clustering and switching) to maximize diagnostic assignment.[133] A model restricted to correct responses and errors had a sensitivity of 0.90 and specificity of 0.89. A second model adding response clustering and switching to the first model produced a sensitivity of 0.93 and specificity of 0.95.

Phonemic (Letter) Fluency

Four studies evaluated phonemic (letter) fluency tasks.[48, 130-132] All cut points were identified by maximizing CATD prediction in the study sample using ROC analysis. Two evaluated the task of naming words beginning with the letter A.[130, 132] For one of these studies, a cut point of <13 had a sensitivity of 0.76 and specificity of 0.74,[130] while for the other study, a cut point of <7 had a sensitivity of 0.72 and specificity of 0.93.[132] One of these studies also reported sensitivity and specificity for the optimal cut points for naming F-words (cut point <9 had a sensitivity of 0.79 and specificity of 0.87), for naming S-words (cut point <11 had a sensitivity of 0.87 and specificity of 0.87), and for the combined total of F, A, and S-word tasks (cut points 30

to 31 had sensitivity ranging from 0.87 to 0.89 and specificity ranging from 0.85 to 0.92).[132] A third study evaluated the combined total of C, F, and L-word tasks and reported that for an optimal cut point of 25, sensitivity was 0.73 and specificity was 0.78.[131]

Combined Semantic and Phonemic Fluency

Finally, three studies[50, 130, 131] evaluated metrics that combined semantic and phonemic fluency performance. One evaluated the difference between semantic and phonemic fluency (number of animals named minus number of F-words named), and reported that for an optimal cut point of -1, sensitivity was 0.53 and specificity was 0.96.[130] The second study also evaluated difference scores (number of words with a given letter named minus number of words from a given category named) and reported a non-significant odds ratio for prediction of classification and no further information.[131] The third study reported that for a combined proportion of intrusion errors (incorrect words produced), at an optimal cut point of 0, sensitivity was 0.39 and specificity was 0.87. For a combined proportion of perseverative errors (repeated responses), at an optimal cut point of 2, sensitivity was 0.67 and specificity was 0.52.[50]

CATD Versus MCI

No studies reported data on tests of verbal fluency for distinguishing CATD from MCI.

Variation in Classification Accuracy by Participant Characteristics

Four studies[66, 109, 130, 132, 134] stratified CATD subjects by clinical severity (i.e., mild, moderate, and severe) and evaluated verbal fluency tests for distinguishing cognitively normal participants from individuals in different CATD severity categories. However, none statistically tested whether optimal cut points or diagnostic accuracy for verbal fluency tests differed between these different CATD severity subgroup-normal cognition comparisons. One study evaluated verbal fluency for distinguishing between CATD and normal cognition stratified by sex, but did not test whether differences in classification rates by sex were statistically significant.

Boston Naming Test (BNT)

Four publications of three studies (n=542)[48, 50, 67, 109] evaluated the 15 and 30-item versions of the BNT,[135] a commonly used test of confrontation naming in which participants are asked to name common objects from line drawings.

Classification Accuracy

CATD Versus Normal Cognition

Two studies compared individuals with CATD (n=192) to demographically similar or matched older adults with normal cognition (n=287).[48, 50, 109] Studies evaluated a variety of BNT versions and scores with no overlap between studies. At an optimal cut point of $\leq$22 on the 30-item BNT, as determined with ROC analysis, one study reported a sensitivity of 0.75 and a specificity of 0.85.[48, 50] Using alternate scoring methods based on semantic (concept) and lexical (word) naming errors, sensitivity ranged from 0.50 to 0.74 and specificity ranged from 0.70 to 0.72.[50]

CATD Versus MCI

One study evaluated the BNT for distinguishing between CATD (n=36) and Petersen criteria MCI[53] (n=27).[67] At an optimal cut point of ≤21 on the 30-item BNT, as determined using ROC analysis in the study sample, sensitivity was 0.64 and specificity was 0.81.

Variation in Classification Accuracy by Participant Characteristics

One study evaluated the 15-item BNT total score for distinguishing CATD from normal cognition using a cut point at 2 SD below the control sample mean in separate CATD severity strata.[109] In participants with mild, moderate, and severe CATD, sensitivities were 0.53, 0.55, and 0.84, respectively, while specificity was 0.92 for each CATD severity group. However, the study did not test whether differences in sensitivity by group were statistically significant. No studies reported data on whether BNT performance for distinguishing CATD from MCI varied by participant characteristics.

Test Combinations

Baseline Study Characteristics

Ten publications of nine eligible studies evaluated test combinations for identifying CATD (Table 4.7). These included three studies that evaluated adding an additional test to the MMSE or MIS,[56, 80, 136] and six studies that evaluated other test combinations.[48, 50, 94, 109, 137-139]

Most studies compared individuals with mild to moderate CATD by NINCDS-ADRDA criteria with older adults with normal cognition as confirmed by a diagnostic workup. Exceptions included one study that defined dementia by CDR and physician diagnosed CATD,[139] two that defined normal cognition by CDR,[137, 139] and one that did not report methods for establishing normality.[56] None used NIA-AA criteria.

Participant mean age was 76 years and 38 percent of participants were male. From three studies reporting, race/ethnicity data were predominantly white (93-100%) in two studies[137, 139] and slightly over half African American in a third study.[136]

Table 4.7. Summary of reported results for primary outcomes: test combinations*

Diagnostic Question	Test Metric	Studies, N (Patients Analyzed)	CATD Prevalence, Median (Range)	Cut Points	SN, Median (Range)	SP, Median (Range)	TP per 1,000 Patients, Median (Range)	TN per 1,000 Patients, Median (Range)	FP per 1,000 Patients, Median (Range)	FN per 1,000 Patients, Median (Range)
CATD vs. Normal Cognition	WMS LM, WAIS DSy, BNT60	2 (n=302)	0.47 (0.44-0.50)	†	0.82 (0.68-0.95)	0.87 (0.74-1.00)	382 (342-421)	462 (368-557)	65 (0-129)	92 (22-161)

BNT60=60-item Boston Naming Test; CATD=Clinical Alzheimer's-type dementia; DSy=Digit Symbol; FN=false negative; FP=false positive; LM=Logical Memory; SN=sensitivity; SP=specificity; TN=true negative; TP=true positive; WAIS=Wechsler Adult Intelligence Scale; WMS=Wechsler Memory Scale

*Data only shown for tests evaluated in 2 or more studies rated low-moderate risk of bias or 1 study with 300 or more participants rated low-moderate risk of bias. No studies reported data on harms of brief cognitive testing for diagnosing CATD. Calculations assume each participant was unique across studies. There was likely overlap from frequently used study cohorts.

†One study[139] used a regression equation where X>0 indicated impairment, and one [137] reported no cut point.

‡No studies reported data on harms of brief cognitive testing for identifying CATD.

Supplementing Brief Stand-Alone Cognitive Tests

Two studies (n=204) evaluated a test protocol that supplemented use of the MMSE with another commonly used test[56, 80] to identify CATD and one study (n=295) evaluated combining the MIS with semantic (category) verbal fluency.[136]

Classification Accuracy

CATD Versus Normal Cognition

One study evaluated combining the MMSE with the clock drawing task.[56] With the MMSE cut point kept constant at 23, the clock drawing scoring method was varied. For double failure (both the MMSE and clock drawing), sensitivity ranged from 0.36 to 0.50 and specificity was 1.00. For single failure (either MMSE or clock drawing), sensitivity ranged from 0.86 to 0.96 and specificity ranged from 0.96 to 1.00. A second study that evaluated combining the MMSE with phonemic (letter) verbal fluency only presented results stratified by CATD severity, which are detailed below.[80] A third study evaluated the combination of MIS and a semantic verbal fluency (animals) task for diagnosis of CATD.[136] Failing both tests (MIS $\leq$4 and animals $\leq$9) had a sensitivity of 0.91 and specificity of 0.81.

CATD Versus MCI

No studies reported data on test combinations of brief, stand-alone cognitive tests with another brief cognitive test for distinguishing CATD from MCI.

Variation in Classification Accuracy by Participant Characteristics

One study evaluated combining the MMSE with a phonemic (letter – "F", "A", and "S") verbal fluency task in a model, stratified by CATD severity.[80] When compared to normal controls, among participants with CATD and MMSE>23, sensitivity and specificity for distinguishing CATD from normal cognition were 0.88 and 0.99, respectively, whereas among participants with MMSE $\leq$23, sensitivity for distinguishing CATD from normal cognition was 1.0 and specificity was 0.99.

Other Test Combinations

Seven publications of six studies (n=1,189) evaluated other brief test combinations,[48, 50, 94, 108, 109, 137-139] primarily including versions and subsets of the BNT, WAIS Digit Symbol, list learning, verbal fluency, TMT-B, WMS Logical Memory, and WMS Visual Reproduction.

Classification Accuracy

CATD Versus Normal Cognition

One study reported that a combination of delayed recall scores from the CERAD list-learning and WMS VR tasks, time to complete TMT B, and the 30-item BNT best discriminated between CATD and normal cognition. Incorporating these test results in regression models, with and without adjustment for age, sensitivity ranged from 0.97 to 0.98 and specificity ranged from 0.79 to 0.82.[48] The same investigators also evaluated a combined intrusion errors score from the 15-item BNT, CERAD list-learning, and semantic and phonemic fluency.[50] The optimal combination, determined by logistic regression, had a sensitivity of 0.29 and specificity of 0.98.

A third study reported that a best-performing combination of tests of CERAD list-learning delayed recall and the 15-item BNT had sensitivity of 0.90 and specificity of 0.92.[109]

Two studies (n=302) evaluated[137, 139] the combination of the 60-item BNT, Digit Symbol and WMS LM for distinguishing CATD from normal cognition.[137, 139] In one of the studies, which compared mild CATD to normal cognition, sensitivity was 0.95 and specificity was 1.0,[139] and in other study, which compared very mild CATD (CDR 0.5) to normal cognition, sensitivity was 0.68 and specificity was 0.74.[137]

Two studies evaluated combinations of semantic (category) fluency plus one other metric.[94, 137] When the WMS VR delayed recall task was added to semantic fluency, sensitivity was 0.96 and specificity was 0.93. When the WMS LM delayed recall task was added to semantic fluency, sensitivity was 0.78 and specificity was 0.74. When the DRS total score was added to semantic fluency, sensitivity was 0.95 and specificity was 0.94.

Finally, one study evaluated a linear logistic combination of the WAIS-R Performance IQ index and the trials total score from the FCSR list learning task, resulting in a sensitivity of 0.93 and specificity of 0.93.

CATD Versus MCI

No studies reported data on other test combinations for distinguishing CATD from MCI.

Variation in Classification Accuracy by Participant Characteristics

One study reported that age and education were not statistically significant in their classification prediction model using the 30-item BNT CERAD list, TMT-B and WMS VR.[48] Otherwise, no studies reported analyses addressing whether diagnostic performance of other test combinations for distinguishing between CATD and either normal cognition or MCI varied by participant characteristics.

Comparative Accuracy of Cognitive Tests

Study Characteristics

Nine studies (n=2,746) reported statistical tests to directly compare accuracy between individual cognitive tests or combinations for distinguishing between CATD and either normal cognition or MCI in the same study population.[49, 51, 52, 54, 61, 89, 106, 112, 133] Most reported NINCDS-ADRDA criteria for the diagnosis of CATD with the exception of two studies that reported DSM-IV criteria.[51, 52] None used NIA-AA criteria. Cognitively normal older adult samples were defined with diagnostic work up with the exception of one sample which self-reported as unimpaired[54] and one which was not described.[52] Participants with MCI were defined consistent with Petersen criteria.[53] For the nine studies that reported comparative diagnostic accuracy, mean participant age was 74 years and 41 percent were male. In the six studies reporting race/ethnicity, all described participants as either exclusively or majority white.[49, 51, 54, 61, 89, 106]

Classification Accuracy

CATD Versus Normal Cognition

Eight studies evaluated the comparative accuracy of cognitive tests for distinguishing CATD from normal cognition, but there was no overlap in the tests compared across studies. In one study, the global Clock Drawing Test (CDT) score was found to significantly improve specificity

(72% vs 63%) over Rouleau scoring total (p<.04, n=279).[49] In a second study (n=478), MoCA classification was statistically significantly better than the MMSE (AUC 0.99 vs. 0.98, p<.05), and the same study found that the traditional MoCA was statistically significantly better than the short MoCA (AUC 0.99 vs. 0.99, p<.05).[51] Other studies reported that classification performance did not statistically significantly differ between the MMSE and BMET (total plus two domain scores) (n=102),[52] the MMSE and HVLT (list learning) trials total (n=380),[54] the MMSE and CERAD total score (n=190),[61] or between the CERAD total score and the CERAD list learning delayed recall (n=190).[61]

One study evaluating DRS summary scores (n=359) reported results for the proportion of participants who were correctly classified.[89] The proportion correctly classified by the Memory subscale (94%) was better than for the Construction (72%, p<0.001), Attention (74%, p<0.001), and Conceptualization (75%, p<0.001) subscales, respectively. In addition, the proportion correctly classified by the Initiation/Perseveration subscale (93%) was better than for the Construction (72%, p<0.001), Attention (74%, p<0.001), and Conceptualization (75%, P<0.001) subscales. [89]

The last two studies examined whether alternate ways of assessing language and memory offer improved classification over traditional neuropsychological measures. In the first (n=85), semantic fluency including correct responses and errors (intrusions and preservations) classified individuals between CATD and normal cognition significantly less well than evaluation of semantic fluency that also included clustering and switching metrics (reviewed above) (p for comparison of AUCs <0.05).[133] In the second of these studies (n=583), a memory process dissociation procedure classified participants statistically significantly better than MMSE, WMS LM immediate recall, WMS paired associate learning, semantic fluency, phonemic fluency, BNT, TMT B, or WAIS-R Digit Symbol, not significantly different from WMS LM delayed recall, and statistically significantly worse than FCSR test free recall.[112]

CATD Versus MCI

Three studies evaluated the comparative accuracy of cognitive tests for distinguishing CATD versus MCI with no overlap in test comparisons across studies. In one study (n=449), compared with a short version of the MoCA, both the full MoCA (AUC 0.83 vs. 0.81, p<0.05) and the MMSE (AUC 0.85 vs. 0.81, n=449, p<0.05) were significantly more accurate.[51] A second study (n=155) reported that the MMSE score better discriminated between CATD and MCI than the CERAD total score (p<0.01) and the CERAD total score performed better than the CERAD list delayed recall (p<0.007).[61] The third study (n=117) reported that the RBANS Delayed Memory Index did not distinguish CATD from MCI differently than did either the RBANS list learning retention or prose/story recall retention scores alone.[106]

Variation in Classification Accuracy by Participant Characteristics

No studies reported data on whether the comparative accuracy of different cognitive tests for distinguishing CATD from either normal cognition or MCI varies by patient characteristics.

Chapter 5. Key Question 2: Biomarkers for Identifying Neuropathologically Confirmed AD

Brain Imaging Techniques

Key Messages

- For distinguishing between neuropathologically-confirmed Alzheimer's disease (AD) and non-AD, studies report:
    - Amyloid positron emission tomography (PET) was highly sensitive and specific for beta-amyloid neuropathology of AD and, based on a single study, may increase classification accuracy when added to clinical evaluation.
    - Fluorodeoxyglucose (FDG)-PET was highly sensitive and moderately specific and, based on a single study, may increase classification accuracy when added to clinical evaluation.
    - Magnetic resonance imaging (MRI) medial temporal atrophy was highly sensitive and specific, and single-photon emission computerized tomography (SPECT) cerebral blood flow had variable accuracy; whereas SPECT plus clinical evaluation had lower sensitivity and higher specificity than clinical evaluation alone in two studies, no studies compared MRI plus clinical evaluation versus clinical evaluation alone.
- For distinguishing neuropathologically-confirmed AD from individual types of non-Alzheimer's dementia, studies report:
    - FDG-PET had high sensitivity and moderate specificity for distinguishing AD from neuropathologically-confirmed frontotemporal lobar degeneration (FTLD) and, based on a single study, may increase classification accuracy when added to a clinical evaluation.
    - MRI medial temporal atrophy had moderate to high sensitivity and low to moderate specificity for distinguishing AD from neuropathologically-confirmed Lewy body disease (LBD) or FTLD.
- Data on classification accuracy of brain imaging for neuropathologically-confirmed AD are limited by:
    - Few studies, small sample sizes, and study heterogeneity (including criteria for AD neuropathology and composition of non-AD comparison group, interval between imaging and autopsy, methods of image acquisition and analysis, and cut points for defining abnormal scans).
- No eligible studies with neuropathologically-confirmed AD evaluated the accuracy for distinguishing AD from non-AD dementia of brain imaging with MRI hippocampal atrophy, computed tomography (CT), tau PET, functional MRI, or imaging combined with cerebrospinal fluid (CSF) biomarkers; and only one study directly compared brain imaging techniques.
- There was minimal data addressing whether the accuracy of brain imaging for identifying AD varied by participant characteristics.

Eligible Studies

We identified 26 eligible publications of 15 unique studies that evaluated the accuracy of brain imaging for distinguishing neuropathologically confirmed AD from neuropathologically confirmed non-AD.[3, 4, 134, 140-162] Of the 15 unique studies, three were rated low risk of bias[140, 146, 147] and 12 were rated medium risk of bias.[3, 134, 141-145, 148-151]

Sixteen publications of seven studies evaluated PET, including four studies of amyloid PET[3, 4, 149, 150, 152-160] and three of FDG PET.[134, 143, 146] In addition, six publications of four studies evaluated SPECT cerebral perfusion[141, 145, 147, 148, 161, 162] and four studies evaluated MRI.[140, 142, 144, 151] No eligible studies investigated accuracy of CT, tau PET, or functional MRI for autopsy-confirmed AD. Appendix D provides evidence tables and summary risk of bias assessments.

Overall Study Characteristics

Characteristics of the 1,362 participants in the 15 analyzed brain imaging studies are shown in Table 5.1. Five studies included only participants with clinical dementia; two included participants with dementia symptoms or possible dementia; and eight enrolled individuals with clinical dementia, mild cognitive impairment (MCI), and/or without cognitive impairment. Clinical Alzheimer's-type dementia (CATD) was most commonly defined by the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders (NINCDS-ADRDA) criteria. Clinical diagnoses of non-AD dementias were also based on established criteria.

Neuropathologically-confirmed AD was defined by a variety of criteria across studies, partly reflecting changes in established criteria over time. The most commonly used criterion was from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD).[163] CERAD and modified CERAD criteria were based on neuritic amyloid plaque density. National Institute of Aging (NIA)-Reagan criteria[164, 165] also were commonly used and incorporated both neuritic plaque density (CERAD) and distribution of neurofibrillary tangles (Braak stage).[166] ADNC criteria incorporated neuritic plaque score (CERAD), total amyloid plaque distribution (Thal phase),[167] and neurofibrillary tangle score (Braak stage).[168] Neuropathologically-confirmed non-AD comparison groups included participants without AD neuropathology, those with a single non-AD neuropathologic diagnosis (e.g., FTLD), and those with multiple co-existing neuropathological diagnoses. For clarity, to describe neuropathologically confirmed non-AD diagnoses from here forward, we use FTLD instead of frontotemporal dementia (FTD), and Lewy body disease (LBD) instead of dementia with Lewy bodies (DLB).

Appendix D provides evidence tables, a forest plot, and summary risk of bias assessments. For each imaging modality, Appendix Tables D.1-D.4 detail participants' clinical diagnoses, clinical diagnostic criteria, and AD and non-AD control group neuropathological criteria for each study.

Table 5.1. Characteristics of brain imaging accuracy studies*

Characteristic	N, Mean, or % (Study Range)	Trials Reporting, N
Number of participants analyzed, total	1,362 (27-184)	15
Race – white, %	85 (66-93)	3
Men, %	53 (14-66)	12
Mean age at dementia symptom onset, y	66 (61-73)	3
Mean age at imaging, y	68 (63-79)	5
Mean age at death, y	78 (72-81)	3
Mean interval between imaging and autopsy, mo	38 (7-71)	12

*For studies with multiple reports, characteristics were extracted from the one with the largest sample size. If that report did not adequately report characteristics, it was used only for participant number and the report with the next largest sample size was used for other characteristics.

Harms

Two amyloid PET studies reported harms, though neither had a nonimaging control group. In one, which used the radiotracer, florbetapir, there were no serious adverse events.[3] The study reported two instances of headache, but no other adverse event occurred in more than one participant or was judged related to the procedure. In the second study, 5 percent of participants who received the radiotracer flutemetamol experienced any treatment-related adverse event, all categorized as mild to moderate.[4] Two participants had flushing considered possibly related to flutemetamol, and two deaths within 24 hours of testing and two nonfatal serious adverse events were considered unrelated to flutemetamol. No other eligible studies on the accuracy of brain imaging for distinguishing AD from non-AD dementia reported data on harms.

From an electronic database search for systematic reviews on the accuracy of brain imaging for dementia published since 2013, we identified 21 systematic reviews, of which two referred to potential imaging harms.[169, 170] One of these two reviews reported that the most common side effects of radiotracers for amyloid PET were pain and skin reaction at the injection site,[170] but only cited a publication that did not report information on harms.[171] The other systematic review included 15 studies investigating 7 Tesla MRI for AD diagnosis, of which one reported one case of tinnitus and another that testing was "without any significant adverse effect."[169] No studies in these two reviews included nonimaging control groups.

Amyloid PET

Study Characteristics

Four studies (n=426) evaluated the accuracy of in vivo amyloid PET brain imaging in participants followed to autopsy. At autopsy, participants were classified by different and often multiple AD neuropathologic criteria. These included CERAD or modified CERAD (n=4 studies), total amyloid plaque or Thal phase (n=3 studies),[150, 153, 156, 157] NIA-Reagan (n=2 studies),[154, 158] or National Institute on Aging-Alzheimer's Association (Amyloid, Braak, CERAD) (NIA-AA ABC) score (n=2 studies).[153, 158, 160] All four studies used different radiotracer compounds, including [^{18}F] labeled flutemetamol,[150] florbetapir,[3] florbetaben,[149] and Pittsburgh compound-B.[153] Amyloid PET images were interpreted quantitatively in all four studies and visually in three studies. Quantitative techniques were automated to compare a weighted average tracer uptake from several cortical regions of interest with cerebellar uptake, with one study also converting metrics for estimating amyloid load into a standardized (Centiloid) scale.[153] Cut points for defining quantitative results as positive/abnormal most often were derived post hoc from within analysis samples and less frequently were prespecified. Visual

methods varied, but all evaluated multiple cortical brain regions for increased tracer uptake. Scans were classified as amyloid positive if uptake was increased in at least two of these cortical regions or an overall tracer uptake score exceeded a set threshold. No studies used the same quantitative cut points or visual classification criteria. Appendix Table D.2 details participants' clinical diagnoses, clinical diagnostic criteria, AD and non-AD control group neuropathological criteria, and criteria for defining amyloid PET images as positive/abnormal.

Classification Accuracy

Table 5.2 summarizes outcomes for amyloid PET.

Table 5.2. Summary of reported results for amyloid PET outcomes*

Diagnostic Question	Studies, N (Patients Analyzed)	AD Prevalence, Median (Range)	Cut Points	SN, Median (Range)	SP, Median (Range)	TP per 1,000 Patients, Median (Range)	TN per 1,000 Patients, Median (Range)	FP per 1,000 Patients, Median (Range)	FN per 1,000 Patients, Median (Range)
AD vs. Non-AD	4 (n=426)	0.64 (0.33-0.79)	†	0.91 (0.79-0.98)	0.92 (0.76-1.0)	599 (261-682)	324 (208-555)	28 (0-119)	65 (13-111)

AD=Alzheimer's disease; FN=false negative; FP=false positive; PET=positron emission tomography; SN=sensitivity; SP=specificity; TN=true negative; TP=true positive

*Two included amyloid PET studies reported data on physical harms, with 1 reporting that florbetapir was well tolerated and associated with no serious adverse events[3], and the other that 5 percent of participants who received flutemetamol experienced mild to moderate treatment-related adverse events, and that 2 deaths and 2 nonfatal serious adverse events were considered unrelated to flutemetamol [4] No other amyloid PET imaging studies for identifying AD reported data on harms.

†Studies variably used visual and quantitative scoring systems, within which all reported using different cut points to define an abnormal scan (i.e., amyloid positive).

AD Versus Non-AD

Median amyloid PET sensitivity from all four studies was 0.91 (range 0.79-0.98) and median specificity was 0.92 (range 0.76-1.0). Two of these studies also reported accuracy of clinical evaluation.[3, 149] In the first of these two studies (n=59), clinical evaluation had sensitivity of 0.72 and specificity of 0.95 for neuropathologically confirmed AD and amyloid PET corrected 10 of 11 clinical false negatives and the one clinical false positive but miscategorized 2 of 28 clinical true positives.[3] In the second study, clinical evaluation had sensitivity of 0.94 and specificity of 0.52, and amyloid PET had sensitivity of 0.98 and specificity of 0.89.[149]

Variation in Classification Accuracy by Participant or Test Characteristics

No studies reported on whether accuracy of amyloid PET imaging for neuropathologically diagnosed AD varied as a function of patient characteristics, but several reported results as a function of test characteristics. For automated techniques of categorizing participants as amyloid PET positive or negative, median sensitivity and specificity were 0.86 (range 0.80 to 0.97) and 0.96 (range 0.82 to 1.0), respectively. In the three studies that visually categorized participants, median sensitivity and specificity were 0.92 (range 0.79 to 0.98) and 0.89 (range 0.76 to 1.0), respectively.[3, 4, 149, 150, 154, 157, 158] Two studies reported that for an interval between imaging and autopsy less than 1 year, sensitivity ranged from 0.89 to 0.96 and specificity ranged from 0.89 to 1.0,[3, 150] while sensitivity and specificity for an interval between 1 and 2.4 years both were above 0.93.[150] Another study reported that classification accuracy in a subset of participants with a scan to autopsy interval <2 years was similar to that for the entire study population (AUC, 0.87, 95% confidence interval [CI], 0.76 to 0.94 vs. 0.91, 95% CI, 0.86 to 0.95,).[153] One study reported that the diagnostic accuracy of amyloid PET for AD appeared similar in several individual brain regions (middle frontal gyrus, anterior cingulate cortex, posterior cingulate cortex) (each with sensitivity ranging from 0.80 to 0.90 and specificity from 0.80 to 1.0), but worse for the hippocampus/parahippocampal gyrus (sensitivity 0.57 to 0.71 and specificity 0.60 to 1.0) and occipital cortex (sensitivity 0.89 and specificity 0.67 to 0.86).[148] Classification accuracy appeared similar regardless of which neuropathologic criteria were used to define AD, including CERAD and modified CERAD (sensitivity range 0.81 to 0.98 and specificity range 0.76 to 1.0),[3, 149, 150, 152, 153, 157-159] total amyloid plaque or Thal phase (sensitivity 0.86 to 0.98 and specificity 0.89 to 1.0),[150, 153, 156, 157] NIA-Reagan (sensitivity 0.79 to 0.93 and specificity 0.91 to 1.0),[154, 158] and NIA-AA ABC score (sensitivity 0.80 to 0.88 and specificity 0.82 to 0.86).[153, 158, 160] Last, one study reported that visual scans read by experts with prior amyloid PET reading experience who also received in-person training were more accurate than those read by individuals with no experience reading amyloid PET scans who were trained with an e-training tool (p=0.03).[157] Otherwise, no studies directly compared accuracy between any of these test characteristic subgroups within the same cohort.

FDG-PET

Study Characteristics

Three studies (n=227) evaluated the accuracy of [^{18}F] FDG-PET imaging of brain glucose metabolism in participants for identifying autopsy-confirmed AD.[134, 143] All used FDG-PET scans to generate visual displays. Rates of each participant's glucose metabolism in different

cortical areas were assigned colors to compare them with rates in the participant's own pons and/or with matching cortical areas in normal controls. Each study then guided raters examining these color maps by designating specific patterns of hypometabolism considered characteristic of AD or other neurodegenerative dementias. Appendix Table D.3 details participants' clinical diagnoses, clinical diagnostic criteria, AD and non-AD control group neuropathologic criteria, and criteria for defining the FDG-PET images as positive/abnormal.

Sixty-one percent of study participants were male and no studies reported race/ethnicity. Mean age at imaging, reported in one study, was 66 years. No study reported mean age at death. The mean interval between FDG-PET imaging and autopsy was 3.4 years (range 2.9 to 4.7).

Classification Accuracy

Table 5.3 summarizes outcomes for FDG-PET.

Table 5.3. Summary of reported results for FDG-PET outcomes*

Diagnostic Question	Studies, N (Patients Analyzed)	AD Prevalence, Median (Range)	Cut Points†	SN, Median (Range)	SP, Median (Range)	TP per 1,000 Patients, Median (Range)	TN per 1,000 Patients, Median (Range)	FP per 1,000 Patients, Median (Range)	FN per 1,000 Patients, Median (Range)
AD vs. Non-AD	2 (n=182)	0.64 (0.57-0.70)	†	0.89 (0.84-0.94)	0.74 (0.73-0.74)	568 (477-659)	268 (217-318)	97 (80-114)	67 (43-91)
AD vs. FTLD	1 (n=45)	0.69	†	0.97 (0.96-0.98)‡	0.66 (0.59-0.73)‡	689	200 (178-222)‡	111 (89-133)‡	22

AD=Alzheimer's disease; FDG PET=fluorodeoxyglucose positron emission tomography; FN=false negative; FP=false positive; FTLD=frontotemporal lobar degeneration; SN=sensitivity; SP=specificity; TN=true negative; TP=true positive

*No studies that evaluated the accuracy of FDG-PET imaging for identifying AD reported data on harms.

†Rates of glucose metabolism in different cortical areas were assigned colors to compare with rates in the participant's own pons or in matching cortical areas in normal controls. Raters visually examined these color maps, for which specific patterns of hypometabolism were considered characteristic of AD versus other neurodegenerative dementias.

‡Sensitivity and specificity were reported separately for transaxial and stereotactic surface projection images.

AD Versus Non-AD

Two studies (n=182) evaluated the sensitivity and specificity of FDG-PET for distinguishing between neuropathologically confirmed AD and the absence of AD.[134, 146] For FDG-PET meeting AD imaging criteria, the sensitivity for neuropathologically confirmed AD ranged from 0.84 to 0.94 and specificity ranged from 0.73 to 0.74.

One study[146] also reported that for neuropathologically confirmed AD, the sensitivity and specificity of FDG-PET (0.84 and 0.74, respectively) were higher than were the sensitivity and specificity of a clinical diagnosis of AD (0.76 and 0.58, respectively). In this study, an initial clinical diagnosis of AD had a positive predictive value for neuropathological AD of 70 percent, which increased to 84 percent with a positive FDG-PET scan and decreased to 31 percent with a negative scan. By comparison, an initial clinical diagnosis of non-AD dementia had a positive predictive value for neuropathological AD of 35 percent, which increased to 70 percent with a positive FDG-PET scan and decreased to 17 percent with a negative scan.

AD Versus FTLD

In one study (n=45), FDG-PET results were evaluated to distinguish between individuals with neuropathological diagnoses of AD (N=31) versus FTLD (N=14).[143] AD expert neurologist raters were informed that study participants had an autopsy-confirmed diagnosis of either AD or FTLD. Sensitivity and specificity of FDG-PET scans for AD were 0.96 and 0.59, respectively, for transaxial images, and 0.98 and 0.73, respectively, for stereotactic surface projection images.

When only clinical case scenarios were used to predict AD versus FTLD neuropathology, sensitivity was 0.85 and specificity was 0.65. When reviewers used clinical case scenarios and FDG-PET images together, sensitivity was 0.98 and specificity was 0.71, similar to results for FDG-PET scans alone.

Variation in Classification Accuracy by Participant Characteristics

Accuracy of FDG-PET for distinguishing between AD and non-AD among individuals with less severe cognitive impairment appeared similar to that seen overall in each of two studies. In the first study, sensitivity and specificity were 0.95 and 0.71, respectively, in patients with questionable or mild cognitive impairment, compared with 0.94 and 0.73, respectively, in participants overall.[134] In the second study, sensitivity and specificity were 0.82 and 0.79, respectively, in patients with Mini-Mental State Exam (MMSE) >23, compared to 0.84 and 0.74, respectively, in participants overall.[146] Neither study reported a test for interaction by severity of cognitive impairment.

SPECT: Cerebral Perfusion

Study Characteristics

Four clinical studies (n=232) evaluated SPECT cerebral perfusion in participants with subsequent autopsy confirmation of AD.[141, 145, 147, 148] SPECT detection of a radioactive tracer circulated in the blood is considered to reflect regional cerebral perfusion and corresponding brain activity. SPECT scans were interpreted to show AD when regional hypoperfusion was present, most commonly in the temporal and/or parietal lobes. Appendix Table D.4 details participants' clinical diagnoses, clinical diagnostic criteria, AD and non-AD control group

neuropathological criteria, and criteria for defining SPECT cerebral perfusion images as positive/abnormal.

In two studies reporting, 54 percent of participants were male. No studies reported race/ethnicity. In one study reporting, mean age at imaging was 67 years, and age at death was 72 years. Mean interval from imaging to autopsy in three studies reporting (n=205) was 4.2 years (range 2.4 to 5.9).

Classification Accuracy

Table 5.4 summarizes outcomes for SPECT cerebral perfusion.

Table 5.4. Summary of reported results for SPECT cerebral perfusion outcomes*

Diagnostic Question	Studies, N (Patients Analyzed)	AD Prevalence, Median (Range)	Cut Points†	SN, Median (Range)	SP, Median (Range)	TP per 1,000 Patients, Median (Range)	TN per 1,000 Patients, Median (Range)	FP per 1,000 Patients, Median (Range)	FN per 1,000 Patients, Median (Range)
AD vs. non-AD	3 (n=205)	0.56 (0.48-0.64)	†	0.64 (0.57-0.94)	0.83 (0.76-0.92)	437 (271-603)	390 (301-479)	48 (42-55)	125 (41-208)

AD=Alzheimer's disease; FN=false negative; FP=false positive; SN=sensitivity; SP=specificity; SPECT=single-photon emission computerized tomography; TN=true negative; TP=true positive.
*No SPECT imaging studies reported data on harms.
†Criteria for defining SPECT cerebral perfusion images as abnormal were variable and not simply quantitative across studies.

AD Versus Non-AD

In three studies (n=205), SPECT cerebral perfusion was used to distinguish between participants with autopsy confirmed presence or absence of AD. The non-AD group included participants with a variety of non-AD neuropathological diagnoses. One study[147] used participants with FTLD, LBD, and vascular dementia (VaD) as the non-AD comparator group.[147] Two studies provided insufficient detail to determine the individual diagnoses in the non-AD comparator group.[141, 145]

In two of three studies (n=132), sensitivity ranged from 0.57 to 0.64 and specificity ranged from 0.76 to 0.92.[145, 147] In the third study (n=73), sensitivity and specificity were 0.94 and 0.85, respectively.[141]

Two studies also evaluated the accuracy of clinical diagnosis alone and of SPECT combined with clinical information compared to the autopsy diagnosis.[145, 147] In both studies, the clinical information combined with SPECT cerebral perfusion had a lower sensitivity and higher specificity than clinical information alone.

Variation in Classification Accuracy by Participant or Test Characteristics

One SPECT study (n=48), conducted in a referral center for early-onset dementia, reported that SPECT classification accuracy did not significantly differ by age at first dementia symptom, MMSE score at first visit, disease duration, or interval between SPECT and death, but the study provided no numerical data.[147]

MRI Medial Temporal Lobe Atrophy (MTA)

Study Characteristics

Four unique studies evaluated the accuracy of MRI structural brain imaging in patients with autopsy-confirmed AD neuropathology, focusing primarily on medial temporal lobe volumes.[140, 142, 144, 151] Smaller medial temporal lobe volumes are presumed to indicate greater medial temporal lobe cell loss (i.e., medial temporal lobe atrophy or MTA), which may reflect neurodegenerative pathology affecting this brain region.

Among the four analyzed studies, T1-weighted volumetric MRI scans were performed on 1.0, 1.5, or 3.0 Tesla MRI scanners. Three examined antemortem MRI scans[142, 144, 151] and one examined post-mortem, formalin-fixed, brain MRIs.[140] In three of these studies, human raters scored MTA using the Scheltens visual rating scale (higher values indicate greater atrophy).[140, 142, 144, 172] The fourth study measured participants' brain grey matter volume in multiple regions of interest, created maps comparing these volumes with a reference database of individuals with normal cognition, and then clustered participants by similarity of atrophy pattern.[151]

Neuropathological diagnosis of AD was based on CERAD[140, 142, 144] or NIA-Reagan criteria.[151, 165] Autopsy-confirmed non-AD controls included: LBD,[142, 151] FTLD,[173] Lewy-related pathology,[140] vascular cognitive impairment,[174] or Alzheimer's borderline-type pathology.[140] Appendix Table D.5 details participants' clinical diagnoses, clinical diagnostic criteria, AD and non-AD control group neuropathological criteria, and criteria for defining MRI images as positive/abnormal for each study.

The four study populations included 183 autopsy-confirmed AD and 232 autopsy-confirmed non-AD cases. AD severity was not reported. Mean age of participants was 75 years and 48 percent were male. Race and education were not reported. Study mean intervals between MRI scan and autopsy ranged between 1.5 to 5.8 years.

Classification Accuracy

Table 5.5 summarizes outcomes for MRI MTA.

Table 5.5. Summary of reported results for MRI MTA outcomes*

Diagnostic Question	Studies, N (Participants Analyzed)	AD Prevalence, Median (Range)	Cut Points (SVRS)	SN, Median (Range)	SP, Median (Range)	TP per 1,000 Patients, Median (Range)	TN per 1,000 Patients, Median (Range)	FP per 1,000 Patients, Median (Range)	FN per 1,000 Patients, Median (Range)
AD vs. non-AD	2 (n=161)[142, 151]	0.33 (0.24-0.42)	†	0.91 (0.91-0.91)	0.89 (0.84-0.94)	300 (217-383)	602 (487-717)	70 (43-96)	28 (22-35)
AD vs. LBD	1 (n=129)[144]	0.78	≥1.5	0.73 (0.64-0.82)	0.68 (0.68-0.68)	504	147	70	279
AD vs. L-rP	1 (n=31)[140]	0.75	≥2	0.83	0.38	613	97	161	129
AD vs. FTLD-Tau	1 (n=52)[144]	0.54	≥2	0.68	0.42	365	192	269	173
AD vs. FTLD-TDP-43	1 (n=39)[144]	0.50	≥0.5	0.96	0.04	482	18	482	18
AD vs. borderline AD	1 (n=55)[140]	0.42	≥2 ≥3‡	0.83 0.43	0.56 0.94	345 182	327 545	255 36	73 236

AD=Alzheimer's disease; FN=false negative; FP=false positive; FTLD=frontotemporal lobar degeneration; LBD=Lewy body disease; L-rP=Lewy-related pathology; MRI=magnetic resonance imaging; MTA=medial temporal atrophy; SN=sensitivity; SP=specificity; SVRS=Scheltens MTA visual rating score; TDP-43=TAR DNA-binding protein 43; TN=true negative; TP=true positive.

*No MRI MTA imaging studies for identifying AD reported data on harms.

†One study used a SVRS cut point of ≥5.5, while the other estimated the ability of probabilistic modeling of atrophy patterns to classify participants into clusters.

‡This study derived and reported results for an optimal cut point of ≥2 and results for a previously suggested [172] cut point of ≥3.

AD Versus Non-AD Dementia

Two unique studies evaluated the accuracy of MRI MTA visual assessment for distinguishing between patients with autopsy-confirmed AD pathology and those with autopsy-confirmed, non-AD neurodegenerative pathology.[142, 151]

In one study, the optimal MTA Scheltens score cut point for differentiating between the AD (n=11) and non-AD groups (n=35) was ≥5.5, with sensitivity and specificity of 0.91 and 0.94, respectively.[142] This was more sensitive and nearly as specific as a clinical diagnosis, which in this study were 0.55 and 1.0, respectively. A second study (n=115) clustered participants by their MRI atrophy pattern and used probabilistic modeling to estimate the ability of these clusters to classify them into AD, LBD, and FTLD TAR DNA-binding protein 43 (TDP-43) groups. The primary regions of neurodegeneration in the autopsy-confirmed AD group included the medial and lateral temporal lobes. The reported sensitivity and specificity of this methodology for autopsy-confirmed AD were 0.91 and 0.84, respectively.[151] This was similar to the sensitivity and specificity of a clinical diagnosis of 0.90 and 0.82, respectively.

AD Versus LBD

Two studies examined the value of Scheltens MTA visual rating scores for differentiating autopsy-confirmed AD from either LBD or Lewy Body pathology. In the first study, which included 101 participants with AD and 28 with LBD, the optimal cut score was ≥1.5.[144] Sensitivity and specificity for autopsy-confirmed AD were 0.64 and 0.68, respectively. In a subgroup analysis, the sensitivity and specificity of this cut score for distinguishing participants with neuropathologically confirmed late onset AD (n=28) from LBD (n=28) were 0.82 and 0.68, respectively. A second study examined the value of Scheltens MTA visual rating scores in differentiating between autopsy-confirmed AD (n=23) and Lewy-body pathology (n=8).[140] The optimal MTA cut point of ≥2 yielded a sensitivity of 0.83 and specificity of 0.38.

AD Versus Borderline AD Pathology

One study examined the value of Scheltens MTA visual rating scores in differentiating between autopsy-confirmed AD (n=23) and borderline AD pathology (n=32).[140] For an optimal cut point defined within the study cohort of ≥2, sensitivity was 0.83 and specificity was 0.56. At a previously suggested cut point of ≥3,[172] sensitivity was 0.43 and specificity was 0.94.

AD Versus FTLD

One study examined Scheltens MTA visual rating scores for differentiating late-onset, autopsy-confirmed AD (mean age at MRI 75 years, n=28) from autopsy-confirmed FTLD-Tau (mean age at MRI 64 years, n=24) and alpha-synuclein-negative (FTLD-TDP-43) (mean age at MRI 60 years, n=28).[144] Analyses were not age matched. For comparison with FTLD-tau, for an optimal cut point defined within the study cohort of ≥2, sensitivity and specificity for autopsy-confirmed AD were 0.68 and 0.42, respectively. For comparison with FTLD-TDP-43, for an optimal cut point defined within the study cohort of ≥0.5, sensitivity and specificity for autopsy-confirmed AD were 0.96 and 0.04, respectively.

Variation in Classification Accuracy by Participant Characteristics

No studies reported data on whether accuracy of MRI MTA for distinguishing neuropathologically confirmed AD from neuropathologically confirmed non-AD dementia varies by patient characteristics.

Brain Imaging Combinations

Amyloid PET Plus CT Versus Amyloid PET Alone

One study (n=68) compared the accuracy of amyloid PET using the flutemetamol tracer plus CT compared with amyloid PET alone to distinguish autopsy-confirmed AD from non-AD.[4] Participants were classified at autopsy based on modified CERAD criteria as positive or negative for neuritic plaques. Mean age was 81 years old, 49 percent were male, and 94 percent were white. Participants' clinical diagnoses were either CATD (44%), other dementing disorders (25%), or no history of cognitive impairment (31%). The mean interval between amyloid PET imaging and death was 3.5 months.

Sensitivity and specificity for amyloid PET alone were 0.86 and 0.92, respectively. Sensitivity and specificity were not reported for CT alone. The difference in accuracy between amyloid PET plus CT and amyloid PET alone was reported to not be significant (AUC 0.93 vs. 0.90**,** no p-value reported). The study did not report data on whether comparative accuracy of amyloid PET plus CT versus amyloid PET varied as a function of patient characteristics.

CSF Biomarkers

Key Messages

- For distinguishing autopsy-confirmed AD from non-AD dementia, evidence shows:
    - Individual CSF biomarkers and ratios were moderately sensitive (range 0.62 to 0.83) and specific (0.53 to 0.69).
    - Based on three small studies that directly compared accuracy of selected individual CSF biomarkers or biomarker ratios, beta amyloid 42 (Aß42)/phosphorylated tau (p-tau) ratio and p-tau appeared more accurate and total tau (t-tau) appeared least accurate.
    - Combinations of CSF biomarkers may have the highest mix of sensitivity (range 0.74 to 0.79) and specificity (0.76 to 0.90).
- For distinguishing autopsy-confirmed AD from LBD, evidence shows:
    - Individual CSF biomarkers and ratios were moderately sensitive (range 0.57 to 0.86) and specific (0.61 to 0.83).
    - Two studies that directly compared accuracy of different CSF biomarkers reported no consistent differences between individual markers or ratios.
- For distinguishing between autopsy-confirmed AD and FTLD, evidence shows:
    - Individual CSF biomarkers and ratios were moderately to highly sensitive (range 0.68 to 0.97) and specific (0.58 to 0.97).
    - Two studies that compared accuracy of different CSF biomarkers suggested that t-tau/Aß42 ratio, Aß42/t-tau ratio, Aß42/p-tau ratio, and p-tau appear more accurate and Aß42 and t-tau appear least accurate.

    - One study found that a model based on CSF biomarkers using one of two analyzed assays improved accuracy compared with clinical evaluation alone, mostly by reclassifying wrongly clinically categorized individuals from FTLD to AD.
- No studies evaluated the accuracy of CSF Aß42/Aß40 ratio or neurofilament light protein, of combinations of CSF markers with individual CSF markers or ratios, or of any CSF marker combined with brain imaging.
- Only one study compared the accuracy of CSF biomarkers added to clinical evaluation versus clinical evaluation alone.
- Data on the classification accuracy of CSF biomarkers for autopsy-confirmed AD are limited by few studies, small sample sizes, and study heterogeneity (including use of different cut points for defining abnormal biomarker levels, typically derived post hoc to optimize classification within individual study samples; composition of non-AD comparison groups; CSF collection to autopsy time interval; assay; and composition of biomarker combinations).
- There was minimal data addressing whether the accuracy of CSF biomarkers for identifying AD varied by participant characteristics.

Eligible Studies

We identified 14 eligible publications of 14 unique studies evaluating the accuracy of CSF biomarkers for identifying autopsy-confirmed AD.[175-188] Five studies were rated high risk of bias and excluded from analyses, with all having concerns about patient selection, index test definition or interpretation, and timing between the biomarker test and autopsy.[177, 180-182, 185] The remaining nine studies were rated medium of risk bias and were analyzed.[175, 176, 178, 179, 181, 183, 184, 186-188]

Overall Study Characteristics

Characteristics of the 927 participants (637 autopsy-confirmed AD, 290 autopsy-confirmed non-AD) enrolled in the nine analyzed studies are shown in Table 5.6.

All studies required participants to have clinical dementia, with three using NINCDS-ADRDA criteria, one reporting use of unspecified standard clinical and cognitive evaluation criteria, one reporting a neurologist evaluation, one enrolling participants from an AD clinic, one stating only that participants had dementia, and two reporting no information.

The classification accuracy of CSF biomarkers for autopsy-confirmed AD versus non-AD dementias was evaluated for individual markers, ratios, or combinations of markers. Individual markers assessed included Aß42,[175, 178, 179, 183, 184, 186] beta amyloid 40 (Aß40),[183] t-tau,[175, 176, 178, 179, 184, 186-188] and p-tau.[179, 183, 184, 186, 188] Three studies evaluated the accuracy of the ratio of t-tau/Aβ42,[175, 178, 186] one assessed the accuracy of the ratio of p-tau/Aβ42,[186] and two assessed the accuracy of other combinations of markers.[183, 186] One study directly compared the classification accuracy of Aβ42 levels, p-tau levels, Aβ42/p-tau ratio, and p-tau/t-tau ratio with each other.[186] CSF concentrations of these biomarker levels were determined from commercially available sandwich enzyme-linked immunosorbent assay (ELISA) or Luminex kits for single and multiple analytes (INNOTEST, Ghent, Belgium). One study compared the accuracy of ELISA versus Luminex CSF measurement of t-tau, p-tau, and Aβ42 for distinguishing autopsy-confirmed AD

from non-AD dementia.[188] No eligible studies investigated the accuracy of Aß42/Aß40 ratio, or neurofilament light protein.

Studies performed post hoc analyses to define optimal cut points for individual CSF biomarkers and biomarker ratios to discriminate autopsy-confirmed AD from autopsy-confirmed non-AD within their study samples using receiver operating characteristic (ROC) curve analysis to maximize the sum of sensitivity and specificity, or, much less commonly, using logistic regression. No cut points were evaluated for the accuracy of combinations of CSF biomarkers.[183, 187] The appendix provides a summary of risk of bias assessments (Appendix Table D.7) and detailed evidence tables (Appendix Table D.8, Figure D.2).

AD was neuropathologically defined using one or more of the following guidelines: CERAD criteria, Braak staging,[166] National Institute on Aging and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease (NIA-Reagan)[189] or unspecified accepted research criteria using a neuropathologist's assessment for neurodegenerative diseases. For autopsy-confirmed non-AD diagnoses, studies employed specific neuropathological criteria for LBD,[190] FTLD,[173, 191, 192] VaD[193] and Creutzfelt-Jakob disease (CJD).[194] No neuropathological criteria were specified for progressive supranuclear palsy (PSP), spinocerebellar ataxia (SCA), normal pressure hydrocephalus (NPH) combined with VaD, or other vascular pathologic conditions.

Table 5.6. Characteristics of CSF classification accuracy studies

Characteristic	N, Mean, or % (Study Range)	Studies Reporting, N
Number of participants analyzed	927 (38 to 217)	9*
Race – white, %	95	1
Men, %	48 (21 to 75)	7
Mean age at dementia symptom onset, y	65 (63 to 71)	5
Mean age at CSF collection, y	73 (68 to 76)	8
Mean age at death, y	76 (76 to 77)	3
Mean interval between CSF collection and autopsy, mo	25 (0 to 75)	6

CSF=cerebrospinal fluid

*The 9 analyzed CSF studies were published from just 3 research centers, but we could not determine if any participants were included in more than 1 study.

Harms

No eligible individual studies on the accuracy of CSF biomarkers for distinguishing AD from non-AD dementia reported data on harms. In a search for systematic reviews of CSF testing for identifying AD published since 2013, we identified a 2018 review that included ten uncontrolled studies that reported data on headaches after lumbar puncture for individuals undergoing evaluation for suspected AD.[17] Participants in the 10 studies were diagnosed with CATD, non-AD neurodegenerative dementia, VaD, MCI, or were cognitively normal. Incidence of post-lumbar puncture headaches ranged from 0.58 percent to 20.3 percent. Though most studies reported incidence of 5 percent or less, two of the three largest studies reported incidence of 8.6 percent and 20.3 percent, respectively. Three studies also reported incidence of non-specific headache, ranging from 4.5 percent to 10.2 percent. Mild headaches appeared more common than moderate or severe headaches.

CSF Aß42 Levels

Two studies evaluated the accuracy of Aß42 levels for distinguishing autopsy-confirmed AD (n=235) from non-AD (n=127).[179, 186] Main results are reported in Table 5.7 (see Appendix Table

D.9 for details). No studies reported data on whether accuracy of CSF Aß42 levels for distinguishing between AD and non-AD dementia varies by participant characteristics.

Table 5.7 Summary of reported results for CSF Aß42 for autopsy-confirmed AD versus non-AD dementias*

Diagnostic Question	Studies, N (Patients Analyzed)	AD Prevalence, Median (Range)	Optimal Cut Points, (pg/mL), Median (Range)	SN, Median (Range)	SP, Median (Range)	TP per 1,000 Patients, Median (range)	TN per 1,000 Patients, Median (Range)	FP per 1,000 Patients, Median (Range)	FN per 1,000 Patients, Median (Range)
AD svs. non-AD	2 (n=362)[179, 186]	0.65 (0.65-0.66)	468 (436-500)	0.77 (0.74-0.79)	0.58 (0.53-0.62)	425 (373-477)	262 (220-303)	88 (41-135)	225 (168-282)
AD vs. FTLD	1 (n=157)[186]	0.89	385.1	0.57	0.88	520	188	167	135

Aß=beta amyloid; AD=Alzheimer's disease; CSF=cerebrospinal fluid; FN=false negative; FP=false positive; FTLD=frontotemporal lobar degeneration; SN=sensitivity; SP=specificity; TN=true negative; TP=true positive

*No eligible studies on the accuracy of CSF Aß42 measures for distinguishing AD from non-AD dementias reported data on harms.

CSF t-tau Levels

Five studies evaluated the accuracy of t-tau levels for distinguishing autopsy-confirmed AD (n=358) from non-AD (n=177).[175, 176, 179, 183, 186] Main results are in Table 5.8 (see Appendix Table D.9 for details). One study reported that accuracy of t-tau levels for distinguishing between autopsy-confirmed AD and non-AD did not significantly vary by patient age or sex.[176] No studies reported data on whether classification accuracy of t-tau levels varied as a function of other participant characteristics.

Table 5.8 Summary of reported results for CSF t-tau for autopsy-confirmed AD versus non-AD dementias*

Diagnostic Question	Studies, N (Patients Analyzed)	AD Prevalence, Median (Range)	Optimal Cut Points, (pg/mL), Median (range)	SN, Median (Range)	SP, Median (Range)	TP per 1,000 Patients, Median (Range)	TN per 1000 Patients, Median (Range)	FP per 1,000 Patients, Median (Range)	FN per 1,000 Patients, Median (Range)
AD vs. non-AD	3 (n=449)[176, 179, 186]	0.66 (0.65-0.85)	472.4 (361-472.5)	0.65 (0.62-0.72)	0.66 (0.64-0.69)	428 (401-609)	226 (103-228)	117 (46-129)	241 (228-244)
AD vs. LBD	1 (n=48)[183]	0.63	459	0.57	0.83	356	311	64	269
AD vs. FTLD	2 (n=195)[175, 186]	0.82 (0.50-0.89)	413 (403-423)	0.68 (0.68-0.68)	0.86 (0.82-0.90)	473 (340-606)	269 (89-450)	35 (19-50)	223 (160-285)
AD vs. VaD	1 (n=158)[186]	0.89	467.9	0.62	0.72	549	82	32	337

AD=Alzheimer's disease; CSF=cerebrospinal fluid; FN=false negative; FP=false positive; FTLD=frontotemporal lobar degeneration; LBD=Lewy body disease; SN=sensitivity; SP=specificity; TN=true negative; TP=true positive; VaD=vascular dementia

*No eligible studies on the accuracy of CSF t-tau measures for distinguishing AD from non-AD dementias reported data on harms.

CSF p-tau Levels

Three studies evaluated the accuracy of p-tau levels for distinguishing autopsy-confirmed AD (n=265) from pooled or individual types of non-AD dementia (n=145).[179, 184, 186] Main results are reported in Table 5.9 (See Appendix Table D.9 for details). No studies reported data on whether classification accuracy of CSF p-tau levels varies by participant characteristics.

Table 5.9 Summary of reported results for CSF p-tau for autopsy-confirmed AD versus non-AD dementias*

Diagnostic Question	Studies, N (Patients Analyzed)	AD Prevalence, Median (Range)	Optimal Cut Points (pg/mL), Median (Range)	SN, Median (Range)	SP, Median (Range)	TP per 1,000 Patients, Median (Range)	TN per 1,000 Patients, Median (Range)	FP per 1,000 Patients, Median (Range)	FN per 1,000 Patients, Median (Range)
AD vs. non-AD	2 (n=362)[179, 186]	0.85 (0.63-0.94)	50.4 (50.4-50.4)	0.79 (0.78-0.80)	0.61 (0.60-0.61)	597 (451-823)	94 (59-293)	48 (0-138)	170 (81-489)
AD vs. LBD	3 (n=325)[179, 184, 186]	0.84 (0.63-0.85)	52.8 (52.8-59.1)	0.77 (0.66-0.77)	0.71 (0.61-0.78)	563 481-631)	104 (97-293)	62 (42-83)	210 (144-290)
AD vs. FTLD	2 (n=262)[179, 186]	0.90 (0.89-0.90)	41.3 (35.3-47.3)	0.86 (0.81-0.91)	0.79 (0.77-0.80)	773 (722-823)	80 (76-83)	22 (19-25)	125 (81-169)
AD vs. VaD	2 (n=269)[179, 186]	0.87 (0.86-0.89)	50.0 (49.9-50.1)	0.80 (0.79-0.80)	0.65 (0.63-0.67)	692 (685-700)	84 (76-91)	45 (38-53)	179 (171-186)
AD vs. CJD	1 (n=101)[179]	0.93	78.5	0.48	1.00	459	59	0	489

AD=Alzheimer's disease; CJD=Creutzfelt-Jakob disease; CSF=cerebrospinal fluid; FN=false negative; FP=false positive; FTLD=frontotemporal lobar degeneration; LBD=Lewy body disease; SN=sensitivity; SP=specificity; TN=true negative; TP=true positive; VaD=vascular dementia

*No eligible studies on the accuracy of CSF p-tau measures for distinguishing AD from non-AD dementias reported data on harms.

CSF Aß42/t-tau or t-tau/Aß42 Ratio

One study evaluated the accuracy of the ratio of Aß42/t-tau[186] and two evaluated the accuracy of the ratio of t-tau/Aß42[175, 178] for distinguishing autopsy-confirmed AD (n=189) from pooled or individual types of non-AD dementia (n=106). Main results are reported in Table 5.10 (see Appendix Table D.9 for details).

In one of these studies, the sensitivity and specificity of a clinical evaluation to distinguish between autopsy-confirmed AD and FTLD were 0.67 and 0.87, respectively, whereas for the optimal t-tau/Aß42 ratio cut point of 0.34, sensitivity was 0.97 and specificity was 0.90.[178] These results suggested that the t-tau/Aß42 ratio may be more sensitive than clinical evaluation, but authors did not report whether t-tau/Aß42 ratio results increased diagnostic accuracy when added to clinical evaluation. No studies reported data on whether accuracy of the CSF Aß42/t-tau ratio or t-tau/Aß42 ratio for distinguishing autopsy-confirmed AD from non-AD dementia varies by participant characteristics.

Table 5.10 Summary of reported results for CSF Aß42/t-tau or t-tau/Aß42 ratio measures for autopsy-confirmed AD versus non-AD dementias*

Biomarker	Diagnostic Question	Studies, N (Patients Analyzed)	AD Prevalence, Median (Range)	Optimal Cut Points	SN, Median (Range)	SP, Median (Range)	TP per 1,000 Patients, Median (Range)	TN per 1,000 Patients, Median (Range)	FP per 1,000 Patients, Median (Range)	FN per 1,000 Patients, Median (Range)
Aß42/t-tau	AD vs. non-AD	1 (n=217)[186]	0.65	1.08	0.75	0.57	484	203	152	161
Aß42/t-tau	AD vs. LBD	1 (n=164)[186]	0.85	0.8	0.61	0.75	521	110	37	33
Aß42/t-tau	AD vs. FTLD	1 (n=157)[186]	0.89	0.97	0.70	0.94	624	102	6	268
t-tau/Aß42	AD vs. FTLD	2 (n=78)[175, 178]	0.63 (0.50-0.75)	0.70 (0.34-1.06)	0.88 (0.79-0.97)	0.94 (0.90-0.97)	562 (395-728)	355 (225-485)	20 (15-25)	64 (23-105)
Aß42/t-tau	AD vs. VaD	1 (n=158)[186]	0.89	0.72	0.56	0.78	496	89	25	390

Aß42=amyloid beta; AD=Alzheimer's disease; CSF=cerebrospinal fluid; FN=false negative; FP=false positive; FTLD=frontotemporal lobar degeneration; LBD=Lewy body disease; SN=sensitivity; SP=specificity; TN=true negative; TP=true positive; VaD=vascular dementia

*No eligible studies on the accuracy of CSF Aß42/t-tau ratio or t-tau/Aß42 ratio measures for distinguishing AD from non-AD dementias reported data on harms.

CSF Aß42/p-tau Ratio

One study evaluated the accuracy of the Aß42/p-tau ratio for distinguishing autopsy-confirmed AD (n=140) from pooled or individual types of non-AD dementia (n=77).[186] Main results are reported in Table 5.11 (see Appendix Table D.9 for details). No studies reported data on whether accuracy of the CSF Aß42/p-tau ratio for distinguishing autopsy-confirmed AD from non-AD dementia varies by participant characteristics.

Table 5.11 Summary of reported results for CSF Aß42/p-tau ratio measures for autopsy-confirmed AD versus non-AD dementias*

Diagnostic Question	Studies, N (Patients Analyzed)	AD Prevalence, Median (Range)	Optimal Cut Points	SN, Median (Range)	SP, Median (Range)	TP per 1,000 Patients, Median (Range)	TN per 1,000 Patients, Median (Range)	FP per 1,000 Patients, Median (Range)	FN per 1,000 Patients, Median (Range)
AD vs. non-AD	1 (n=217)[186]	0.65	9.11	0.83	0.60	535	213	142	110
AD vs. LBD	1 (n=164)[186]	0.85	8.46	0.80	0.58	683	85	61	171
AD vs. FTLD	1 (n=157)[186]	0.89	9.77	0.86	0.82	767	89	19	125
AD vs. VaD	1 (n=168)[186]	0.89	5.3	0.56	0.78	496	89	25	390

Aß42=amyloid beta; AD=Alzheimer's disease; CSF=cerebrospinal fluid; FN=false negative; FP=false positive; FTLD=frontotemporal lobar degeneration; LBD=Lewy body disease; SN=sensitivity; SP=specificity; TN=true negative; TP=true positive; VaD=vascular dementia

*No eligible studies on the accuracy of CSF Aß42/p-tau ratio for distinguishing AD from non-AD dementias reported data on harms.

Combinations of CSF Tests

Aß42 + p-tau

AD Versus FTLD

One study evaluated the accuracy of the combination of Aß42, t-tau and p-tau for distinguishing autopsy-confirmed AD (n=61) from FTLD (n=14).[188] CSF biomarkers were analyzed using both ELISA and Luminex assays. Whereas clinical evaluation had a sensitivity of 0.80 and specificity of 0.80, a regression model including CSF Aβ42 and p-tau measured using the Luminex assay had a sensitivity of 0.98 and specificity of 0.93. CSF testing improved accuracy compared to clinical evaluation mostly by recategorizing participants with autopsy-confirmed AD who had been incorrectly clinically classified as having FTLD. CSF testing also corrected a small number of false positives and incorrectly recategorized a small number of true positives from clinical evaluation. Authors also created a regression model of CSF markers using ELISA assay results, but did not report how this affected classification accuracy compared with clinical evaluation.

Aß42 + t-tau

AD Versus Non-AD Dementia

One study evaluated the accuracy of the combination of Aß42 and t-tau for distinguishing autopsy-confirmed AD (n=66) from a pooled group including both participants with non-AD

dementia and other neurological diseases (n=39) (see Appendix Table D.9 for details).[187] The combination of Aß42 and t-tau was categorized as normal or abnormal, without specifying how this was defined, and had a sensitivity of 0.74 and specificity of 0.90. In a nonidentical, but overlapping sample of participants (n=108, including 79 with clinical AD and 29 with a clinical diagnosis of 'other dementia'), sensitivity and specificity of clinical evaluation were 0.85 and 0.67, respectively.

Aß42/Aß40 Ratio + Aß42 + Aß40 + p-tau

AD Versus Non-AD Dementia

One study evaluated the accuracy of the combination of Aß42/Aß40 ratio + Aß42 + Aß40 + p-tau for distinguishing autopsy-confirmed AD (n=73) from non-AD dementia (n=38) (see Appendix Table D.9 for details).[183] The different CSF biomarkers were incorporated into a decision tree model to optimally categorize participants. The best decision tree model had a sensitivity and specificity of 0.79 and 0.76, respectively.

Variation in Classification Accuracy by Participant Characteristics

No studies reported data on whether accuracy of combinations of CSF biomarkers for distinguishing autopsy-confirmed AD from non-AD dementia varies by participant characteristics.

Comparative Accuracy of CSF Biomarkers

Study Characteristics

Among the seven studies (n=780) that evaluated the accuracy of at least two different CSF biomarkers for distinguishing AD from either pooled non-AD dementia or from individual types of non-AD dementia,[175, 176, 178, 179, 183, 184, 186] three reported statistical tests to directly compare accuracy between individual CSF biomarkers or combinations.[176, 179, 186]

Classification Accuracy

AD Versus Non-AD Dementias

For distinguishing autopsy-confirmed AD from non-AD, two studies reported that p-tau performed better than t-tau (AUC 0.72 vs. 0.59, $p<0.001$[186] and $p=0.048$[179] respectively), but that p-tau did not differ from Aβ42 ($p\geq0.408$ in both studies).[179, 186] In one of these studies, p-tau classification accuracy also did not differ from the Aβ42/t-tau ratio (AUC 0.72 vs. 0.68, p=0.29) or the Aβ42/p-tau ratio (AUC 0.72 vs. 0.77, p=0.10).[186] This study also reported that the Aβ42/p-tau ratio performed better than Aβ42 (AUC 0.77 vs. 0.68, p=0.004), t-tau (AUC 0.77 vs. 0.59, p<0.001), and the Aβ42/t-tau ratio (AUC 0.77 vs. 0.68, p=0.001).[186] In another study, one model including t-tau alone and a separate model including both t-tau and Aβ were no different for distinguishing autopsy-confirmed AD (n=74) from non-AD dementia (n=13) (AUC 0.80 vs. 0.81, p=0.60).[176] In a fourth study, in a subset of individuals in whom clinical evaluation had not been able to discriminate between AD and non-AD dementia, a sequential decision tree that included p-tau and Aβ42/Aβ40 correctly classified 7 of 16 of these individuals, and a decision tree that also included Aβ40 correctly categorized 10 of the 16 (p=0.30 [calculated by review authors]).[183]

AD Versus FTLD

For distinguishing between autopsy-confirmed AD (n=140) and FTLD (n=17), one study found that the Aβ42/p-tau ratio performed better than Aβ42 (AUC 0.89 vs. 0.78, p=0.020) or t-tau alone (AUC 0.89 vs. 0.75, p=0.004), but not differently than the Aβ42/t-tau ratio (AUC 0.89 vs. 0.86, p=0.28).[186] P-tau did not significantly differ from Aβ42, t-tau, or the Aβ42/t-tau ratio ($p \geq 0.12$ for all comparisons). In two other studies (n=78), t-tau/Aβ42 ratio had a numerically higher AUC compared with other CSF tests (t-tau and Aβ42 in both, and p-tau and p-tau/Aβ42 ratio in one), but no test for statistical significance was reported.[175, 178]

AD Versus LBD

For distinguishing between autopsy-confirmed AD (n=140) and LBD (n=24), one study found that the Aβ42/t-tau ratio performed no differently than p-tau or the Aβ42/p-tau ratio ($p \geq 0.36$ for both comparisons).[186] In a second study (n=48), p-tau appeared to have a higher sensitivity compared with t-tau (0.77 vs. 0.57), with similar specificity (0.78 vs. 0.83, respectively), but no test for statistical significance was reported.[184]

AD Versus CJD

For distinguishing between autopsy-confirmed AD (n=140) and CJD (n=13), one study found that the p-tau/t-tau ratio performed better than Aβ42 (p=0.004), t-tau (p=0.04), or the Aβ42/p-tau ratio (p=0.003), but the Aβ42/p-tau ratio did not significantly differ from Aβ42 or t-tau ($p \geq 0.22$ for both comparisons).[186]

AD Versus VaD

For distinguishing between autopsy-confirmed AD (n=140) and VaD (n=18), one study found that neither p-tau nor the Aβ42/p-tau ratio significantly differed from either t-tau or the Aβ42/t-tau ratio ($p \geq 0.37$ for all comparisons).[186]

Variation in Classification Accuracy by Participant Characteristics

No studies reported data on whether the comparative accuracy of different CSF biomarkers for distinguishing autopsy-confirmed AD from non-AD dementia varies by participant characteristics.

Comparative Accuracy of CSF Assays

Study Characteristics

One study compared the accuracy of ELISA versus Luminex assays for Aβ42, t-tau, and p-tau for distinguishing between autopsy-confirmed AD (n=110) and FTLD (n=26).[188] The ELISA assay was from INNOTEST (Ghent, Belgium), while the Luminex xMAP platform was from INNOBIA AlzBio3, Immunogenetics (Ghent, Belgium). The AD group (n=110) included participants with "pure" AD (n=71), LBD (n=1), AD-LBD (n=24), AD-FTLD (n=2), FTLD-AD (n=6), or LBD-AD (n=6).

Classification Accuracy

Regression analysis was used in part of the study cohort to select the combination of biomarkers that maximized accuracy and kappa index distinguishing between participants with AD and FTLD. This model then was applied to the remaining cohort participants to obtain

sensitivity, specificity, and the ROC curve. However, the derivation of these models was performed separately for the ELISA and Luminex assays, and the biomarkers in the final ELISA model were t-tau and Aβ42, while those in the final Luminex model were p-tau and Aβ42.

In a supplement, this study reported that the sensitivity and specificity for clinical evaluation to distinguish AD from non-AD when not counting participants who had AD pathology mixed with another neuropathological diagnosis (i.e., excluding mixed AD) were 0.77 and 0.64, respectively. The sensitivity and specificity for clinical evaluation to distinguish AD from non-AD when counting participants with mixed AD were 0.71 and 0.83, respectively. For distinguishing AD from FTLD, when not counting participants with mixed AD or mixed FTLD, the sensitivity and specificity of clinical evaluation were 0.89 and 0.81, respectively. When including participants with mixed AD and mixed FTD, sensitivity and specificity of clinical evaluation for distinguishing AD from FTLD were 0.96 and 0.77, respectively. For ELISA, the model sensitivity and specificity for distinguishing AD from FTLD were 0.90 and 0.82, respectively. For Luminex, the model sensitivity and specificity for distinguishing AD from FTLD were 1.0 and 0.88, respectively. The study did not report statistical testing to directly compare classification accuracy of clinical evaluation alone with CSF testing added to clinical evaluation.

Variation in Classification Accuracy by Participant Characteristics

The accuracy of the ELISA and Luminex assays for distinguishing between AD and non-AD dementia did not differ when participants were stratified by cognitive impairment ($p \geq 0.24$ for both assays). Otherwise, no studies reported data on whether the comparative accuracy of different CSF biomarker assays for identifying autopsy-confirmed AD varies by participant characteristics.

Blood Biomarkers

No studies reported data on the accuracy of blood biomarkers for distinguishing autopsy-confirmed AD from non-AD dementia.

Chapter 6. Key Question 3: Prescription Drugs Versus Placebo for Cognition, Function, and Quality of Life

Donepezil Versus Placebo

Key Messages

- In older adults with mild to moderate clinical Alzheimer's-type dementia (CATD), evidence for donepezil versus placebo showed:
    - Small statistically significant improvements for cognition (low strength of evidence [SOE]), global staging (moderate SOE), and clinical impression of change (moderate SOE).
    - Increased risk for serious adverse events (low SOE) and withdrawals due to adverse events (low SOE) at standard doses (targeting 10 mg/day).
    - Insufficient evidence for function or quality of life.
- In older adults with moderate to severe CATD, evidence for donepezil versus placebo showed:
    - Small statistically significant improvements for cognition (moderate SOE), function (low SOE), and clinical impression of change (low SOE).
    - No difference in serious adverse events (low SOE), but increased withdrawals due to adverse events (low SOE) at standard doses.
    - Insufficient evidence for quality of life and global staging.
- Efficacy compared with placebo was increased for both 10 mg/day and 5 mg/day donepezil; though 10 mg/day donepezil increased risk of serious adverse events and withdrawals due to adverse events compared with placebo, 5 mg/day donepezil and placebo did not differ for these harms.

Eligible Studies

Based on a high-quality systematic review published in 2018,[195] we identified 24 eligible publications reporting 17 unique trials of ≥24 weeks duration that compared donepezil with placebo, reported results for cognition, function, quality of life, global staging, clinical impression of change, or harms, and were considered low or medium risk of bias.[196-219] We found one additional eligible study with low or medium risk of bias (ROB) not included in this prior review,[220] bringing to 18 the total included and analyzed in the current review.

Four trials that directly compared donepezil 5 mg/day with 10 mg/day[204, 211] and slow-release donepezil 23 mg/day with standard-release donepezil 10 mg/day[221-223] are reported in a section of this chapter titled "Donepezil Dosage Comparisons."

Appendix Tables E.1-E.10 provide evidence tables, summary ROB assessments, and strength of evidence for key comparisons and outcomes.

Baseline Study Characteristics

Characteristics of the 4,742 participants enrolled in the 18 analyzed donepezil versus placebo trials are shown in Table 6.1. Participants were primarily community dwelling, but two trials enrolled participants in residential care.[213, 217] Most study participants were categorized with mild or moderate CATD (e.g., Mini-Mental State Exam [MMSE] score 10 to 26) and approximately

one-quarter of participants were in studies restricted to individuals with severe CATD.[196, 204, 205, 219] All trials lasted 24 to 26 weeks except for two of 52 to 54 weeks.[209, 217] Most often, donepezil dosing was titrated up to 10 mg/day, but three trials compared fixed doses of 5 mg/day and 10 mg/day to placebo.[197, 204, 211]

Table 6.1. Baseline characteristics of donepezil versus placebo trials

Characteristic	N, Mean, or % (Study Range)	Trials Reporting, N
Number of participants enrolled	4,742 (35 to 818)	18
Age, mean	75 (67 to 86)	18
Men, %	35 (18 to 46)	18
Race – white, %	71 (0 to 100)	10
Alzheimer's disease severity*	**NA**	18
Early-stage, %	3 (n=153)	1
Mild or moderate, %	61 (n=2,870)	11
Moderate or severe, %	6 (n=290)	1
Severe, %	26 (n=1,206)	4
Any (included mild, moderate, or severe), %	5 (n=208)	1
MMSE, mean	15 (6 to 24)	17

MMSE=Mini-Mental State Examination; NA=not applicable
*Alzheimer's disease severity was based on that reported by the individual trials.

Outcomes

Table 6.2 summarizes the primary efficacy and harms results between donepezil and placebo. For efficacy, in patients with mild to moderate CATD treated for 24 weeks, donepezil improved several outcomes compared with placebo. For treatment up to 10 mg/day, these included small mean improvements in cognition (weighted mean difference in MMSE change, 1.0 [95% confidence interval (CI), 0.7 to 1.4]; standardized mean difference (SMD), 0.30 [95% CI, 0.16 to 0.44]), increased likelihood that cognition improved (absolute risk difference [ARD], 19%; number needed to treat [NNT], 5.3) or did not worsen (ARD, 23%; NNT, 4.3), and increased likelihood clinical impression of change improved (ARD, 12%; NNT, 8.3) or did not worsen (ARD, 14%; NNT, 7.2). However, donepezil did not increase the likelihood of a moderate or marked improvement in clinical impression of change and evidence was insufficient to draw conclusions about function or quality of life. In a 1-year trial, donepezil was associated with less worsening in MMSE (-0.5 vs. -2.0, $p<0.001$),[217] while a single trial reporting on change in patient residence to a different level of independence found that through 54 weeks two participants (0.9%) each in the donepezil and placebo groups entered a nursing facility.[209] For patients with moderate to severe CATD treated for 24 to 26 weeks, compared with placebo, donepezil resulted in small mean improvements in cognition and function, and increased likelihood that clinical impression of change improved (ARD, 10%; NNT, 10) or did not worsen (ARD, 11.2%; NNT, 8.9). However, no studies of patients with moderate to severe CATD reported data on brief multidomain cognitive batteries, quality of life or staging. For treatment with 5 mg/day, efficacy compared with placebo appeared similar in magnitude to that for 10 mg/day compared with placebo, both in patients with mild to moderate CATD and moderate to severe CATD.

For harms, donepezil up to 10 mg/day increased risk of withdrawals due to adverse events in patients with mild to moderate CATD and those with moderate to severe CATD (both low SOE), and increased serious adverse events only in patients with mild to moderate CATD (low SOE) (Table 6.2). Donepezil and placebo did not statistically differ for confusion (5.8% vs. 6.3%; RR, 0.91 [95% CI, 0.61 to 1.38], n=4 trials),[197, 199, 213, 217] falls (7% in each arm, n=3 trials),[204, 212, 219]

restlessness (2% in each arm, p=0.44; n=2 trials),[203, 204] tremor (8% vs. 2%, p=0.07, n=1 trial),[213] abnormal gait (12% vs. 8%, p=0.33, respectively; n=1 trial)PN Tariot, JL Cummings [213] or mortality (1.4% vs. 2.3%; Peto odds ratio [OR], 0.68 [95% CI, 0.43 to 1.08], n=12 trials).[196, 197, 199, 204, 205, 207, 209, 211, 213, 217, 220, 224] Donepezil 5 mg/day did not increase risk of either serious adverse events or withdrawals due to adverse events compared with placebo. No studies reported data on somnolence or stroke.

Appendix Tables E.4-E.10 provide detailed evidence tables and assessments of strength of evidence for key comparisons and outcomes.

Table 6.2. Summary of findings for primary outcomes: donepezil versus placebo

Domain	# Studies/ Design (n Analyzed) Timing	CATD Population	Findings (Incidence, Change from Baseline)	Strength of Evidence
Cognition-Brief Stand-Alone Tests	4 RCT (n=806) 24 weeks	Mild to moderate	**Mean MMSE change:** *Up to 10 mg/d:* Favors donepezil (SMD, 0.30 [95% CI, 0.16 to 0.44]; 4 trials, n=806)[208, 211, 213, 220] *5 mg/d:* Favors donepezil (SMD, 0.29 [95% CI, 0.19 to 0.39]; 1 trial, n=301)[211]	Low
	4 RCT (n=1,102) 24-26 weeks	Moderate to severe	**Mean MMSE change:** *Up to 10 mg/d:* Favors donepezil (SMD, 0.29 [95% CI, 0.17 to 0.40]; 4 trials, n=1,102)[196, 199, 205, 224]	Low
Cognition-Brief Multidomain Batteries	8 RCT (n=1,654) 24 weeks	Mild to moderate†	**Likelihood ADAS-Cog unchanged/improved (≥0):** *10 mg/d:* Favors donepezil (80% vs. 58%; ARD, 23% [95% CI, 14% to 32%]; NNTB, 4 [95% CI, 3 to 7]; RR, 1.39 [95% CI, 1.20 to 1.62]; 1 trial, n=445)[211] **Likelihood ≥4-point ADAS-Cog improvement:** *10 mg/d:* Favors donepezil (46% vs. 27%; ARD, 19% [95% CI, 10% to 29%]; NNTB, 5 [95% CI, 3 to 10]; RR, 1.70 [95% CI, 1.27 to 2.28]; 1 trial, n=445)[211] **Mean ADAS-Cog change:** *10 mg/d:* Favors donepezil (SMD, -0.39 [95% CI, -0.54 to -0.25]; 8 trials, n=1,654)[197, 203, 207, 210-212, 214, 220] *5 mg/d:* Favors donepezil (SMD, -0.32 [95% CI, --0.44 to -0.20]).[197]	Low
Cognition-Domain Level Tests Typically Part of a Larger Battery	1 RCT (n=153)[212] 24 weeks	Early stage	**Computerized Memory Battery Test:** *10 mg/d:* No overall results reported; donepezil statistically improved vs. placebo 4 of 8 components, not statistically different in 4 of 8 components.	Insufficient
Function	1 RCT (n=246) 24 weeks	Mild to moderate	**Mean ADCS-ADL change:** *Up to 10 mg/d:* SMD, -0.02 [95% CI, -0.27 to 0.23]; 1 trial, n=246)[220]	Insufficient
	3 RCT (n=733) 24-26 weeks	Severe	**Mean ADCS-ADL change:‡** *Up to 10 mg/d:* Favors donepezil (SMD, 0.18 [95% CI, 0.03 to 0.32]; 3 trials, n=733)[196, 204, 219] *5 mg/d:* SMD, 0.18 [95% CI, -0.10 to 0.46]; 1 trial, n=198)[204]	Low (only for up to 10 mg/d dose)
Quality of Life	2 RCT (n=969) 24 weeks	Mild to moderate	**Mean participant-rated QOL change:** *Up to 10 mg/d:* SMD, -0.07 (95% CI, -0.21 to 0.06); 2 trials, n=815 [197, 211] *5 mg/d*: Statistically favored donepezil (only graphical data reported, p=0.05; 1 trial, n=316)[211]	Insufficient

Domain	# Studies/ Design (n Analyzed) Timing	CATD Population	Findings (Incidence, Change from Baseline)	Strength of Evidence
Staging	4 RCT (n=1,256) 24 weeks	Mild to moderate	**Mean global staging (CDR) change:**† *Up to 10 mg/d*: Favors donepezil SMD, -0.38 [95% CI, -0.50 to -0.25])[197, 203, 211, 213] *5 mg/d:*[197, 211] Favors donepezil (SMD, -0.36 [95% CI, -0.53 to -0.20])[197, 211]	Moderate
Clinical Impression of Change*	4 RCT (n=1,585) 24 weeks	Mild to moderate	**Likelihood unchanged/improved:** *Up to 10 mg/d:* Favors donepezil (67% vs. 53%; ARD, 14% [95% CI, 9% to 19%]; NNTB, 7 [95% CI, 5 to 11]; RR, 1.29 [95% CI, 1.18 to 1.41]; 4 trials, n=1,585)[197, 203, 207, 211] *5 mg/d:* Favors donepezil (65% vs. 52%; ARD, 13% [95% CI, 7 to 19]; NNTB, 8 [95% CI, 5 to 14]; RR, 1.26 [95% CI, 1.14 to 1.39]; 3 trials, n=1075)[197, 203, 211] **Likelihood improved:** *10 mg/d:* Favors donepezil (28% vs. 16%; ARD, 12% [95% CI, 8% to 16%]; NNTB, 8 [95% CI, 6 to 13]; RR, 1.89 [95% CI, 1.46 to 2.45]; 4 trials, n=1,585)[197, 203, 207, 211] *5 mg/d:* Favors donepezil (29% vs. 14%; ARD, 15% [95% CI, 10 to 19]; NNTB, 7 [95% CI, 5 to 10]; RR, 2.02 [95% CI, 1.44 to 2.82]; 3 trials, n=1075)[197, 203, 211] **Likelihood moderately/markedly improved:** *10 mg/d:* No difference (15% vs. 11%; ARD, 3.2% [95% CI, -3.6% to 9.9%]; NNTB, 31 [95% CI, NNTB 10 to ∞ to NNTH 28]; RR, 1.28 [95% CI, 0.76 to 2.17]; 2 trials, n=383)[203, 205, 207] *5 mg/d:* No difference (16% vs. 12%; ARD, 4.0% [95% CI, -4.2 to 12.3]; NNTB, 25 [95% CI, NNTB 8 to ∞ to NNTH 24]; RR, 1.35 [95% CI, 0.73 to 2.50]; 1 trial, n=263)[203] **Mean CIBIC-Plus score:** *10 mg/d:* Favors donepezil (SMD 1.17 (95% CI, 0.50 to 1.85); 1 trial, n=40)[208]	Moderate

Domain	# Studies/ Design (n Analyzed) Timing	CATD Population	Findings (Incidence, Change from Baseline)	Strength of Evidence
	5 RCT (n=1,398) 24-26 weeks	Severe (79%) or moderate to severe (21%)	**Likelihood unchanged/improved:** *Up to 10 mg/d:* Favors donepezil (69% vs. 56%; ARD, 13% [95% CI, 8% to 18]; NNTB, 7 [95% CI, 6 to 13]; RR, 1.23 [95% CI, 1.10 to 1.37]; 5 trials, n=1,398)[196, 199, 204, 205, 218] *5 mg/d:* No difference (63% vs. 54%; ARD, 9% [95% CI, -5 to 23]; NNTB, 11 [95% CI, NNTB 4 to ∞ to NNTH 20]; RR, 1.17 [95% CI, 0.92 to 1.48]; 1 trial, n=194)[204] **Likelihood improved:** *Up to 10 mg/d:* Favors donepezil (38% vs. 28%; ARD, 10% [95% CI, 5% to 15%]; NNTB, 10 [95% CI, 7 to 20]; RR, 1.34 [95% CI, 1.13 to 1.58]; 4 trials, n=1,152)[196, 204, 205, 219] *5 mg/d:* No difference (33% vs. 24%; ARD, 9% [95% CI, -4 to 22]; NNTB, 11 [95% CI, NNTB 5 to ∞ to NNTH 25]; RR, 1.39 [95% CI, 0.88 to 2.19]; 1 trial, n=194)[204] **Likelihood moderately/markedly improved:** *Up to 10 mg/d:* No difference (14% vs. 12%; ARD, 2.1% [95% CI, -3.8% to 8.0%]; NNTB, 48 [95% CI, NNTB 13 to ∞ to NNTH 26]; RR, 1.41 [95% CI, 0.90 to 2.21]; 2 trials, n=508)[204, 224] *5 mg/d:* No difference (4% vs. 6%; ARD, -2% [95% CI, -8 to 5]; NNTB, 50 [95% CI, NNTB 20 to ∞ to NNTH 12]; RR, 0.74 [95% CI, 0.22 to 2.54]; 1 trial, n=194)[204] **Mean CIBIC-Plus score:** *10 mg/d:* Favors donepezil (graphical display only)[199]	Low
SAE	8 RCT (n=2,521) 24-54 weeks	Mild to moderate	*Up to 10 mg/d:* Donepezil increased risk (10.7% vs. 8.7%; ARD, 2% [95% CI, -0.3 to 4.3]; NNTH, 50 [95% CI, NNTH 23 to ∞ to NNTB 333]; RR, 1.32 [95% CI, 1.03 to 1.68]; 8 trials, n=2,521)[197, 207, 209, 211-213, 217, 220] *5 mg/d:* No difference (4.5% vs. 5.6%; ARD, -1% [95% CI, -5.8 to 3.8]; NNTB, 100 [95% CI, NNTB 17 to ∞ to NNTH 26]; RR, 0.82 [95% CI, 0.31 to 2.14]; 1 trial, n=316) [211]	Low
	4 RCT (n=1,153) 24-26 weeks	Severe (75%) or moderate to severe (25%)	*Up to 10 mg/d:* No difference (13.3% vs. 15.6%; ARD, -2.3% [95% CI, -6.4 to 1.8]; NNTB, 43 [95% CI, NNTB 16 to ∞ to NNTH 56]; RR, 0.87 [95% CI, 0.66 to 1.15]; 4 trials, n=1,153)[199, 204, 205, 219] *5 mg/d:* No difference (11.9% vs. 14.2%; ARD, -2.4 [95% CI, -11.6 to 6.8]; NNTB, 42 [95% CI, NNTB 9 to ∞ to NNTH 15]; RR, 0.83 [95% CI, 0.41 to 1.69]; 1 trial, n=206)[204]	Low
Withdrawals Due to Adverse Events	11 RCT (n=3,180) 24-54 weeks	Mild to moderate	*Up to 10 mg/d:* No difference (10.0% vs. 7.4%; ARD, 2.6% [95% CI, 0.7 to 4.6]; NNTH, 38 [95% CI, 22 to 143]; RR, 1.22 [95% CI, 0.93 to 1.62]; 11 trials, n=3,180)[197, 203, 206-209, 211-213, 217, 220] *5 mg/d:* No difference (7.8% vs. 8.7%; ARD, -1% [95% CI, -4.6 to 2.7]; NNTB, 100 [95% CI, NNTB 22 to ∞ to NNTH 37]; RR, 0.89 [95% CI, 0.57 to 1.39]; 2 trials, n=861) [197, 211]	Low

Domain	# Studies/ Design (n Analyzed) Timing	CATD Population	Findings (Incidence, Change from Baseline)	Strength of Evidence
	7 RCT (n=1,559) 24-26 weeks	Severe (81%) or moderate to severe (19%)	*Up to 10 mg/d:* Donepezil increased risk (12.6% vs. 8.1%; ARD, 4.5% [95% CI, 1.5 to 7.6]; NNTH, 23 [95% CI, 14 to 67]; RR, 1.54 [95% CI, 1.13 to 2.10]; 5 trials, n=1,559)[196, 199, 204, 205, 210, 214, 219] *5 mg/d:* No difference (8.0% vs. 10.5%; ARD, -2.6 [95% CI, -10.4 to 5.3]; NNTB, 38 [95% CI, NNTB 10 to ∞ to NNTH 19]; RR, 0.76 [95% CI, 0.32 to 1.80]; 1 trial, n=206)[204]	Low

ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS-ADL=Alzheimer Disease Cooperative Study–Activities of Daily Living–Severe Version; ARD=absolute risk difference; CATD=Clinical Alzheimer's-type dementia; CDR= Clinical Dementia Rating Scale; CGIC= Clinical Global Impression of Improvement; CI=confidence interval; CIBIC-Plus= Clinician's Interview-Based Impression of Change with caregiver input; MMSE=Mini-Mental State Examination; NNTB=number needed to treat to produce 1 additional benefit; NNTH=number needed to treat to produce 1 additional harm; QOL=quality of life; RCT=randomized controlled trial; RR=relative risk; SAE=serious adverse events; SMD=standardized mean difference

*Clinical impression of change was measured using the -Plus (k=6 trials, n=2,256)[196, 197, 204, 205, 207, 211] or CGIC (k=2 trials, n=481).[203, 219]

†One trial reported that CDR-Sum of the Boxes did not significantly differ between treatment groups, but provided no data.[212]

‡Other function measures reported in single trials included the Interview for Deterioration in Daily living activities in Dementia[197] and the Disability Assessment for Dementia.[199, 207]

Variation in Outcomes by Participant Characteristics

No studies reported whether the effect of donepezil versus placebo on cognition, function, quality of life, global staging, clinical impression of change, or harms varied as a function of participant characteristics. Two trials performed an exploratory analysis based on disease severity at baseline as defined by MMSE score.[207, 220] One of these trials reported that donepezil improved ADAS-Cog scores compared with placebo in participants with baseline MMSE ≤18, but not in those with baseline MMSE >18.[207] The second trial reported that donepezil and placebo did not differ for change from baseline for Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) or Clinician's Interview-Based Impression of Change with caregiver input (CIBIC-Plus) in either participants with baseline MMSE 20-26 or baseline MMSE 10-19.[220] However, neither trial reported a test for interaction.

Donepezil Dosage Comparisons

Key Messages

- In older adults with CATD, the evidence for donepezil 23 mg/day compared with 10 mg/day showed:
  - No difference in cognition, function, or clinical impression of change (all low SOE).
  - Insufficient evidence to draw conclusions about quality of life.
  - Increased risk of withdrawals due to adverse events (moderate SOE), but no difference for serious adverse events (low SOE).
- In older adults with mild to moderate CATD, the evidence for donepezil 10 mg/day compared with 5 mg/day showed:
  - Mixed results for cognition (low SOE).
  - No difference in clinical impression of change (low SOE).

    - Insufficient evidence for function, quality of life, or staging.
    - Increased risk of serious adverse events (low SOE) and withdrawals due to adverse events (moderate SOE).
- In older adults with moderate to severe CATD, the evidence for donepezil 10 mg/day compared with 5 mg/day showed:
    - No difference in cognition or function (both low SOE).
    - Improvement for clinical impression of change (low SOE).
    - Insufficient evidence to draw conclusions about quality of life, staging, serious adverse events, or withdrawals due to adverse events.

Eligible Studies

Based on a high-quality systematic review published in 2018,[195] we identified five eligible publications of five unique trials of at least 24 weeks duration that compared donepezil doses and reported results for cognition, function, quality of life, staging, clinical impression of change or harms. These included two that compared high-dose 23 mg/day donepezil to standard-dose 10 mg/day donepezil,[221, 223] and three that compared 10 mg/day donepezil to 5 mg/day donepezil.[197, 204, 211] We found no additional eligible studies published after the May 2017 search date of this previous systematic review. Appendix Tables E.4-E.10 provide evidence tables, summary ROB assessments, and strength of evidence for key comparisons and outcomes.

Baseline Study Characteristics

Characteristics of the 2,886 participants enrolled in the five analyzed trials are shown in Table 6.3. Most participants were community-dwelling and lived with a caregiver. All trials were 24 weeks in duration. Two trials compared sustained-release high-dose 23 mg/day donepezil with standard-dose 10 mg/day donepezil.[221, 223] Three trials compared 10 mg/day donepezil with 5 mg/day donepezil.[197, 204, 211]

Table 6.3. Baseline characteristics of donepezil versus donepezil trials

Characteristic	N, Mean, or % (Study Range)	Trials Reporting, N
Number of participants enrolled	2,886 (351 to 1467)	5
Age, mean	74 (72 to 78)	5
Men, %	36 (21 to 41)	5
Race – % white	72 (0 to 99)	4
Alzheimer's disease severity*	**NA**	2
Mild†, %	25 (n=681)	2
Moderate†, %	6 (n=162)	2
Mild to Moderate†, %	30 (n=855)	2
Moderate to severe, %	51 (n=1434)	1
Severe, %	19 (n=528)	2
MMSE, mean	14 (8 to 20)	5

MMSE=Mini-Mental State Examination; NA=not applicable

*Alzheimer's disease severity was based on that reported by the individual trials.

†Participants categorized as mild severity, and those categorized separately as moderate severity, also were included together as part of the population of mild to moderate severity.

Outcomes

Table 6.4 summarizes the primary efficacy and harms results from trials that directly compared different donepezil doses. For efficacy, donepezil 23 mg/day and 10 mg/day did not differ for cognition, function, or clinical impression of change (all low SOE). By comparison, donepezil 10 mg/day increased the likelihood of improvement for brief multidomain cognitive tests and clinical impression of change compared with 5 mg/day when evaluated using categorical responder analyses but not as continuous outcome measures (all low SOE). Donepezil 10 mg/day and 5 mg/day did not differ for brief cognitive tests commonly used as stand-alone tests or for function tests (all low SOE). No studies that directly compared different donepezil doses reported data on quality of life, disease staging, or change in residence to a different level of independence.

For harms, when directly compared, donepezil 23 mg/day and 10 mg/day did not differ for serious adverse events (low SOE), but the higher dose increased risk of withdrawals due to adverse events (moderate SOE). Donepezil 23 mg/day and 10 mg/day doses did not statistically differ for risk of confusion (1.3% vs. 1.1%, p=0.82; 2 trials),[221, 223] somnolence (2.1 % vs. 0.8%, p=0.08; 2 trials),[221, 223] falls considered serious treatment-emergent adverse events (0.6% vs. 0.4%),[221, 223] or mortality (0.7% vs. 0.9%, p=0.46; 2 trials).[221, 223] No studies comparing these doses reported data on extrapyramidal symptoms or stroke. When directly compared with donepezil 5 mg/day, the higher dose of 10 mg/day appeared to increase risk of both serious adverse events and withdrawals due to adverse events. However, donepezil 10 mg/day and 5 mg/day doses did not statistically differ for risk of confusion (7% vs. 6%, 1 trial),[197] falls (6.3% vs. 6.9%; 1 trial)[204] or mortality (1.0% vs. 0.6%; Peto odds ratio 1.69 [95% CI, 0.42 to 6.80]; 3 trials).[197, 204, 211] No studies comparing these doses reported data on somnolence, extrapyramidal symptoms or stroke.

Appendix Tables E.4-E.10 provide detailed evidence tables and assessments of strength of evidence for key comparisons and outcomes.

Table 6.4. Summary of findings for primary outcomes: donepezil dose comparisons

Domain	# Studies/ Design (n Analyzed) Timing	CATD Population	Findings (Incidence, Change from Baseline)	Strength of Evidence
Cognition-Brief Stand-Alone Tests	1 RCT (n=303) 24 weeks	Mild to moderate	**Mean change in MMSE:** *10 mg/d vs. 5 mg/d*: No difference (SMD, 0.04 [95% CI, -0.29 to 0.16]; 1 trial, n=303)[211]	Low
	1 RCT (n=1,370) 24 weeks	Moderate to severe	**Mean change in MMSE:** *23 mg/d vs. 10 mg/d:* No difference (SMD, 0.04 [95% CI, -0.07 to 0.15]; 1 trial, n=1,370)[221]	Low
Cognition-Brief Multi-Domain Batteries	1 RCT (n=302) 24 weeks	Mild to moderate	**Likelihood ≥4-point ADAS-Cog improvement:** *10 mg/d vs. 5 mg/d:* Favors 10 mg/d (54% vs. 38%; ARD, 16% [95% CI, 4 to 27]; NNTB, 6 [95% CI, 4 to 25]; RR, 1.42 [95% CI, 1.11 to 1.82]; 1 trial, n=302)[211] **Mean ADAS-Cog change:** *10 mg/d vs. 5 mg/d:* No difference (SMD, -0.06 [95% CI, -0.29 to 0.16]; 1 trial, n=302)[211]	Low for each
	3 RCT (n=1,892) 24 weeks	Moderate to severe	**Mean change in SIB:** *23 mg/d vs. 10 mg/d*: No difference (SMD, 0.10, [95% CI, -0.02 to 0.21]; 2 trials, n=1,704)[221, 223] *10 mg/d vs. 5 mg/d*: No difference (SMD, 0.20 [95% CI, -0.09 to 0.48]; 1 trial, n=188)[204]	*23 vs 10 mg/d*: Low *10 vs 5 mg/d*: Low

Domain	# Studies/ Design (n Analyzed) Timing	CATD Population	Findings (Incidence, Change from Baseline)	Strength of Evidence
Cognition-Brief Stand-Alone Tests	1 RCT (n=303) 24 weeks	Mild to moderate	**Mean change in MMSE:** *10 mg/d vs. 5 mg/d*: No difference (SMD, 0.04 [95% CI, -0.29 to 0.16]; 1 trial, n=303)[211]	Low
	1 RCT (n=1,370) 24 weeks	Moderate to severe	**Mean change in MMSE:** *23 mg/d vs. 10 mg/d:* No difference (SMD, 0.04 [95% CI, -0.07 to 0.15]; 1 trial, n=1,370)[221]	Low
Function	2 RCT (n=1,557) 24 weeks	Moderate to severe	**Mean change in ADCS-ADL-severe scale:** *23 mg/d vs. 10 mg/d*: No difference (SMD, 0.0 [95% CI, -0.11 to 0.11], 1 trial, n=1,369)[221] *10 mg/d vs. 5 mg/d*: No difference (SMD, -0.03 [95% CI, -0.32 to 0.25]; 1 trial, n=187)[204]	*23 vs 10 mg/d*: Low *10 vs 5 mg/d*: Low
Clinical Impression	1 RCT (n=298) 24 weeks	Mild to moderate	**Likelihood ≥3-point CIBIC-Plus improvement:** *10 mg/d vs. 5 mg/d*: No difference (25% vs. 26%; ARD, -1% [95% CI, -11 to 9]; NNTH, 100 [95% CI, NNTH 9 to ∞ to NNTB 9]; RR, 0.95 [95% CI, 0.64 to 1.40]; 1 trial, n=298)[211]	Low
	3 RCT (n=1,892) 24 weeks	Moderate to severe	**Likelihood improved:** *23 mg/d vs. 10 mg/d*: No difference (21.5% vs. 21%; ARD, 0.4 [95% CI, -4 to 4]; NNTB, 250 [95% CI, NNTB 25 to ∞ to NNTH 25]; RR, 0.90 [95% CI, 0.58 to 1.40]; 2 trials, n=1,704)[221, 223] 1*0 mg/d vs. 5 mg/d:* Favors 10 mg/d (47% vs. 32%; ARD, 14 [95% CI, 1 to 28]; NNTB, 7 [95% CI, 4 to 100]; RR, 1.45 [95% CI, 1.01 to 2.08]; 1 trial, n=188)[204]	*23 vs 10 mg/d*: Low *10 vs 5 mg/d*: Low
SAE	2 RCT (n=855) 24 weeks	Mild to moderate	*10 mg/d vs. 5 mg/d*: Higher risk with 10 mg/d (10.2% vs. 6.1%; ARD, 4.1% [95% CI, 0.5 to 7.8]; NNTH, 24 [95% CI, 13 to 200]; RR, 1.67 [95% CI, 1.04 to 2.66]; 2 trials, n=855)[197, 211]	Low
	3 RCT (n=1,982) 24 weeks	Moderate to severe	*23 mg/d vs. 10 mg/d*: No difference (9.0% vs. 9.3%; ARD, -0.3 [95% CI, -3.1 to 2.5]; NNTB, 333 [95% CI, NNTB 32 to ∞ to NNTH 40]; RR, 1.06 [95% CI, 0.64 to 1.74]; 2 trials, n=1,785)[221, 223] *10 mg/d vs. 5 mg/d*: 10.4% vs. 11.9%; (ARD, -1.5% [95% CI, -10.2 to 7.3]; RR, 0.88 [95% CI, 0.40 to 1.93]; 1 trial, n=197)[204]	*23 vs 10 mg/d*: Low *10 vs 5 mg/d*: Insufficient
Withdrawals Due to Adverse Events	2 RCT (n=855) 24 weeks	Mild to moderate	*10 mg/d vs. 5 mg/d*: Higher risk with 10 mg/d (17.4% vs. 7.8%; ARD, 9.6% [95% CI, 5.3 to 14.1]; NNTH, 10 [95% CI, 7 to 19]; RR, 2.24 [95% CI, 1.52 to 3.29]; 2 trials, n=855)[197, 211]	Moderate
	3 RCT (n=2,015) 24 weeks	Moderate to severe	*23 mg/d vs. 10 mg/d*: Higher risk with 23 mg/d (18.4% vs. 8.3%; ARD, 10.1 [95% CI, 7.1 to 13.2]; NNTH, 10 [95% CI, 8 to 14]; RR, 2.22 [95% CI, 1.67 to 2.96]; 2 trials, n=1,818)[221, 223] *10 mg/d vs. 5 mg/d*: 13.5% vs. 7.9% (ARD, 5.6% [95% CI, -3 to 14.3]; RR, 1.71 [95% CI, 0.74 to 3.94]; 1 trial, n=197)[204]	*23 vs 10 mg/d*: Moderate *10 vs 5 mg/d*: Insufficient

ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognition; ADCS-ADL-Severe=Alzheimer's Disease Cooperative Study–Activities of Daily Living–Severe Version; ARD=absolute risk difference; CATD=Clinical Alzheimer's-type dementia; CI=confidence intervals; CIBIC=Clinician's Interview-Based Impression of Change; MMSE=Mini-Mental State Examination; NNTB=number needed to treat to produce 1 additional benefit; NNTH=number needed to treat to produce 1 additional harm; RCT=randomized controlled trial; RR=risk ratio; SAE=serious adverse events; SIB=Severe Impairment Battery; SMD=standardized mean difference

Variation in Outcomes by Participant Characteristics

In a *post hoc* analysis in one trial in individuals with moderate to severe CATD, 23 mg/day donepezil improved Severe Impairment Battery (SIB) scores more than 10 mg/day donepezil among participants with baseline MMSE ≤16 ($p<0.001$), but not among those with MMSE 17 to 20 ($p<0.94$).[221] However, no test of interaction was reported.

Galantamine Versus Placebo and Galantamine Dose Comparisons

Key Messages

- In older adults with mild to moderate CATD, evidence for galantamine compared with placebo showed:
  - Improvement in cognition (low SOE).
  - Increased risk for withdrawals due to serious adverse events (low SOE).
  - Insufficient evidence for individual cognitive domains, function, quality of life, clinical impression of change, or serious adverse events.
- In older adults with moderate to severe CATD, evidence for galantamine compared with placebo was insufficient for all efficacy and harms outcomes.
- In older adults with mild to moderate CATD, evidence directly comparing different galantamine doses was insufficient for all efficacy and harms outcomes.

Eligible Studies

We identified nine eligible publications of seven unique trials reporting results for cognition, function, quality of life, global staging, clinical impression of change, or harms.[225-233] Four unique trials were assessed as having high ROB, and were therefore not used in our analysis.[228-233] We analyzed the findings of the three remaining medium ROB trials, including two that compared galantamine with placebo,[225, 226] and one that directly compared different dosages of galantamine.[227] Appendix Tables E.11-E.15 provide evidence tables, summary ROB assessments, and strength of evidence for key comparisons and outcomes.

Baseline Study Characteristics

Characteristics of the 1,060 participants enrolled in the two analyzed trials that compared galantamine with placebo are shown in Table 6.5. One of these trials enrolled community-dwelling participants and compared galantamine 24 mg/day and 32 mg/day with placebo,[226] while the other enrolled individuals residing in residential homes, nursing homes, or geriatric residences and compared galantamine 24 mg/day with placebo.[225] Both trials lasted 26 weeks.

Table 6.5. Baseline characteristics of galantamine versus placebo trials

Characteristic	N, Mean, or % (Study Range)	Trials Reporting, N
Number of participants enrolled	1,060 (407 and 653)	2
Age, mean	77 (72 and 84)	2
Men, %	30 (19 and 37)	2
Race – white, %	NR	0
Alzheimer's disease severity*	**NA**	
Mild or moderate, %	62 (n=653)	1

Characteristic	N, Mean, or % (Study Range)	Trials Reporting, N
Severe, %	38 (n=407)	1
MMSE, mean	15.3 (9 and 20)	2

MMSE=Mini-Mental State Examination; NA=not applicable; NR=not reported
*Alzheimer's disease severity was based on that reported by the individual trials.

One 28-week open-label trial (n=34) enrolled participants with mild to moderate CATD and directly compared galantamine 16 mg/day with galantamine 24 mg/day.[227]

Outcomes

Table 6.6 summarizes the primary efficacy and harms results between galantamine and placebo. For efficacy, galantamine improved cognition compared with placebo (low SOE), but evidence was insufficient for function or global change measures. No studies reported data on quality of life, staging or change in patient residence to a different level of independence.

For harms, galantamine increased risk of withdrawals due to adverse events in individuals with mild to moderate CATD (low SOE), but evidence was insufficient in those with severe CATD. Evidence was insufficient to draw conclusions about differences between galantamine and placebo for serious adverse events. In one trial reporting, galantamine and placebo did not statistically differ for falls (12% vs. 11%),[225] but mortality was lower in the galantamine group (4.0% vs. 11.0%, p=0.01).[225] No studies reported data on confusion, somnolence, extrapyramidal symptoms or stroke.

The single trial that directly compared galantamine 16 mg/day and 24 mg/day reported that treatment groups did not differ for cognition or function but provided no numerical data.[227]

Appendix Tables E.12-E.15 provide detailed evidence tables and strength of evidence for key comparisons and outcomes.

Table 6.6. Summary of findings for primary outcomes: galantamine versus placebo

Domain	# Studies/ Design (n Analyzed) Timing	CATD Population	Findings (Incidence, Change from Baseline)	Strength of Evidence
Cognition - Brief Multidomain Batteries	1 RCT[226] (n=653) 26 weeks	Mild to moderate	**Likelihood ≥4-point ADAS-Cog improvement:** *32 mg/d:* Favors galantamine (32% vs. 15%; ARD, 17% [95% CI, 10% to 25%]; NNTB, 6 [95% CI, 4 to 10]; RR, 2.17, [95% CI, 1.49 to 3.15]) *24 mg/d:* Favors galantamine (29% vs. 15%; ARD, 14% [95% CI, 7% to 22%]; NNTB, 7 [95% CI, 5 to 14]; RR, 1.95, [95% CI, 1.34 to 2.86]) **Likelihood ADAS-Cog unchanged/improved (≥0):** *32 mg/d:* Favors galantamine (60% vs. 41%; ARD, 19% [95% CI, 10% to 28%]; NNTB, 5 [95% CI, 4 to 10]; RR, 1.46, [95% CI, 1.21 to 1.78]) *24 mg/d:* Favors galantamine (63% vs. 41%; ARD, 22% [95% CI, 13% to 31%]; NNTB, 5 [95% CI, 3 to 8]; RR, 1.53, [95% CI, 1.27 to 1.85]) **Mean ADAS-Cog change:** *32 mg/d:* Favors galantamine (MD, 3.1 [95% CI, 1.9 to 4.4]; SMD, 0.52 [95% CI, 0.33 to 0.71]) *24 mg/d:* Favors galantamine (MD, 2.9 [95% CI, 1.6 to 4.1]; SMD, 0.50 [95% CI, 0.31 to 0.69])	Low
	1 RCT[225] (n=407) 26 weeks	Severe	**Mean SIB change:** *24 mg/d:* SMD, 0.29 (95% CI, 0.10 to 0.49).	Insufficient

Domain	# Studies/ Design (n Analyzed) Timing	CATD Population	Findings (Incidence, Change from Baseline)	Strength of Evidence
Cognition-Domain Level Tests	1 RCT[225] (n=407) 6 months	Severe	**Mean SIB subscale changes:** *24 mg/d:* Compared with placebo, galantamine statistically improved memory (p=0.006), but not language (p=0.064) or attention (p=0.075)	Insufficient for each domain
Function	2 RCT[225, 226] (n=653) 26 weeks	Mild to moderate	**Mean DAD change:** *32 mg/d:* SMD 0.22 (95% CI, 0.03 to 0.41) *24 mg/d:* SMD, 0.18 (95% CI, -0.01 to 0.37)	Insufficient
	1 RCT[225] (n=407) 26 weeks	Severe	**Mean MDS-ADL change:** *24 mg/d:* SMD, -0.10 (95% CI, -0.32 to 0.12)	Insufficient
Clinical Impression of Change*	1 RCT[226] (n=653) 26 weeks	Mild to Moderate	**Likelihood unchanged/improved:** *32 mg/d:* 66% vs. 50% placebo; ARD, 16% [95% CI, 6% to 25%]; RR, 1.32 [95% CI, 1.11 to 1.57]) *24 mg/d:* 62% vs. 50% placebo (ARD, 12% [95% CI, 2% to 21%]; RR, 1.24 [95% CI, 1.04 to 1.48]) **Likelihood improved:** *32 mg/d:* 24% vs. 16% placebo; ARD, 8% [95% CI, 0.2% vs. 16%]; RR, 1.49 [95% CI, 1.00 to 2.22]) *24 mg/d:* 17% vs. 16% placebo (ARD, 1% [95% CI, -6% vs. 9%]; RR, 1.08 [95% CI, 0.70 to 1.65]) **Likelihood moderately/markedly improved:** *32 mg/d:* 4.5% vs. 0.5% placebo; ARD, 4% [95% CI, 1% vs. 7%]; RR, 9.23 [95% CI, 1.18 to 72.16]) *24 mg/d:* 3.5% vs. 0.5% placebo (ARD, 3% [95% CI, 0.25% vs. 6%]; RR, 6.90 [95% CI, 0.86 to 55.56])	Insufficient
SAE	1 RCT[226] (n=653) 26 weeks	Mild to moderate	12%-13% for both galantamine groups and placebo group; 1 trial, n=653.[226]	Insufficient
	1 RCT[225] (n=407) 26 weeks	Severe	17.9% vs. 21% (ARD, -3.1% [95% CI, -10.8 to 4.6]]; RR, 0.85 [95% CI, 0.57 to 1.27]; 1 trial, n=407)[225]	Insufficient
Withdrawals Due to Adverse Events	1 RCT[226] (n=653) 26 weeks	Mild to moderate	Galantamine increased risk: 18% vs 8.8%; ARD, 9.2% [95% CI, 4 to 14.4]; NNTH, 11 [95% CI, 7 to 25]; RR, 2.04 [95% CI, 1.27 to 3.28]; 1 trial, n=653)[226]	Low
	1 RCT[225] (n=407) 26 weeks	Severe	14.5% vs. 15.5%; ARD, -1% [95% CI, -7.9 to 5.9]; RR, 0.94 [95% CI, 0.59 to 1.49]; 1 trial, n=407)[225]	Insufficient

ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; ARD=absolute risk difference; CATD= Clinical Alzheimer's-type Dementia; CI=confidence interval; DAD=Disability Assessment for Dementia; MD=mean difference; MDS-ADL=7-item Minimum Data Set Activities of Daily Living Self-Performance scale; NNTB=number needed to treat to produce 1 additional benefit; NNTH=number needed to treat to produce 1 additional harm; RCTs=randomized controlled trial; RR=risk ratio; SAE=serious adverse events; SIB=Severe Impairment Battery; SMD=standardized mean difference
*Clinical Impression of Change was evaluated using the Clinician's Interview-Based Impression of Change-Plus Caregiver Input

Variation in Outcomes by Participant Characteristics

One trial of 653 participants with mild to moderate CATD (baseline MMSE scores 11 to 24) found that the relative benefits of galantamine compared with placebo on the 11-item ADAS-Cog scale appeared larger in patients with baseline MMSE <18 than in those with baseline MMSE ≥18.[226] A second trial conducted in 407 participants with severe CATD (baseline MMSE 5 to 12) reported that the effect of galantamine versus placebo on mean total SIB score at 6 months did not vary as a function of baseline MMSE score (p=0.92).[225] However, authors did not report a test for interaction. No studies assessed whether participant characteristics modified the effects of galantamine versus placebo on other efficacy or harms outcomes.

Rivastigmine Versus Placebo

Key Messages

- In older adults with mild to moderate CATD, the evidence for rivastigmine 12 mg/day oral or 9.5 mg/day transdermal patch compared with placebo showed:
    - Small improvement in cognition (low SOE for brief cognitive tests commonly used as individual stand-alone tests, moderate SOE for brief multidomain batteries), function (low SOE), staging (low SOE), and clinical impression of change (moderate SOE), and insufficient evidence for attention.
    - Increased withdrawals due to adverse events (moderate SOE), but no difference in serious adverse events (low SOE).
- In older adults with mild to moderate CATD, the evidence for rivastigmine 4 mg/day oral or 4.6 mg/day transdermal patch compared with placebo showed:
    - No difference in cognition (moderate SOE for brief cognitive tests commonly used as individual stand-alone tests, low SOE for brief multidomain batteries), function (low SOE), and insufficient evidence in global staging, but a less than small improvement in clinical impression of change (low SOE).
    - No difference in serious adverse events or withdrawals due to adverse events (low SOE).
- In older adults with moderate to severe CATD, the evidence for rivastigmine 12 mg/day oral or 9.5 mg/day transdermal patch compared with placebo showed small improvement in clinical impression of change (low SOE) and insufficient evidence for cognition.

Eligible Studies

Based in part on a high-quality 2015 systematic review (search date March 2015),[234] we identified 26 eligible publications of eight unique randomized controlled trials of at least 24 weeks duration, that compared rivastigmine with placebo, and reported results for cognition, function, quality of life, global staging, clinical impression of change, or harms.

Of the eight eligible trials, three were rated high ROB (two for high attrition) and not analyzed.[235-237] The five remaining trials were included in analyses.[238-242] Appendix Tables E.16-E.23 provide evidence tables, summary ROB assessments, and strength of evidence for key comparisons and outcomes.

Baseline Study Characteristics

Characteristics of the 3,674 participants enrolled in the five analyzed trials are shown in Table 6.7. Participants were primarily community dwelling at baseline. Four trials enrolled participants with baseline MMSE scores of either 10 to 26, or 10 to 20.[239-241, 243] One trial (n=218) enrolled only participants with a MMSE score of 5 to 12 and a Global Deterioration Scale (GDS) stage of 5 to 6.[242] Treatment duration for all five trials was 24 or 26 weeks.

Table 6.7. Characteristics of the rivastigmine versus placebo trials

Characteristic	N, Mean, or % (Study Range)	Trials Reporting, N
Number of participants enrolled, total	3,674 (218 to 1,195)	5
Age, mean	73 (71 to 78)	5
Men, %	35 (23 to 41)	5
Race – white, %	83 (75 to 97)	2
Alzheimer's disease severity*	NA	
Early stage, %	0	0
Mild or moderate, %	94 (n=3,456)	4
Moderate or severe, %	6 (n=218)	1
Severe, %	0	0
Any (included mild, moderate, or severe), %	0	0
MMSE, mean	17 (9 to 20)	5

MMSE=Mini-Mental State Examination; NA=not applicable

*Alzheimer's disease severity was based on that reported by the individual trials.

Rivastigmine was administered orally or as a transdermal patch. Three trials evaluated oral rivastigmine only,[239, 242, 243] one evaluated the patch only,[241] and one evaluated both delivery methods.[240] Targeted oral doses were 4 mg/day and 12 mg/day in divided doses, and targeted patch doses were 4.6 mg/day, 9.5 mg/day, and 17.4 mg/day. The 9.5 mg/day to 12 mg/day doses were categorized as standard and the 4 mg/day to 4.6 mg/day doses were categorized as low. The 17.4 mg/day dose exceeds the maximum FDA recommended for the rivastigmine patch (13.3 mg/day), so results are included only in Appendix Tables E.18-E.23 and are not discussed further in the report text.

Outcomes

Table 6.8 summarizes the primary efficacy and harms outcomes from the five studies with low or medium risk of bias that compared rivastigmine with placebo. For efficacy, in patients with mild to moderate CATD treated for 24 to 26 weeks, rivastigmine 12 mg/day oral and 9.5 mg/day patch each improved several outcomes compared with placebo. These included brief cognitive tests commonly used as individual stand-alone tests (low SOE), brief multidomain cognitive batteries (moderate SOE), function (low SOE), staging (low SOE), and clinical impression of change (moderate SOE). Evidence was insufficient for attention. However, rivastigmine 4 mg/day oral and 4.6 mg/day patch did not differ from placebo for brief cognitive tests commonly used as individual stand-alone tests (moderate SOE), brief multidomain cognitive batteries (low SOE), evidence was inconsistent for clinical impression of change (low SOE), and evidence was insufficient for staging. No studies reported data comparing rivastigmine with placebo for quality of life or change in patient residence to different level of independence. In patients with moderate to severe CATD treated for 26 weeks, rivastigmine 12 mg/day oral showed small improvement in clinical impression of change (low SOE) and insufficient evidence for cognition.

For harms, no rivastigmine dose differed with placebo for risk of serious adverse events (low SOE). However, rivastigmine 12 mg/day oral or 9.5 mg/day patch compared with placebo appeared to increase risk of withdrawals due to adverse events (moderate SOE). Rivastigmine 4 mg/day oral or 4.6 mg/day patch did not differ with placebo for risk of withdrawals due to adverse events (low SOE). Rivastigmine and placebo did not appear to differ for risk of mortality, whether for 12 mg/day oral or 9.5 mg/day patch (0.6% vs. 0.4%; peto OR, 1.18 [95% CI, 0.40 to 3.51]),[240-243] or for 4 mg/day oral or 4.6 mg/day patch (2 deaths in 1,054 participants in all treatment groups combined[241, 243]). In another trial that compared rivastigmine 12 mg/day

oral administered either twice or three times daily with placebo, no deaths occurred.[239] No studies reported information about confusion, somnolence, falls, extrapyramidal symptoms or stroke.

Appendix Tables E.18-E.23 provide detailed evidence tables and strength of evidence for key comparisons and outcomes.

Table 6.8. Summary of findings for primary outcomes:* rivastigmine versus placebo†

Domain	# Studies/ Design (n Analyzed) Timing	CATD Population	Findings (Incidence, Change from Baseline)	Strength of Evidence
Cognition-Brief Stand-Alone Tests	4 RCT (n=2,917) 24-26 weeks	Mild to moderate	**Mean MMSE change:** *12 mg/d PO or 9.5 mg/d patch:* Favors rivastigmine (SMD, 0.24 [95% CI, 0.14 to 0.34]; 4 trials, n=2,439)[239-241, 243] *4 mg/d PO or 4.6 mg/d patch:* No difference (SMD, -0.02 [95% CI, -0.15 to 0.10]; 2 trials, n=968)[241, 243] **Mean 10-point Clock-Drawing change:** *12 mg/d PO or 9.5 mg/d patch:* 0.2 for 12 mg/d PO or 0.3 for 9.5 mg/d patch vs. -0.1 for placebo (p=0.15 and p=0.08 vs. placebo, respectively); 1 trial, n=760[240]	**12/9.5:** Low **4/4.6:** Moderate
Cognition-Brief Multidomain Batteries	4 RCT (n=2,978) 24-26 weeks	Mild to moderate	**Likelihood ≥4-point ADAS-Cog improvement:** *12 mg/d PO or 9.5 mg/d patch:* Favors rivastigmine (25% vs. 17%; ARD, 8% [95% CI, 4% to 11%]; NNTB, 13 [95% CI, 9 to 25]; RR, 1.47 [95% CI, 1.22 to 1.79]; 3 trials, n=1,819)[243, 239, 240] *4 mg/d PO or 4.6 mg/d patch:* No difference (17% vs. 19%; ARD, -2% [95% CI, -9% to 6%]; NNTH, 50 [95% CI, NNTH 11 to ∞ to NNTB 17]; RR, 0.91 [95% CI, 0.60 to 1.38]; 1 trial, n=407).[243] **Mean ADAS-Cog change:** *12 mg/d PO or 9.5 mg/d patch:* Favors rivastigmine (SMD, -0.26 [95% CI, -0.34 to -0.18]; 4 trials, n=2,470)[239-241, 243] *4 mg/d PO or 4.6 mg/d patch:* No difference (SMD, -0.08 [95% CI, -0.25 to 0.10]; 2 trials, n=1,011)[241, 243]	**12/9.5:** Moderate **4/4.6:** Low
	1 RCT (n=210) 26 weeks	Moderate to severe	**Mean SIB change:** *12 mg/d PO or 9.5 mg/d patch:* SMD, 0.30 (95% CI, 0.03 to 0.57); 1 trial, n=210[242]	**12/9.5:** Insufficient
Cognition-Domain Level Tests Typically Part of a Larger Battery	1 RCT (n=739) 24 weeks	Mild to moderate	**Mean TMT-Part A (attention) change:** *12 mg/d PO or 9.5 mg/d patch:* SMD, -0.32 (95% CI, -0.47 to -0.16); 1 trial, n=739[240]	**12/9.5:** Insufficient

Domain	# Studies/ Design (n Analyzed) Timing	CATD Population	Findings (Incidence, Change from Baseline)	Strength of Evidence
Function‡	4 RCT (n=2,979) 24-26 weeks	Mild to moderate	**Likelihood ≥10% PDS improvement:** *12 mg/d PO or 9.5 mg/d patch:* Favors rivastigmine 33% vs. 20%; ARD, 13% [95% CI, 5% to 22%]; NNTB, 8 [95% CI, 5 to 20]; RR, 1.65 [95% CI, 1.19 to 2.29]; 1 trial, n=421)[243] *4 mg/d PO or 4.6 mg/d patch:* No difference (20% vs. 20%; 1 trial, n=448)[243] **Mean PDS change:** *12 mg/d PO or 9.5 mg/d patch:* Favors rivastigmine (SMD, 0.21 [95% CI, 0.09 to 0.33]; 2 trials, n=1,151) [239, 243] *4 mg/d PO or 4.6 mg/d patch:* No difference (SMD, -0.09 [95% CI, -0.27 to 0.09]; 1 trial, n=478)[243] **Mean ADCS-ADL change:** *12 mg/d PO or 9.5 mg/d patch:* Favors rivastigmine (SMD, 0.21 [95% CI, 0.09 to 0.33]; 1 trials, n=782)[240] **Mean DAD change:** *12 mg/d PO or 9.5 mg/d patch:* Favors rivastigmine (SMD, 0.19 [95% CI, 0.03 to 0.37]); 1 trial, n=536)[241] *4 mg/d PO or 4.6 mg/d patch:* No difference (SMD, 0.11 [95% CI, -0.06 to 0.28]); 1 trial, n=536[241]	**12/9.5:** Low **4/4.6:** Low
Staging	2 RCT (n=1,400) 26 weeks	Mild to moderate	**Mean GDS change:*** *12 mg/d PO or 9.5 mg/d patch:* Favors rivastigmine (SMD, 0.27 [95% CI, 0.15 to 0.39]; 2 trials, n=1,158)[239, 243] *4 mg/d PO or 4.6 mg/d patch:* SMD, 0.05 (95% CI, -0.13 to 0.23); 1 trial, n=480[243]	**12/9.5:** Low **4/4.6:** Insufficient
Clinical Impression of Change‡	4 RCT (n=2,665) 24-26 weeks	Mild to moderate	**Likelihood unchanged/improved:** *12 mg/d PO or 9.5 mg/d patch:* Favors rivastigmine (70% vs. 59%; ARD, 11% [95% CI, 5% to 16%]; NNTB, 9 [95% CI, 6 to 20]; RR, 1.16 [95% CI, 1.04 to 1.29]; 2 trials, n=1,315)[240, 241] *4 mg/d PO or 4.6 mg/d patch:* No difference (62% vs. 57%; ARD, 5% [95% CI, -4 to 13]; NNTB, 20 [95% CI, NNTB 8 to ∞ to NNTH 25]; RR, 1.08 [95% CI, 0.94 to 1.25];1 trial, n=536[241] **Likelihood improved:** *12 mg/d PO or 9.5 mg/d patch:* Favors rivastigmine (31% vs. 21%; ARD, 10% [95% CI, 7% to 14%]; NNTB, 10 [95% CI, 7 to 14]; RR, 1.47 [95% CI, 1.20 to 1.80]; 4 trials, n=2,201)[240, 243] *4 mg/d PO or 4.6 mg/d patch:* Favors rivastigmine (25% vs. 18%; ARD, 7% [95% CI, 2 to 13]; NNTB, 14 [95% CI, 8 to 50]; RR, 1.39 [95% CI, 1.09 to 1.78]; 2 trials, n=931[241, 243] **Likelihood moderately/markedly improved:** *12 mg/d PO or 9.5 mg/d patch:* No difference (10% vs. 6%; ARD, 4% [95% CI, 1% to 7%]; NNTB, 25 [95% CI, 14 to 100]; RR, 1.46 [95% CI, 0.93 to 2.29]; 2 trials, n=1,315)[240, 241] *4 mg/d PO or 4.6 mg/d patch:* No difference (4.5% vs. 2%; ARD, 2.6% [95% CI, -0.4 to 5.5]; NNTB, 38 [95% CI, NNTB 18 to ∞ to NNTH 250]; RR, 2.38 [95% CI, 0.85 to 6.67]; 1 trial, n=536[241]	**12/9.5:** Moderate **4/4.6:** Low

Domain	# Studies/ Design (n Analyzed) Timing	CATD Population	Findings (Incidence, Change from Baseline)	Strength of Evidence
	1 RCT (n=210) 26 weeks	Moderate to severe	**Likelihood improved:** *12 mg/d PO or 9.5 mg/d patch:* Favors rivastigmine (22% vs. 9%; ARD, 13% [95% CI, 3 to 22]; NNTB, 8 [95% CI, 5 to 33]; RR, 2.34 [95% CI, 1.17 to 4.68]; 1 trial, n=210[242]	**12/9.5:** Low
SAE	5 RCT (n=3,352) 24-26 weeks	All severity	*12 mg/d PO or 9.5 mg/d patch:* No difference (11.2% vs. 10.1%; ARD, 1% [95% CI, -1 to 3]; NNTH, 100 [95% CI, NNTH 33 to ∞ to NNTB 100]; RR, 1.07 [95% CI, 0.86 to 1.34]; 5 trials, n=2,828)[239-243] *4 mg/d PO or 4.6 mg/d patch:* No difference (8.2% vs. 9.3%; ARD, -1.1 [95% CI, -4.5 to 2.3]; NNTB, 91 [95% CI, NNTB 22 to ∞ to NNTH 43]; RR, 0.88 [95% CI, 0.60 to 1.30]; 2 trials, n=1,049)[241, 243]	**12/9.5:** Low **4/4.6:** Low
Withdrawals Due to Adverse Events	5 RCT (n=3,362) 24-26 weeks	All severity	*12 mg/d PO or 9.5 mg/d patch:* Rivastigmine increased risk (12.7% vs. 6.9%; ARD, 5.8% [95% CI, 3.7 to 8]; NNTH, 17 [95% CI, 13 to 27]; RR, 1.88 [95% CI, 1.35 to 2.61]; 5 trials, n=2,836)[239-243] *4 mg/d PO or 4.6 mg/d patch:* No difference (10.6% vs. 7.0%; ARD, 3.6 [95% CI, 0.2 to 7]; NNTH, 28 [95% CI, 14 to 500]; RR, 1.49 [95% CI, 0.92 to 2.42]; 2 trials, n=1,053)[241, 243]	**12/9.5:** Moderate **4/4.6:** Low

ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS-CGIC=Alzheimer's Disease Cooperative Study—Clinical Global Impression of Change; ARD=absolute risk difference; CATD=Clinical Alzheimer's-type Dementia; CI=confidence interval; CIBIC-Plus=Clinician Interview Based Impression of Change Incorporating Caregiver Information Scale; DAD=Disability Assessment for Dementia; GDS=Global Deterioration Scale; MMSE=Mini-Mental State Examination; NNTB=number needed to treat to produce 1 additional benefit; NNTH=number needed to treat to produce 1 additional harm; PDS=Progressive Deterioration Scale; PO=oral; RCT=randomized controlled trial; RR=risk ratio; SAE=serious adverse events; SIB= Severe Impairment Battery; SMD=standardized mean difference; TMT=Trail Making Test

*An additional trial was reported in a prior systematic review[234] to have compared change in GDS between rivastigmine and placebo, but data could not be obtained.[242]

†Strength of evidence not graded for 17.4 mg/day patch dose because this exceeds the FDA approved maximum dose.

‡Clinical Impression of Change was evaluated using the CIBIC-Plus or ADCS-CGIC.

Variation in Outcomes by Participant Characteristics

No studies reported whether participant characteristics modified the effect of rivastigmine on cognition, function, quality of life, global staging, clinical impression of change, or harms.

Rivastigmine Dosage Comparisons

Key Messages

- In older adults with mild to moderate CATD, evidence for standard-dose rivastigmine (12 mg/day oral or 9.5 mg/day patch) compared with low-dose rivastigmine (4 mg/day oral or 4.6 mg/day patch) showed:
    - No difference in clinical impression of change (low SOE) or serious adverse events (low SOE).
    - Insufficient evidence about cognition, function, global staging, quality of life, or withdrawals due to adverse events.
- In older adults with mild to moderate CATD, evidence for rivastigmine 12 mg/day oral compared with 9.5 mg/day or 13.3 mg/day patch showed:

    - No difference in clinical impression of change (low SOE) or cognition tests for attention (low SOE).
    - Insufficient evidence about brief cognitive tests commonly used as individual stand-alone tests, brief multidomain cognitive batteries, cognition tests for executive function, function, staging, quality of life, serious adverse events, and withdrawals due to adverse events.
- In older adults with mild to moderate CATD, evidence for 12 mg/day oral rivastigmine in three divided doses compared with two divided doses was insufficient to draw conclusions for all efficacy and harms outcomes.

Eligible Studies

Based in part on a high-quality 2015 systematic review (search date March 2015),[234] we identified 33 eligible publications of 11 unique randomized controlled trials of at least 24 weeks duration, that directly compared rivastigmine with another rivastigmine dose or delivery route, and reported results for cognition, function, quality of life, global staging, clinical impression of change, or harms. Of the 11 eligible trials, six were rated high risk of bias (most commonly for high attrition) and not analyzed.[235, 237, 244-247] The five remaining trials were included in analyses.[239-241, 243, 248] Appendix Tables E.18-E.23 provide evidence tables, summary risk of bias assessments, and strength of evidence for key comparisons and outcomes

Baseline Study Characteristics

Characteristics of the 2,973 participants in the rivastigmine arms in the five analyzed trials are shown in Table 6.9. Participants were primarily community dwelling at baseline. Treatment duration for four trials was 24 or 26 weeks. One trial had an open-label phase following which "decliners" were enrolled in a 48-week double-blind phase; we analyzed the blinded data only at 24 weeks due to high attrition with longer followup.[248] All trials enrolled participants with mild to moderate CATD severity at baseline (MMSE entry criteria ranged from 10-20 to 10-26).[239-241, 243, 248] However, the open-label decliners trial likely included a minority of individuals with MMSE <10 at baseline of its double-blind phase better categorized with moderate to severe CATD.[248]

Rivastigmine was administered orally or as a transdermal patch. Two trials evaluated oral rivastigmine only,[239, 243] two evaluated patch only,[241, 248] and one evaluated both.[240] Targeted oral doses were 4 mg/day and 12 mg/day in divided doses, and targeted patch doses were 4.6 mg/day, 9.5 mg/day, 13.3 mg/day (maximum recommended by the Food and Drug Administration) and 17.4 mg/day. As stated in the Rivastigmine versus Placebo section above, results for the 17.4 mg/day dose are included only in Appendix Tables E.18-E.23.

Table 6.9. Characteristics of the rivastigmine dose comparison trials

Characteristic	N, mean, or % (Study Range)	Trials Reporting, N
Number of participants enrolled, total	2,973 (456 to 893)	5
Age, mean	74 (71 to 76)	5
Men, %	36 (32 to 42)	5
Race – white, %	87 (75 to 97)	2
Alzheimer's disease severity – mild to moderate, %*	100 (n=2,973)†	5
MMSE, mean	17 (14 to 20)	5

MMSE=Mini-Mental State Examination

†One trial enrolled participants with mild to moderate CATD in an open-label phase, but baseline MMSE for a subsequent double-blind phase was 14.2 (SD 4.7), suggesting approximately 20% of participants then had an MMSE <10, and may no longer have been categorized as mild to moderate CATD.[248]

Outcomes

Table 6.10 summarizes the primary efficacy and harms from the five trials that compared different rivastigmine doses. For comparative effectiveness, evidence was insufficient to draw conclusions between any rivastigmine dose comparisons for brief cognitive tests commonly used as individual stand-alone tests, brief multidomain cognitive batteries, function, staging, or clinical impression of change. No studies reported data on quality of life or change in patient residence to a different level of independence.

For harms, evidence was mostly insufficient about any differences between rivastigmine doses for risk of serious adverse events or withdrawals due to adverse events. In one trial, participants randomized to 13.3 mg/day rivastigmine patch and 9.5 mg/day patch did not appear to differ for risk of confusion (1.8% vs. 2.1%)[248] or falls (4.3% vs. 3.5%).[248] In four trials that reported on mortality, two deaths occurred in the 12 mg/day oral group compared with five in the 9.5 mg/day patch group,[240] two deaths occurred in the 12 mg/day oral group compared with none in the 4 mg/day oral group,[243] no deaths occurred in the 9.5 mg/day patch group compared with one death in the 4.6 mg/day patch group,[241] and no deaths occurred in either of two 12 mg/day oral dosing groups.[239] No studies reported data on somnolence, extrapyramidal symptoms or stroke.

Appendix Tables E.18-E.23 provide detailed evidence tables and strength of evidence for key comparisons and outcomes.

Table 6.10. Summary of findings for primary outcomes:* rivastigmine dose comparisons

Domain	# Studies/ Design (n Analyzed) Timing	CATD Population	Findings (Incidence, Change from Baseline)	Strength of Evidence
Cognition-Brief Stand-Alone Tests	4 RCT (n=1,926) 24-26 weeks	Mild to moderate	**Mean MMSE change:** *12 mg/d PO or 9.5 mg/d patch vs. 4 mg/d PO or 4.6 mg/d patch:* SMD, 0.22 (95% CI, -0.01 to 0.44); 2 trials, n=966[241, 243] *9.5 mg/d patch vs. 12 mg/d PO or 13.3 mg/d patch:* SMD, 0.09 (95% CI, -0.08 to 0.27); 1 trial, n=506[240] *12 mg/d PO in 3 doses vs. 2 doses:* SMD, 0.25 (95% CI, 0.07 to 0.43); 1 trial, n=454[239] **Mean 10-point Clock Drawing change:** *12 mg/d PO* vs. *9.5 mg/d patch:* 0.3 vs. 0.2; p not reported; 1 trial, n=491[240]	All insufficient

Domain	# Studies/ Design (n Analyzed) Timing	CATD Population	Findings (Incidence, Change from Baseline)	Strength of Evidence
Cognition-Brief Multidomain Batteries	5 RCT (n=2,450) 24-26 weeks	Mild to moderate	**Likelihood ≥4-point ADAS-Cog improvement:** *12 mg/d PO or 9.5 mg/d patch vs. 4 mg/d PO or 4.6 mg/d patch:* 29% vs. 17% (RR, 1.70 [95% CI, 1.15 to 2.52]; 1 trial, n=359)[243] *9.5 mg/d patch vs. 12 mg/d PO or 13.3 mg/d patch:* 28.2% vs. 28.5%; ARD, -0.2% [95% CI, -8.1 to 7.7]; RR, 0.99 [95% CI, 0.75 to 1.31]; 1 trial, n=501)[240] *12 mg/d PO in 3 doses vs. 2 doses:* 23% vs. 18% (estimated from graphical data, p=NR); 1 trial, n=455[239] **Mean ADAS-Cog change:** *12 mg/d PO or 9.5 mg/d patch vs. 4 mg/d PO or 4.6 mg/d patch:* SMD, -0.27 (95% CI -0.60 to 0.07]); 2 trials, n=1,018[241, 243] *9.5 mg/d vs. 12 mg/d-13.3 mg/d:* SMD, 0.00 (95% CI, -0.18 to 0.18) in 1 trial, n=501[240]; MD, -1.2, statistically favored 13.3 mg/d vs. 9.5 mg/d (p=0.04) in 1 trial, n=476[248] *12 mg/d in 3 doses vs. 2 doses:* SMD, -0.19 [95% CI, -0.38 to -0.01]); 1 trial, n=455[239]	All insufficient
Cognition-Domain Level Tests Typically Part of a Larger Battery	2 RCT (n=993) 24 weeks	Mild to moderate	**Mean TMT-Part A (attention) change:** *9.5 mg/d patch vs. 12 mg/d PO or 13.3 mg/d patch:* No difference. SMD, 0.04 (95% CI, -0.14 to 0.22) in 1 trial, n=481;Winblad, 2007 #216} and not statistically significant (p=0.11) in 1 trial, n=512[248] **Mean TMT-Part B (executive function) change:** *9.5 mg/d patch vs. 12 mg/d PO or 13.3 mg/d patch:* Not statistically significant (p=0.78); 1 trial, n=471[248]	**9.5 vs. 12/13.3** Low (attention) All others insufficient
Function	5 RCT (n=2,448) 24-26 weeks	Mild to moderate	**Likelihood ≥10% PDS improvement:** *12 mg/d PO or 9.5 mg/d patch vs. 4 mg/d PO or 4.6 mg/d patch:* 29% vs. 19% (ARD, 10% [95% CI, 3 to 18]; RR, 1.56 [95% CI, 1.12 to 2.16; 1 trial, n=482)[243] **Mean PDS change:** *12 mg/d PO or 9.5 mg/d patch vs. 4 mg/d PO or 4.6 mg/d patch:* SMD, 0.26 (95% CI, 0.08 to 0.44); 1 trial, n=482[243] *12 mg/d in 3 doses vs. 2 doses:* SMD, 0.10 (95% CI, -0.09 to 0.28); 1 trial, n=452[239] **Mean DAD change:** *12 mg/d PO or 9.5 mg/d patch vs. 4 mg/d PO or 4.6 mg/d patch*: SMD, 0.11 (95% CI, -0.06 to 0.27); 1 trial, n=538[241] **Mean ADCS-ADL change:** *9.5 mg/d vs. 12 mg/d-13.3 mg/d:* SMD, 0.04 (95% CI, -0.13 to 0.22) in 1 trial, n=501[240]; results statistically favored 13.3 vs. 9.5 mg/d (p<0.001) for IADL domain in 1 trial, n=475[248]	All insufficient
Staging	2 RCT (n=940) 26 weeks	Mild to moderate	**Mean GDS change:** *12 mg/d PO or 9.5 mg/d patch vs. 4 mg/d PO or 4.6 mg/d patch:* SMD, 0.20 (95% CI, 0.02 to 0.38]); 1 trial, n=484[243] *12 mg/d in 3 doses vs. 2 doses:* SMD, 0.29 (95% CI, 0.10 to 0.47); 1 trial, n=456[239]	All insufficient

Domain	# Studies/ Design (n Analyzed) Timing	CATD Population	Findings (Incidence, Change from Baseline)	Strength of Evidence
Clinical Impression*	4 RCT (n=1,837) 24-26 weeks	Mild to moderate	**Likelihood improved:** *12 mg/d PO or 9.5 mg/d patch vs. 4 mg/d PO or 4.6 mg/d patch:* No difference (29% vs. 26%; ARD,3% [95% CI, -3% to 9%]; NNTB, 33 [95% CI, NNTB 11 to ∞ to NNTH 33]; RR, 1.17 [95% CI, 0.94 to 1.47]; 2 trials, n=892)[241, 243] *9.5 mg/d patch vs. 12 mg/d PO or 13.3 mg/d patch:* No difference. 31% vs. 36% (ARD, -5% [95% CI, -14 to 3]; NNTH, 20 [95% CI, NNTH 7 to ∞ to NNTB 33]; RR, 0.85 [95% CI, 0.67 to 1.09]; 1 trial, n=501)[240] *12 mg/d PO in 3 doses vs. 2 doses:* 30% vs. 23% (estimated from graphical data, p=NR); 1 trial, n=435[239] **Mean ADCS-CGIC change:** *9.5 mg/d vs. 12 mg/d-13.3 mg/d:* No difference (SMD, 0.00 [95% CI, -0.18 to 0.18]; 1 trial, n=501)[240] **Mean CIBIC-Plus change:** *12 mg/d in 3 doses vs. 2 doses:* SMD, -0.15 (95% CI, -0.34 to 0.03); 1 trial, n=444[239]	**12/9.5 vs. 4/4.6:** Low **9.5 vs. 12/13.3:** Low **12 mg/d in 3 vs. 2 doses:** Insufficient
SAE	4 RCT (n=2,093) 24-26 weeks	Mild to moderate	*12 mg/d PO or 9.5 mg/d patch vs. 4 mg/d PO or 4.6 mg/d patch:* No difference (11% vs. 8%; ARD, 3% [95% CI, -0.8 to 6.3]; NNTH, 33 [95% CI, NNTH 16 to ∞ to NNTB 125]; RR, 1.34 [95% CI, 0.93 to 1.95]; 2 trials, n=1,053)[241, 243] *9.5 mg/d vs. 12 mg/d-13.3 mg/d:* 8% vs. 7%; ARD, 1% [95% CI, -3.5 to 5]; RR, 1.11 [95% CI, 0.63 to 2.00]; 1 trial, n=585)[240] *12 mg/d in 3 doses vs. 2 doses:* 18% vs. 18% (ARD, 0% [95% CI, -7 to 7]; RR, 1.00 [95% CI, 0.67 to 1.50]; 1 trial, n=455)[239]	**12/9.5 vs. 4/4.6:** Low **All others:** Insufficient
Withdrawals Due to Adverse Events	4 RCT (n=2,100) 24-26 weeks	Mild to moderate	*12 mg/d PO or 9.5 mg/d patch vs. 4 mg/d PO or 4.6 mg/d patch:* 17% vs. 11%; ARD, 6% [95% CI, 2 to 10]; RR, 1.63 [95% CI, 0.49 to 5.50]; 2 trials, n=1,055)[241, 243] *9.5 mg/d vs. 12 mg/d-13.3 mg/d:* 9.6% vs. 8.1%; ARD, 1.5% [95% CI, -3.1 to 6.1]; RR, 1.18 [95% CI, 0.70 to 1.99]; 1 trial, n=590)[240] *12 mg/d in 3 doses vs. 2 doses:* 11% vs. 17% (ARD, -6% [95% CI, -12 to 0]; RR, 0.63 [95% CI, 0.39 to 1.02];1 trial, n=455)[239]	All insufficient

ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS-ADL=Alzheimer's Disease Cooperative Study—Activities of Daily Living; ADCS-CGIC=Alzheimer's Disease Cooperative Study—Clinical Global Impression of Change; ARD=absolute risk difference; CATD=Clinical Alzheimer's-type dementia; CI=confidence intervals; CIBIC-Plus=Clinician Interview Based Impression of Change Incorporating Caregiver Information Scale; DAD=Disability Assessment for Dementia; GDS=Global Deterioration Scale; MD=mean difference; MMSE=Mini-Mental State Examination; NNTB=number needed to treat to produce 1 additional benefit; NNTH=number needed to treat to produce 1 additional harm; NR=not reported; PDS=Progressive Deterioration Scale; PO=oral; RCT=randomized controlled trial; RR=risk ratio; SAE=serious adverse events; SMD=standardized mean difference; TMT=Trail Making Test

*Clinical Impression of Change was evaluated using the CIBIC-Plus or ADCS-CGIC.

Variation in Outcomes by Participant Characteristics

No studies reported whether participant characteristics modified the effect of rivastigmine dose on cognition, function, quality of life, global staging, clinical impression of change, or harms.

Memantine Versus Placebo

Key Messages

- In older adults with mild to moderate CATD who were not being treated with a cholinesterase inhibitor, the evidence for memantine compared with placebo showed:
  - No difference for function (low SOE).
  - Small improvement for clinical impression of change (low SOE).
  - Insufficient evidence about cognition, serious adverse events, or withdrawals due to adverse events.
  - No evidence about quality of life or staging of disease.
- In older adults with mild to moderate CATD who were being treated with a cholinesterase inhibitor, evidence for memantine compared with placebo showed:
  - No difference in clinical impression of change (low SOE).
  - Insufficient evidence about cognition, function, serious adverse events, or withdrawals due to adverse events.
  - No evidence about quality of life or staging of disease.
- In older adults with moderate to severe CATD who were being treated with a cholinesterase inhibitor, the evidence for memantine compared with placebo showed:
  - Inconsistent effects on cognition (low SOE for improvement on brief battery, insufficient SOE for brief tests commonly used as individual stand-alone tests).
  - No difference in function (low SOE).
  - Small improvement in clinical impression of change (low SOE).
  - Insufficient evidence about serious adverse events and withdrawals due to adverse events.
  - No evidence about quality of life or staging of disease.

Eligible Studies

We identified 31 eligible publications of 16 unique randomized controlled trials that compared memantine with placebo in adults with CATD and reported results for cognition, function, quality of life, global staging, clinical impression of change, or harms.[249-279] Ten trials had high ROB and were excluded from analyses.[249, 251-256, 258, 261, 264] The most common reason for high ROB was high attrition, including for all four eligible trials of 52 weeks or longer that did not report shorter-term outcomes.[255, 256, 261, 264] The remaining six trials had medium ROB and were analyzed.[250, 257, 259, 260, 262, 263] Appendix Tables E.24-E.29 provide evidence tables, summary ROB assessments, and strength of evidence for key comparisons and outcomes.

Baseline Study Characteristics

Characteristics of the 2,227 participants in the six analyzed trials are shown in Table 6.11, organized by category of treatment comparison: (1) memantine versus placebo in patients untreated with a cholinesterase inhibitor;[250] (2) add-on memantine versus placebo in patients continuing stable pre-study (≥3-6 months) cholinesterase inhibitor treatment;[257, 260, 262, 263] and (3) randomization of individuals receiving pre-study cholinesterase inhibitor treatment (≥3 months) to continued cholinesterase inhibitor monotherapy, discontinuation of cholinesterase inhibitor, replacement of cholinesterase inhibitor with memantine monotherapy, or continuation of cholinesterase inhibitor plus add-on memantine.[259]

All trials included participants with probable CATD, with one [257]also including participants with possible AD.[259] Two trials enrolled participants with mild to moderate CATD (n=836), with a mean baseline MMSE of 17 (range 10-22).[250, 262] The other four trials enrolled participants with moderate to severe CATD (n=1,391),[257, 259, 260, 263] with a mean baseline MMSE of 10 (range 3-17). Nearly all study participants were community-dwelling,[260] and all were required to have a competent caregiver. Mean participant age was 77 years, 64 percent were female, and 93 percent were white.

Five trials evaluated memantine doses of 20 mg once daily, or 10 mg taken twice daily[250, 259, 260, 262, 263] and one trial evaluated extended-release memantine 28 mg once daily.[257]

Table 6.11. Baseline characteristics of memantine versus placebo trials by type of drug comparison, with and without continued cholinesterase inhibitor

Treatment Comparison	Characteristic	N, Mean, or % (Study Range)	Trials Reporting, N
Memantine vs. placebo (no cholinesterase inhibitor)	Number of participants enrolled, n	403	1
	Age, years	79	1
	Men, %	41	1
	White race, %	91	1
	Mild to Moderate Alzheimer's disease severity*, %	100	1
	Prior dementia medication use (mostly donepezil), %	66	1
	MMSE, mean	17 (10-22)	1
Memantine vs. placebo (added on to stable cholinesterase inhibitor)	Number of participants enrolled, n (range)	1,529 (15 to 677)	4
	Age, years	76	4
	Men, %	35 (13 to 48)	4
	White race, %	93 (91 to 94)	2
	Mild to moderate Alzheimer's disease severity:* %	28 (n=433)	1
	Moderate to severe Alzheimer's disease severity:* %	72 (n=1,096)	3
	MMSE, mean	12 (3 to 22)	4
Memantine vs. placebo (half of each group continued prior cholinesterase inhibitor)	Number of participants enrolled, n	295	1
	Age, years	77	1
	Men, %	35	1
	White race, %	95	1
	Moderate to severe Alzheimer's disease severity,*, %	100	1
	MMSE, mean (range included)	9 (5-13)	1

MMSE=Mini-Mental State Examination

*Alzheimer's disease severity was based on that reported by the individual trials.

Memantine Versus Placebo (Without Cholinesterase Inhibitor)

Outcomes

Table 6.12 summarizes the primary efficacy and harms results between memantine and placebo in patients not receiving a cholinesterase inhibitor. Results were based on a single eligible trial that randomized 403 participants with mild to moderate CATD to memantine 20 mg daily versus placebo for 24 weeks.[250]

For efficacy, evidence was insufficient to draw conclusions about between group differences for change in brief multidomain cognitive batteries and low strength evidence showed no between group differences for change in function (low SOE). Although likelihood of clinical impression of change not worsening (i.e., either any improvement or no change) was greater with memantine than placebo (low SOE), no studies reported on likelihood of improvement or of moderate or marked improvement. Further, no studies reported data on brief cognitive tests

commonly used as individual stand-alone tests, quality of life, staging, or change in patient residence to a different level of independence.

For harms, evidence was insufficient to draw conclusions about between treatment group differences for serious adverse events or withdrawals due to adverse events. Although memantine increased risk of somnolence versus placebo (7% vs. 1%; RR, 7.03 [95% CI, 1.62 to 30.56]), treatment groups did not statistically differ for risk of confusion (5% vs. 3.5%; RR, 1.44 [95% CI, 0.56 to 3.70]), falls (7.4% vs. 7.5%; RR, 1.00 [95% CI, 0.50 to 2.00]) or mortality (0.5% vs. 0.5%; RR, 1.00 [95% CI, 0.06 to 15.96]). No studies reported data on extrapyramidal symptoms or stroke.

Table 6.12. Summary of findings for primary outcomes: memantine versus placebo (none receiving cholinesterase inhibitor)

Domain	# Studies/ Design (n Analyzed) Timing	CATD Population	Findings (Incidence, Change from Baseline)	Strength of Evidence
Cognition: Brief Multidomain Batteries	1 RCT[250] (n=403) 24 weeks	Mild to moderate	**Mean ADAS-Cog change**: Observed cases analysis*: SMD, -0.13 (95% CI, -0.35 to 0.09)	Insufficient
Function	1 RCT[250] (n=403) 24 weeks	Mild to moderate	**Mean ADCS-ADL change**: No difference (observed cases analysis: SMD, 0.00 [95% CI, -0.21 to 0.21])†	Low
Clinical Impression of Change‡	1 RCT[250] (n=403) 24 weeks	Mild to moderate	**Likelihood unchanged/improved**: Favors memantine (67% vs. 51%; ARD, 17% [95% CI, 7% to 26%]; NNTB, 6 [95% CI, 4 to 14]; RR, 1.33 [95% CI, 1.12 to 1.57]) **Mean CIBIC-Plus change**: Favors memantine: SMD, -0.27 [95% CI, -0.49 to -0.05])	Low
SAE	1 RCT[250] (n=403) 24 weeks	Mild to Moderate	10% vs. 10% (ARD, 0% [95% CI, -5.8 to 5.9]; RR, 1.00 [95% CI, 0.56 to 1.81])	Insufficient
Withdrawals Due to Adverse Events	1 RCT[250] (n=403) 24 weeks	Mild to Moderate	9.5% vs. 5% (ARD, 4.5% [95% CI, -0.5 to 9.5]; RR, 1.91 [95% CI, 0.91 to 4.00])	Insufficient

ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS-ADL=Alzheimer's Disease Cooperative Study–Activities of Daily Living; ARD=absolute risk difference; CATD=Clinical Alzheimer's-type Dementia; CI=confidence interval; CIBIC-Plus=Clinician Interview Based Impression of Change Incorporating Caregiver Information Scale; NNTB=number needed to treat to produce 1 additional benefit; RCT=randomized controlled trial; RR=risk ratio; SAE=serious adverse events; SMD=standardized mean difference

*Results varied by analytic method used for missing data (results statistically significantly favored memantine when missing data imputed using mixed methods repeated measures or last observation carried forward analyses).

†Memantine and placebo did not differ for change in ADCS-ADL between baseline and 24 weeks regardless of which analytical method was used to account for missing data.

‡Clinical Impression of Change was evaluated using the CIBIC-Plus.

Variation in Outcomes by Participant or Drug Characteristics

Last, no studies reported on whether efficacy of memantine versus placebo in individuals not receiving a cholinesterase inhibitor varied as a function of participant characteristics, or by drug dose, duration or delivery route. Appendix Tables E.24-E.29 provide detailed evidence tables and strength of evidence for key comparisons and outcomes.

Memantine Versus Placebo (With Cholinesterase Inhibitor)

Outcomes

Table 6.13 summarizes the primary efficacy and harms from the five trials that compared memantine with placebo in adults with CATD who were receiving a stable cholinesterase inhibitor. For efficacy, in adults with mild to moderate CATD, add-on memantine and add-on placebo did not differ for function or clinical impression of change (both low SOE), and evidence was insufficient to draw conclusions about differences in cognition. No studies reported data on quality of life, global staging, or change in patient residence to a greater level of dependence. In adults with moderate to severe CATD, add-on memantine resulted in small improvements in clinical impression of change and brief multidomain cognitive batteries, but not function (all low SOE). Evidence in this population was insufficient to draw conclusions about between-treatment differences in brief cognitive tests commonly used as individual stand-alone tests or domain-level cognitive tests typically part of a larger battery, and no studies reported data on quality of life, staging, or change in patient residence to a different level of independence.

For harms, evidence was insufficient to draw conclusions about differences between add-on memantine and add-on placebo for serious adverse events (9.9% vs. 9.3%; ARD, 0.6% [95% CI, -2.9% to 4.1%]; RR, 1.06 [95% CI, 0.73 to 1.53]; 2 trials),[257, 262] or withdrawals due to adverse events (8.1% vs. 8.4%; ARD, -0.2% [95% CI, -3% to 2.5%]; RR, 0.92 [95% CI, 0.49 to 1.71]; 3 trials).[257, 262, 263] In addition, treatment groups did not statistically differ for confusion (4.5% vs. 2.7%; ARD, 1.8% [95% CI, -0.1% to 3.7%]; RR, 1.62 [95% CI, 0.70 to 3.76]; 3 trials),[257, 262, 263] somnolence (2.9% vs. 1.2%; ARD, 1.7% [95% CI, -0.4% to 3.9%]; RR, 2.46 [95% CI, 0.78 to 7.75]; 1 trial),[257] falls (7.4% vs. 8.5%; ARD, -1.1% [95% CI, -3.6% to 1.4%]; RR, 0.87 [95% CI, 0.56 to 1.36]; 4 trials),[257, 259, 263] stroke (1.2% vs. 1.7%; ARD, -0.5% [95% CI, -1.9% to 1.1%]; RR, 0.73 [95% CI, 0.25 to 2.12]; 2 trials)[257, 259] or mortality (3.4% vs. 4.3%; ARD, -0.9% [95% CI, -2.9% to 1.1%]; RR, 0.76 [95% CI, 0.44 to 1.34]; 3 trials).[257, 259, 262] No studies reported data on extrapyramidal symptoms.

Table 6.13. Summary of findings for primary outcomes: memantine versus placebo (all continuing stable pre-trial cholinesterase inhibitor), by baseline CATD severity

Domain	# Studies/ Design (n Analyzed) Timing	CATD Population	Findings (Incidence, Change from Baseline)	Strength of Evidence
Cognition: Brief Stand-Alone Tests	1 RCT[262] (n=433) 24 weeks	Mild to moderate	**Mean MMSE change:*** SMD, -0.11 (95% CI, -0.31 to 0.09)	Insufficient
	2 RCT[259, 260] (n=310) 24-30 weeks	Moderate to severe	**Mean MMSE change:** SMD, 0.47 [95% CI, 0.14 to 0.80]; 1 trial, n=295[259]† **MMSE at end of treatment:** SMD, -0.77 (95% CI, -1.82 to 0.28); 1 trial, n=15[260]	Insufficient
Cognition: Brief Multidomain Batteries	1 RCT[262] (n=433) 24 weeks	Mild to moderate	**Mean ADAS-Cog change:** SMD, 0.04 (95% CI, -0.16 to 0.25)	Insufficient
	2 RCT[257, 263] (n=1,081) 24 weeks	Moderate to severe	**Mean SIB change:** Favors add-on memantine (SMD, 0.27 [95% CI, 0.12 to 0.42])	Low

Domain	# Studies/ Design (n Analyzed) Timing	CATD Population	Findings (Incidence, Change from Baseline)	Strength of Evidence
Cognition-Domain Level Tests Typically Part of a Larger Battery	2 RCT (n=692) [257, 260] 24 weeks	Moderate to severe	**Mean verbal fluency (language) change:‡** *28 mg/d extended release:* SMD, 0.23 (95% CI, 0.07 to 0.38); 1 trial, n=677[257]	Insufficient
Function	1 RCT[262] (n=433) 24 weeks	Mild to moderate	**Mean ADCS-ADL change:** No difference (SMD, 0.12 [95% CI, -0.08 to 0.32])**	Low
	3 RCT[257, 259, 263] (n=1,229) 24-30 weeks	Moderate to severe	**Mean ADCS-ADL change:** No difference (SMD, 0.14 [95% CI, -0.01 to 0.29]; 2 trials, n=983) [257, 263] **Mean BADLS change:** No difference (SMD, -0.26 [95% CI, -0.58 to 0.07]; 1 trial, n=246)[259]	Low
Clinical Impression of Change	1 RCT[262] (n=433) 24 weeks	Mild to moderate	**Mean CIBIC-Plus change:** No difference (SMD, 0.00 [95% CI, -0.20 to 0.20])	Low
	2 RCT[257, 263] (n=1,081) 24 weeks	Moderate to severe	**Mean CIBIC-Plus change:** Favors add-on memantine (SMD, -0.25 [95% CI, -0.37 to -0.12])	Low
SAE	1 RCT [262] (n=433) 24 weeks	Mild to Moderate	12.4% add-on memantine vs. 13.9% add-on placebo (ARD, -1.4% [95% CI, -7.8 to 4.9]; RR, 0.90 [95% CI, 0.55 to 1.45])	Insufficient
	1 RCT[257] (n=676) 24 weeks	Moderate to severe	8.2% add-on memantine vs. 6.3% add-on placebo (ARD, 1.9% [95% CI, -2 to 5.8]; RR, 1.31 [95% CI, 0.76 to 2.26])	Insufficient
Withdrawals Due to Adverse Events	1 RCT[262] (n=433) 24 weeks	Mild to Moderate	4.8% add-on memantine vs. 7.9% add-on placebo (ARD, -3.1% [95% CI, -7.5 to 1.3]; RR, 0.61 [95% CI, 0.30 to 1.23])	Insufficient
	2 RCT[257, 263] (n=1,081) 24 weeks	Moderate to severe	9.0% add-on memantine vs. 8.6% add-on placebo (ARD, 0.4% [95% CI, -3 to 3.8]; RR, 0.98 [95% CI, 0.38 to 2.57])	Insufficient

ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS-ADL=Alzheimer's Disease Cooperative Study–Activities of Daily Living; ARD=absolute risk difference; BADLS=Bristol Activities of Daily Living Scale; CATD=Clinical Alzheimer's-type Dementia; CI=confidence intervals; CIBIC-Plus=Clinician Interview-Based Impression of Change Plus Caregiver Input; LOCF=last observation carried forward; NNTH=number needed to treat to produce 1 additional harm; MMSE=Mini-Mental State Examination; OC=observed cases; RCT=randomized controlled trial; RR=risk ratio; SAE=serious adverse event; SIB=Severe Impairment Battery; SMD=standardized mean difference

*Results shown are for LOCF analysis, but results consistently showed no statistical difference between memantine and placebo regardless of the analytic method used to account for missing data.

†Results reported are for add-on memantine vs. add-on placebo in patients previously on stable cholinesterase inhibitor treatment. Participants also were randomized to cholinesterase inhibitor continuation vs. discontinuation (cholinesterase inhibitor placebo), which did not interact with the memantine/placebo results (p=0.14).

‡Results are shown for LOCF analyses at week 30. Results statistically favored add-on memantine vs. add-on placebo based on OC analyses at week 24 (p=0.01). LOCF results were not reported at week 24 and OC results were not reported at week 30. Data on memory, executive function, and attention was only available from a separate small trial (n=15) and are detailed in Appendix E. [260]

**Results shown are for OC analysis, but results consistently showed no statistical difference between memantine and placebo regardless of the analytic method used to account for missing data.

Variation in Outcomes by Participant Characteristics

In adults with CATD who continued prior cholinesterase inhibitor treatment, no studies reported data on whether the efficacy of add-on memantine compared with add-on placebo varied as a function of participant characteristics, or memantine dose, duration, or delivery route.

Chapter 7. Key Question 4: Supplements Versus Placebo for Cognition, Function, and Quality of Life

Eligible Studies

We identified 48 eligible publications of 42 unique trials reporting results for cognition, function, quality of life, global staging, clinical impression of change, or harms. Among unique, eligible trials, we identified 28 that evaluated the efficacy of 15 different supplements that were rated as high risk of bias (ROB) and excluded from analyses.

Specific supplements evaluated in these excluded trials included ginkgo biloba (6 trials), [208, 280-287] acetyl-l-carnitine (5 trials),[288-292] ginseng (3 trials), [293-295] curcumin (2 trials), [296, 297] lecithin (2 trials), [298, 299] vitamin E (2 trials), [300, 301] coconut oil (1 trial),[302] folic acid (1 trial), [303] multivitamin (1 trial), [304] oral nicotinamide adenine dinucleotide (1 trial), [305] ninjin'yoeito (1 trial), [306] Colostrinin® and selenium (1 trial), [307] thiamine (1 trial)[308] and resveratrol (1 trial). [309] Most of these trials were rated high ROB based on high attrition bias, [208, 280-289, 300] while high detection or reporting bias, [290, 298, 301] and high selection bias[305, 306] were less common. For many supplements, the only eligible trials were high ROB. Additionally, one trial examining the nutritional drink Souvenaid® and two trials examining omega-3 fatty acids were assessed as high ROB and not included in our analysis for these supplements. [310-313]

We analyzed the findings of the 11 remaining trials with low or medium ROB, which examined the following supplements: Souvenaid® (two trials), omega-3 fatty acids (two trials), omega-3 fatty acids and alpha lipoic acid (one trial), antioxidants (one trial), choline alfoscerate (one trial), prolonged release melatonin (one trial), sodium selenate (one trial), soy isoflavones (one trial), copper (one trial), and folic acid combined with vitamin B (one trial). [314-326] Appendix F provides evidence tables, summary ROB assessments, and strength of evidence for key comparisons and outcomes.

Souvenaid®

Key Messages

- In older adults with CATD, evidence for the nutritional drink Souvenaid® compared with placebo showed:
    - No difference for function, serious adverse events, or withdrawals due to adverse events (low strength of evidence [SOE]).
    - Insufficient evidence to draw conclusions for cognition, quality of life, staging, or clinical impression of change.

Baseline Study Characteristics

Three publications reporting two trials (n=786) examined the efficacy of Souvenaid®, a nutritional drink consisting of omega-3 fatty acids, phospholipids, vitamins (B12, B6, C, and E), folate, and selenium. [315-317] One trial enrolled community-dwelling subjects with mild clinical Alzheimer's-type dementia (CATD) (Mini-Mental State Exam [MMSE] ≥20). [315, 316] One trial enrolled participants' with mild to moderate CATD severity (MMSE 14 to 24). [317] Participant mean age was 76 years, 49 percent of participants were male, and race was not reported. Treatment duration for both trials was 24 weeks.

Outcomes

Table 7.1 summarizes primary efficacy and harms results. For efficacy, Souvenaid® and placebo did not differ for change in function (low SOE) and evidence was insufficient to draw conclusions about differences in brief multidomain cognitive batteries and staging. No studies reported data on brief cognitive tests commonly used as individual stand-alone tests, domain level cognitive tests, quality of life, clinical impression of change, or change in patient residence to a different level of independence.

For harms, risk of serious adverse events and withdrawals due to adverse events did not differ between Souvenaid® and placebo (both low SOE). In one trial reporting, confusion was reported in one placebo group participant and incident falls was reported in one participant each in the Souvenaid® and placebo groups. [315, 316] No trial reported data on somnolence, extrapyramidal symptoms, stroke or mortality.

Table 7.1. Summary of findings for primary outcomes: Souvenaid® versus placebo

Domain	# Studies/ Design (n Analyzed) Timing	CATD Population	Findings (Incidence, Change from Baseline)	Strength of Evidence
Cognition - Brief Multidomain Batteries	2 RCT[315-317] (N=786) 24 weeks	Mild (33%), or mild to moderate (67%)	**Mean NTB change:** SMD, 0.30 (95% CI, 0.06 to 0.54) **Mean ADAS-Cog change:** SMD, 0.06 (95% CI, -0.13 to 0.25)	Insufficient
Function	2 RCTs[315-317] (N=786) 24 weeks	Mild (33%), or mild to moderate (67%)	**Mean ADCS-ADL change:** No difference (SMD, -0.01 [95% CI, -0.19 to 0.18]) **Mean DAD score at 24 weeks:** No difference (p=0.36)	Low
Staging	1 RCT[317] (N=527) 24 weeks	Mild	**Mean CDR-SOB change:** SMD, 0.01 (95% CI, -0.18 to 0.19)	Insufficient
SAE	2 RCT[315-317] (N=786) 24 weeks	Mild (33%), or mild to moderate (67%)	No difference (9.4% vs. 10.3%; ARD, -0.9% [95% CI, -5 to 3.3]; NNTB, 111 [95% CI, NNTB 20 to ∞ to NNTH 30]; RR, 1.01 [95% CI, 0.50 to 2.02])	Low
Withdrawals Due to Adverse Events	2 RCT[315-317] (N=786) 24 weeks	Mild (33%), or mild to moderate (67%)	No difference (1.3% vs. 1.5%; ARD, -0.3 [95% CI, -1.9 to 1.4]; NNTB, 333 [95% CI, NNTB 53 to ∞ NNTH 71]; RR, 0.84 [95% CI, 0.25 to 2.84])	Low

ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS-ADL= Alzheimer's Disease Cooperative Study–Activities of Daily Living; ARD=absolute risk difference; CATD=Clinical Alzheimer's-type Dementia; CDR-SOB=Clinical Dementia Rating-Sum of Boxes; CI=confidence interval; DAD=Disability Assessment for Dementia; NNTH=number needed to treat to produce 1 additional harm; NTB=Neuropsychological Test Battery; RCT=randomized controlled trial; RR=risk ratio; SAE=serious adverse events; SMD=standardized mean difference

Variation in Outcomes by Participant or Drug Characteristics

No studies reported on whether Souvenaid® efficacy or harms varied as a function of participant characteristics, or by drug dose, duration or delivery route. Appendix Tables F.2-F.5 provide detailed evidence tables and strength of evidence for key comparisons and outcomes.

Omega-3 Fatty Acids

Key Messages

- In older adults with CATD, evidence for omega-3 fatty acids compared with placebo showed:
    - No difference for cognition (low SOE).
    - Insufficient evidence to draw conclusions about function, quality of life, staging, clinical impression of change, serious adverse events, or withdrawals due to adverse events.

Baseline Study Characteristics

Three publications reporting two trials (n=230) examined the efficacy of omega-3 fatty acids on cognition, function, and quality of life in patients with CATD.[318-320] Both trials were medium ROB. Mean age across both study populations was 74 years, and approximately 47 percent of participants were male. Neither trial reported race. Treatment duration was 6 months for one trial and 12 months for the other trial. The trials enrolled participants with mild to moderate CATD, with a mean MMSE score of 23 across both studies (MMSE 15 to 26). Participants were community dwelling. One trial used capsules with docosahexaenoic acid (430 mg) and eicosapentaenoic acid (150 mg).[318, 319] The other trial used capsules of fish oil concentrate with docosahexaenoic acid (675 mg) and eicosapentaenoic acid (975 mg).[320]

Outcomes

Table 7.2 summarizes primary efficacy and harms results. For efficacy, omega-3 fatty acids and placebo did not differ for cognition, but evidence was insufficient to draw conclusions about differences for function or staging. No studies reported data on domain-level cognitive tests, quality of life, clinical impression of change or change in patient residence to a different level of independence.

For harms, evidence was insufficient to draw conclusions about differences between omega-3 fatty acids and placebo for risk of serious adverse events[320] and withdrawals due to adverse events. [318, 319] One study reported one participant with an incident fall and no deaths in the omega-3 fatty acid group and reported two with a fall and one death in the placebo group. [320] No studies reported data on somnolence, confusion, extrapyramidal symptoms or stroke.

Table 7.2. Summary of findings for primary outcomes: omega-3 fatty acids versus placebo

Domain	# Studies/ Design (n Analyzed) Timing	CATD Population	Findings (Incidence, Change from Baseline)	Strength of Evidence
Cognition - Brief Stand-Alone Tests	2 RCT[318-320] (N=230) 6-12 months	Mild to Moderate	**Mean MMSE change to 12 months:** No difference (-4.3 omega-3 fatty acid group vs. -4.6 placebo, p=0.80) **Mean MMSE score at 6 months:** No difference (22.8 omega-3 fatty acid group vs. 22.4 placebo)	Low

Domain	# Studies/ Design (n Analyzed) Timing	CATD Population	Findings (Incidence, Change from Baseline)	Strength of Evidence
Cognition - Brief Multidomain Batteries	2 RCT[318-320] (N=230) 6-12 months	Mild to Moderate	**Mean ADAS-Cog change to 12 months:** No difference (4.4 omega-3 fatty acid group vs. 3.2 placebo, p=0.86) **Mean ADAS-Cog score at 6 months:** No difference (27.7 omega-3 fatty acid group vs. 28.3 placebo)	Low
Function	1 RCT[320] (N=26) 12 months	Mild to Moderate	**Mean IADL change:** SMD, -0.99 (95% CI, -1.77 to -0.18) **Mean ADL change:** 2.5 omega-3 fatty acid group vs. 2.9 placebo, p=0.83	Insufficient
Staging	1 RCT [318, 319] (N=204) 6 months	Mild to Moderate	**Mean CDR-SOB at 6 months:** 6.2 omega-3 fatty acid group vs. 6.5 placebo, p=0.59	Insufficient
SAE	1 RCT[320] (N=26) 12 months	Mild to Moderate	8% in both treatment groups collectively, but results not separated by treatment group.	Insufficient
Withdrawals Due to Adverse Events	1 RCT[318, 319] (N=204) 6 months	Mild to Moderate	9% in both treatment groups collectively, but results not separated by treatment group.	Insufficient

ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADL=activities of daily living; CATD= Clinical Alzheimer's-type Dementia; CDR-SOB=Clinical Dementia Rating-Sum of Boxes; CI=confidence interval; IADL=instrumental activities of daily living; MMSE=Mini-Mental State Examination; RCT=randomized controlled trial; SAE=serious adverse events; SMD=standardized mean difference

Variation in Outcomes by Participant or Drug Characteristics

One trial reported *post hoc* analyses showing no statistically significant difference between omega-3 fatty acids and placebo for MMSE change from baseline in either participants with baseline MMSE ≥24 (p=0.40) or <24 (p=0.15). Authors also reported that treatment effects did not differ within participant groups defined by MMSE <22 or >27 but provided no data. Authors did not report any test for interaction. No studies reported on whether omega-3 fatty acid efficacy and harms varied as a function of other participant characteristics, or supplement formulation, dose, duration, or delivery route. Appendix Tables F.6-F.9 provide detailed evidence tables and strength of evidence for key comparisons and outcomes.

Additional Supplements

Key Messages

- Evidence was insufficient to draw conclusions about the efficacy and harms of the following supplements, for which all eligible trials were medium ROB, and results were analyzed:
    - Omega-3 fatty acids combined with alpha lipoic acid, antioxidants, choline alfoscerate, prolonged release melatonin, sodium selenite, soy isoflavones, copper, and folic acid combined with vitamin B (each supplement was studied in 1 trial only).
- Evidence was insufficient to draw conclusions about the efficacy and harms of the following supplements, for which all eligible trials were rated high ROB, and results were not analyzed:

    - Ginkgo biloba (6 trials), acetyl-l-carnitine (5 trials), ginseng (3 trials), curcumin (2 trials), lecithin (2 trials), vitamin E (2 trials), coconut oil (1 trial), folic acid (1 trial), multivitamin (1 trial), oral nicotinamide adenine dinucleotide (1 trial), ninjin'yoeito (1 trial), Colostrinin® (1 trial), selenium (1 trial), thiamine (1 trial), and resveratrol (1 trial).
- No eligible studies were identified that examined the efficacy or harms of Prevagen (apoaequorin), phosphotidylserine or Huperzine.

Baseline Study Characteristics

Eight publications reporting eight trials examined the efficacy of omega-3 fatty acids combined with alpha lipoic acid,[320] antioxidants,[321] choline alfoscerate,[322] prolonged release melatonin,[323] sodium selenite,[324] soy isoflavones,[325] copper,[326] and folic acid combined with vitamin B,[314] respectively. All trials were medium ROB. Six studies enrolled subjects with mild and/or moderate CATD,[320-324] while two did not specify the severity of enrolled subjects.[325, 326]

Primary Outcomes

Though collectively these eight trials reported a few statistically significant results favoring individual supplements compared with placebo, evidence was insufficient to draw conclusions about differences between each of these supplements compared with placebo for all reported efficacy and harms outcomes.

For a trial that compared omega-3 fatty acids plus alpha lipoic acid versus placebo (n=26), results statistically favored the supplement combination on an IADL function measure, but not for cognition or an ADL function measure.[320] For a trial of add-on prolonged release melatonin compared with add-on placebo in participants who continued cholinesterase inhibitor treatment (n=80), results statistically favored the add-on melatonin group for change in cognition (MMSE, ADAS-Cog) and function (IADL).[323] In a trial that compared choline alfoscerate with placebo (n=261), results statistically favored choline alfoscerate for cognition (MMSE, ADAS-Cog), global staging (Global Deterioration Scale [GDS]), and clinical impression of change (Clinical Global Impression [CGI]).[322]

By comparison, individual trials on antioxidant supplementation (n=52), sodium selenate (n=40), soy isoflavones (n=65), add-on copper (n=68), and folic acid combined with vitamin B (n=409) reported no difference between the supplement and placebo for all measured domains.[314, 321, 324-326] Trials reported limited information about harms. Appendix Tables F.10-F.43 provide detailed evidence tables and strength of evidence for key comparisons and outcomes.

Chapter 8. Key Question 5: Prescription Drugs Versus Other Active Treatments for Cognition, Function, and Quality of Life

Prescription Drugs Versus Prescription Drugs

Galantamine Versus Donepezil

Key Messages

- In older adults with moderate clinical Alzheimer's-type dementia (CATD), evidence was insufficient to draw conclusions about the comparative effectiveness and harms of galantamine versus donepezil.

Eligible Studies

We identified three eligible publications of three unique trials that compared galantamine with donepezil and reported results for cognition, function, global staging, clinical impression of change, or harms.[327-329] Two trials were high risk of bias (ROB) and excluded from analyses.[328, 329] The remaining trial was medium ROB.[327] Appendix Tables G.1-G.4 provide evidence tables, summary ROB assessments, and strength of evidence for key comparisons and outcomes.

Baseline Study Characteristics

Trial participants (n=188) were required to have a baseline Mini-Mental State Examination (MMSE) score between 9 and 18, and were considered to have moderate CATD. Participants must not have received previous galantamine or donepezil but could have received another cholinesterase inhibitor or other cognitive enhancer more than 30 days before study entry. Mean participant age was 73 years, 38 percent of participants were male, and 99 percent were white. Mean baseline MMSE was 15. Participants were randomized to galantamine up to 24 mg/day or donepezil up to 10 mg/day for 52 weeks. Residential status was not described, but participants were required to have a reliable caregiver.

Outcomes

Table 8.1 summarizes the primary efficacy and harms results. For efficacy, evidence was inconsistent and insufficient to draw conclusions about differences between galantamine and donepezil for brief cognitive tests commonly used as individual stand-alone tests, brief multidomain batteries or function. No studies reported data on domain-level cognitive tests, quality of life, staging, clinical impression of change, or change in patient residence to a different level of independence.

For harms, evidence was insufficient to draw conclusions about differences between galantamine and donepezil for risk of serious adverse events (18.6% vs. 19.8%; absolute risk difference [ARD], -1.2% [95% confidence interval (CI), -12.5 to 10.0]; risk ratio [RR], 0.94 [95% CI, 0.52 to 1.69]) or withdrawals due to adverse events (13% each; ARD, 0.2% [95% CI, -9.5 to 9.9]; RR, 1.02 [95% CI, 0.49 to 2.11]). Incident falls were reported for 16.5 percent of galantamine participants versus 8.8 percent in the donepezil group (p=0.12). Mortality was 2

percent for galantamine and 3 percent for donepezil. No studies reported data on somnolence, confusion, extrapyramidal symptoms or stroke.

Appendix Tables G.1-G.4 provides detailed evidence tables and strength of evidence for key comparisons and outcomes.

Table 8.1. Summary of findings for primary outcomes: galantamine versus donepezil

Domain	# Studies/ Design (n Analyzed) Timing	CATD Population	Findings (Incidence, Change from Baseline)	Strength of Evidence
Cognition-Brief Stand-Alone Tests	1 RCT[327] (n=182) 52 weeks	Moderate	**Likelihood MMSE unchanged/improved (≥0):** 55.2% galantamine vs. 32.5% donepezil (ARD, 22.7% [95% CI, 7.9 to 37.5]; RR, 1.70 [95% CI, 1.17 to 2.47]) **Mean MMSE change:** SMD, 0.28 (95% CI, -0.02 to 0.57)	Insufficient
Cognition - Brief Multidomain Batteries	1 RCT[327] (n=182) 52 weeks	Moderate	**Likelihood ADAS-Cog unchanged/improved (≤0):** 44.9% galantamine vs. 31.7% donepezil (ARD, 13.2% [95% CI, -1.2 to 27.7]; RR, 1.42 [95% CI, 0.96 to 2.10]) **Mean ADAS-Cog change:** SMD, -0.16 [95% CI, -0.45 to 0.13])	Insufficient
Function	1 RCT[327] (n=182) 52 weeks	Moderate	**Likelihood BADLS unchanged/improved (≤0):** 39.3% galantamine vs. 39% donepezil, p>0.05 **Mean BADLS change:** SMD, -0.03 (95% CI, -0.32 to 0.26)	Insufficient
SAE	1 RCT[327] (n=188) 52 weeks	Moderate	18.6% galantamine vs. 19.8% donepezil (ARD, -1.2% [95% CI, -12.5 to 10.0])	Insufficient
Withdrawals Due to Adverse Events	1 RCT[327] (n=188) 52 weeks	Moderate	13.4% galantamine vs. 13.2% donepezil (ARD, 0.2% [95% CI, -9.5 to 9.9])	Insufficient

ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; ARD=absolute risk difference; BADLS=Bristol Activities of Daily Living Scale; CATD= Clinical Alzheimer's-type Dementia; CI=confidence intervals; MMSE=Mini-Mental State Examination; RCT=randomized controlled trial; RR=risk ratio; SAE=serious adverse events; SMD=standardized mean difference

Variation in Outcomes by Participant or Drug Characteristics

Within the subgroup of participants with baseline MMSE scores of 12 to 18, those allocated to galantamine compared with donepezil had less worsening at 1 year for both MMSE score (-0.32 vs. -2.0 points, $p \leq 0.0005$) and 11-item Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) score (1.6 vs. 4.1, $p \leq 0.05$). However, results were not separately reported for participants with MMSE scores of 9 to 11, and no test for interaction was reported. No studies reported data about whether comparative effectiveness of galantamine versus donepezil varied as a function of drug dose, duration, or delivery route.

Memantine Versus Donepezil

Key Messages

- In older adults with mild to moderate CATD, evidence was insufficient to draw conclusions about the comparative effectiveness and harms of memantine versus donepezil.

Eligible Studies

We identified one eligible publication of one unique trial that compared memantine with donepezil and reported results for cognition, function, global staging, clinical impression of change, or harms. [330] ROB was medium. Appendix Tables G.5-G.8 provide evidence tables, summary ROB assessments, and strength of evidence for key comparisons and outcomes.

Baseline Study Characteristics

The trial enrolled 67 participants with CATD, a baseline MMSE – Spanish version ≥16 points, and Clinical Dementia Rating Scale (CDR) stage of 1 or 2. Mean age was 77 years, and 30 percent of participants were male. The trial was conducted in Spain and information about race was not reported. Mean MMSE was 23. Participants were randomized to memantine 20 mg/day versus donepezil titrated up to 10 mg/day for 24 weeks. Residential status was not reported, but participants were required to have a reliable caregiver.

Outcomes

Table 8.2 summarizes the primary comparative effectiveness and harms results. For comparative effectiveness, evidence was insufficient to draw conclusions about differences between memantine and donepezil for brief multidomain cognitive batteries and function, and no studies reported data on brief cognitive tests commonly used as individual stand-alone tests, domain level cognitive tests, function, quality of life, staging, clinical impression of change, or change in patient residence to a different level of independence.

No studies reported data on serious adverse events, withdrawals due to adverse events, confusion, somnolence, falls, extrapyramidal symptoms, stroke or mortality.

Table 8.2. Summary of findings for primary outcomes: memantine versus donepezil

Domain	# Studies/ Design (n Analyzed) Timing	CATD Population	Findings (Incidence, Change from Baseline)	Strength of Evidence
Cognition - Brief Multidomain Batteries	1 RCT[330] (n=67) 24 weeks	Mild to Moderate	**Mean ADAS-Cog change:** SMD, 0.14 (95% CI, -0.35 to 0.64])	Insufficient
Function	1 RCT[330] (n=67) 24 weeks	Mild to Moderate	**Mean DAD change:** SMD, 0.13 (95% CI, -0.37 to 0.62)	Insufficient

ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; CATD=Clinical Alzheimer's-type Dementia; CI=confidence interval; DAD=Disability Assessment for Dementia; RCT=randomized controlled trials; SMD=standardized mean difference

Variation in Outcomes by Participant or Drug Characteristics

Last, no studies reported on whether the comparative effects of memantine and donepezil varied as a function of participant characteristics, or by drug dose, duration or delivery route.

Appendix Tables G.5-G.8 provide detailed evidence tables and strength of evidence for key comparisons and outcomes.

Memantine Versus Antipsychotics

Key Message

- In older adults with moderate to severe CATD who were residing in care homes and receiving antipsychotics, evidence was insufficient to draw conclusions about the comparative effectiveness of memantine versus continued antipsychotics on function.

Eligible Studies

We identified one eligible publication of one unique trial that compared continued antipsychotic medication versus memantine and reported results for cognition, function, quality of life, global staging, clinical impression of change, or harms in patients with CATD.[331] Only results for function were rated low or medium ROB and were analyzed; results for other outcomes were rated high ROB (primarily for high attrition) and excluded from analyses.

Baseline Study Characteristics

This trial enrolled 199 participants with probable or possible CATD. Participants were living in care homes in the UK or Norway and were already receiving an antipsychotic. There was no CATD severity inclusion criterion, but the mean baseline MMSE score of 8 (SD 6.4) suggested that participants had moderate to severe CATD. Participant mean age was 83 years, and 31 percent were male. Participants were randomized to antipsychotic continuation (risperidone 0.5 mg, olanzapine 5 mg, quetiapine 50 mg, or haloperidol 0.5 mg, once or twice daily as needed) versus switching to memantine 10 to 20 mg/day. Treatment duration was 24 weeks. Appendix Tables G.9-G.12 provide evidence tables, summary ROB assessments, and strength of evidence for key comparisons and outcomes.

Outcomes

Table 8.3 summarizes the primary efficacy and harms results. For comparative effectiveness, evidence was insufficient to draw conclusions about differences for function, and no studies reported data on brief cognitive tests commonly used as individual stand-alone tests, brief multidomain batteries, domain level cognitive tests, quality of life, staging, clinical impression of change, or change in patient residence to a different level of independence.

For harms, evidence was insufficient to draw conclusions about differences between treatment groups for serious adverse events. Incidence of stroke was zero in the memantine group and 2.5 percent in the continued antipsychotic group, and mortality occurred in 9.0 percent in the memantine group and 4.0 percent in the continued antipsychotic group. No studies reported data on withdrawals due to adverse events, confusion, somnolence, falls or extrapyramidal symptoms.

Table 8.3. Summary of findings for primary outcomes: memantine versus antipsychotic continuation

Domain	# Studies/ Design (n Analyzed) Timing	CATD Population	Findings (Incidence, Change from Baseline)	Strength of Evidence
Function	1 RCT[331] (n=164) 24 weeks	Moderate to severe, care home residents, receiving antipsychotics	**Mean BADLS score at 24 weeks:** SMD, 0.03 [95% CI, -0.27 to 0.34])	Insufficient
SAE	1 RCT[331] (n=199) 24 weeks	Moderate to severe, care home residents, receiving antipsychotics	18 total SAE memantine group vs. 25 total SAE antipsychotic group	Insufficient

BADLS=Bristol Activities of Daily Living Scale; CATD=Clinical Alzheimer's-type dementia; CI=confidence interval; RCT=randomized clinical trial; SAE=serious adverse events; SMD=standardized mean difference

Variation in Outcomes by Participant or Drug Characteristics

Last, no studies reported on whether the comparative effects of memantine and continued antipsychotic varied as a function of participant characteristics, or by drug dose, duration or delivery route. Appendix Tables G.9–G.12 provide detailed evidence tables and strength of evidence for key comparisons and outcomes.

Supplements Versus Prescription Drugs

Key Messages

- In older adults with CATD, evidence was insufficient to draw conclusions about the comparative effectiveness of supplements versus prescription drugs for all efficacy and harms outcomes.
    - Between gingko biloba, vitamin E, or Huannao Yicong Formula (HYF) versus donepezil; vitamin E versus rivastigmine; and saffron extract versus memantine for cognition, function, quality of life, disease staging, clinical impression of change, serious adverse events, or withdrawals due to adverse events.
    - Single eligible trials for Vitamin E versus memantine in patients who continue cholinesterase inhibitors, gingko biloba versus rivastigmine, and Yishen Huazhuo decoction group versus donepezil were rated high ROB and thus not analyzed.

Eligible Studies

We identified eight eligible publications of eight unique trials that evaluated the comparative effectiveness of supplements versus prescription medications for the outcomes of cognition, function, quality of life, staging, clinical impression of change, or harms, in adults with CATD.[208, 300, 332-338] Four articles were assessed as high ROB and not analyzed.[300, 333-336, 338] The remaining four trials were assessed as medium ROB.[208, 334, 335, 337, 338]

Gingko Biloba Versus Donepezil

Baseline Study Characteristics

One trial (n=50) evaluated the comparative effectiveness of gingko biloba versus donepezil in adults with mild to moderate CATD.[208] Participation required a diagnosis of primary degenerative dementia of the Alzheimer's type with a mean Brief Cognitive Rating Scale

(BCRS) score of 3-5, a Hachinski Ischemic Score (HIS) of <4, and an estimated premorbid IQ of >80 based on a global assessment. Mean age was 69 years and 46 percent of participants were male. Mean baseline MMSE score was 18.7. Participants were assigned to gingko biloba 160 mg/day (n=25) or donepezil 5 mg/day (n=25) for 24 weeks. An additional 26 participants were randomized to placebo and analyses comparing donepezil to placebo and gingko biloba to placebo are reported in Chapters 6 and 7, respectively. Appendix Tables G.13-G.17 provide evidence tables, summary ROB assessments, and strength of evidence for key comparisons and outcomes.

Outcomes

Table 8.4 summarizes comparative effectiveness and harms results for gingko biloba versus donepezil. For comparative effectiveness, evidence was insufficient to draw conclusions about differences between treatments for brief cognitive tests commonly used as individual stand-alone tests or clinical impression of change, and no data were reported for brief multidomain batteries, domain level cognitive tests, function, quality of life, global staging, or change in patient residence to a different level of independence.

For harms, evidence was insufficient to draw conclusions about between treatment differences in withdrawals due to adverse events, while no studies reported data on serious adverse events, confusion, sedation, falls, extrapyramidal symptoms, stroke, or mortality.

Table 8.4. Summary of findings for primary outcomes: gingko biloba versus donepezil

Domain	# Studies/ Design (n Analyzed) Timing	CATD Population	Findings (Incidence, Change from Baseline)	Strength of Evidence
Cognition-Brief Stand-Alone Tests	1 RCT[208] (n=50) 24 weeks	Mild to moderate	**Mean MMSE change:** SMD, -0.18 (95% CI, -0.80 to 0.43) **Mean SKT change:** SMD, 0.0 (95% CI, -0.61 to 0.61)	Insufficient
Clinical Impression of Change	1 RCT[208] (n=50) 24 weeks	Mild to moderate	**Mean CGI-2 change:** SMD, 0.0 (95% CI, -0.61 to 0.61)	Insufficient
Withdrawals Due to Adverse Events	1 RCT[208](n=50) 24 weeks	Mild to moderate	0% gingko biloba vs. 16% donepezil (ARD, -16% [95% CI, -31 to -1]; RR, 0.11 [95% CI, 0.01 to 2.0])	Insufficient

ARD=absolute risk difference; CATD=Clinical Alzheimer's-type Dementia; CI=Confidence Interval; CGI-2=Clinical Global Impression item 2; MMSE=Mini-Mental State Examination; RCT=randomized controlled trial; RR=risk ratio; SKT=Syndrom Kurz Test; SMD=standardized mean difference

Variation in Outcomes by Participant or Drug Characteristics

Last, no studies reported on whether the comparative effects of gingko biloba and donepezil varied as a function of participant characteristics, or by drug dose, duration or delivery route. Appendix Tables G.13-G.17 provide detailed evidence tables and strength of evidence for key comparisons and outcomes.

Vitamin E Versus Donepezil

Baseline Study Characteristics

One trial (n=40) evaluated the comparative effectiveness of vitamin E versus donepezil in adults with mild to severe CATD.[335] Participants met Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria for CATD and had a diagnosis of probable CATD per National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria. Mean age was 66 years and 47 percent of participants were male. The mean baseline MMSE score was 16. Participants were assigned to receive donepezil up to 10 mg/day (n=20) versus vitamin E 2000 IU/day (n=20) for 6 months. Appendix Tables G.13-G.17 provide evidence tables, summary ROB assessments, and strength of evidence for key comparisons and outcomes.

Outcomes

Table 8.5 summarizes comparative effectiveness and harms results. For comparative effectiveness, evidence was insufficient to draw conclusions about differences between treatment groups for brief cognitive tests commonly used as individual stand-alone tests and brief multidomain cognitive batteries, and no data were reported on domain level cognitive tests, function, quality of life, global staging, clinical impression of change, or change in patient residence to a different level of independence.

For harms, evidence was insufficient to draw conclusions about between treatment differences for withdrawals due to adverse events and no studies reported data on serious adverse events, confusion, sedation, falls, extrapyramidal symptoms, stroke, or mortality.

Table 8.5. Summary of findings for primary outcomes: vitamin E versus donepezil

Domain	# Studies/ Design (n Analyzed) Timing	CATD Population	Findings (Incidence, Change from Baseline)	Strength of Evidence
Cognition-Brief Stand-Alone Tests	1 RCT[335] (n=40) 26 weeks	Mild to severe	**Mean MMSE score at 26 weeks:** SMD -0.42 (95% CI, -1.06 to 0.23)	Insufficient
Cognition-Brief Multidomain Batteries	1 RCT[335] (n=40) 26 weeks	Mild to severe	**Mean ADAS-Cog score at 26 weeks:** SMD, -0.61 (95% CI, -1.26 to 0.04) **Mean WAIS subscale score (including verbal and performance scales) at 26 weeks:** SMD -0.45 (95% CI, -1.09 to 0.20)	Insufficient
Withdrawals Due to Adverse Events	1 RCT[335] (n=40) 26 weeks	Mild to severe	No withdrawals for adverse events reported for either group.	Insufficient

ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognition; CATD=Clinical Alzheimer's-type Dementia; CI=Confidence Interval; MMSE=Mini-Mental State Examination; RCT=randomized controlled trial; SMD=standardized mean difference; WAIS=Wechsler Adult Intelligence Scale

Variation in Outcomes by Participant or Drug Characteristics

Last, no studies reported on whether the comparative effects of vitamin E and donepezil varied as a function of participant characteristics, or by drug dose, duration or delivery route.

Appendix Tables G.13-G.17 provide provides detailed evidence tables and strength of evidence for key comparisons and outcomes.

Huannao Yicong Formula Versus Donepezil

Baseline Study Characteristics

One trial (n=60) evaluated the comparative effectiveness of Huannao Yicong Formula (HYF) versus donepezil in adults with mild to moderate CATD.[337] Participation required a diagnosis of CATD according to DSM-IV criteria and National Institute on Aging-Alzheimer's Association (NIA-AA) guidelines with a baseline MMSE of 10-26, CDR of 0.5 to 2, Hamilton Depression Scale score <20, Montreal Cognitive Assessment (MoCA) <26, and HIS <4. Mean age was 62 years and 25 percent of participants were male. The mean baseline MMSE score was 21.8. Participants were assigned to receive either HYF 5 gm twice daily plus placebo once daily (n=30) or donepezil 5 mg/day plus placebo twice daily (n=30) for 6 months. Appendix Tables G.13-G.17 provide evidence tables, summary ROB assessments, and strength of evidence for key comparisons and outcomes.

Outcomes

Table 8.6 summarizes comparative effectiveness and harms results for HYF versus donepezil. For comparative effectiveness, evidence was insufficient to draw conclusions about between group differences in brief cognitive tests commonly used as individual stand-alone tests or brief multidomain cognitive batteries, but no studies reported data on domain level cognitive tests, function, quality of life, global staging, clinical impression of change, or change in patient residence to a different level of independence.

For harms, evidence was insufficient to draw conclusions about between group differences in serious adverse events. No participants in either treatment group died or had a serious adverse event. Otherwise, no studies reported data on withdrawals due to adverse events, confusion, somnolence, falls, extrapyramidal symptoms, or stroke.

Table 8.6. Summary of findings for primary outcomes: HYF versus donepezil

Domain	# Studies/ Design (n Analyzed) Timing	CATD Population	Findings (Incidence, Change from Baseline)	Strength of Evidence
Cognition-Brief Stand-Alone Tests	1 RCT[337] (n=60) 6 months	Mild to moderate	**Mean MMSE score at 6 months:** Data reported only graphically, but HYF and donepezil reported to not differ (p>0.05) **Mean MoCA score at 6 months:** Scores statistically significantly improved in each treatment group, but no between group comparisons reported	Insufficient
Cognition-Brief Multidomain Batteries	1 RCT[337] (n=60) 6 months	Mild to moderate	**Mean ADAS-Cog score at 6 months:** Data reported only graphically, but HYF and donepezil reported to not statistically differ (p>0.05)	Insufficient
Serious Adverse Events	1 RCT[337] (n=60) 6 months	Mild to moderate	No serious adverse events reported in either group	Insufficient

ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognition; CATD=Clinical Alzheimer's-type Dementia; HYF=Huannao Yicong Formula; MMSE=Mini-Mental State Examination; MoCA=Montreal Cognitive Assessment; RCT=randomized controlled trial

Variation in Outcomes by Participant or Drug Characteristics

Last, no studies reported on whether the comparative effects of HYF and donepezil varied as a function of participant characteristics, or by drug dose, duration or delivery route. Appendix Tables G.13-G.17 provide provides detailed evidence tables and strength of evidence for key comparisons and outcomes.

Vitamin E Versus Rivastigmine

Baseline Study Characteristics

One trial (n=40) evaluated the comparative effectiveness of blinded vitamin E versus open-label rivastigmine in adults with mild to severe CATD.[335] Participants met DSM-IV criteria for CATD and had a diagnosis of probable CATD per NINCDS-ADRDA criteria. Mean age was 65.3 years and 47 percent of participants were male. The mean baseline MMSE score was 16. Participants were assigned to receive either vitamin E 2000 IU/day (n=20) or rivastigmine titrated up to 6 mg twice daily (n=20) for 26 weeks. Appendix Tables G.13-G.17 provide evidence tables, summary ROB assessments, and strength of evidence for key comparisons and outcomes.

Outcomes

Table 8.7 summarizes comparative effectiveness and harms results for vitamin E versus rivastigmine. For comparative effectiveness, evidence was insufficient to draw conclusions about between treatment differences in brief cognitive tests commonly used as individual stand-alone tests or brief multidomain cognitive batteries, but no studies reported data on domain level cognitive tests, function, quality of life, global staging, clinical impression of change, or change in patient residence to a different level of independence.

For harms, evidence was insufficient to draw conclusions about between treatment differences in withdrawals due to adverse events and no studies reported data on serious adverse events, confusion, sedation, falls, extrapyramidal symptoms, stroke, or mortality.

Table 8.7. Summary of findings for primary outcomes: vitamin E versus open-label rivastigmine

Domain	# Studies/ Design (n Analyzed) Timing	CATD Population	Findings (Incidence, Change from Baseline)	Strength of Evidence
Cognition-Brief Stand-Alone Tests	1 RCT[335] (n=40) 26 weeks	Mild to severe	**Mean MMSE change:** SMD -0.42, (95% CI -1.09 to 0.27)	Insufficient
Cognition-Brief Multidomain Batteries	1 RCT[335] (n=40) 26 weeks	Mild to severe	**Mean ADAS-Cog score at 26 weeks:** SMD -0.71, (95% CI, -1.40 to -0.01) **Mean WAIS subscale score at 26 weeks (included verbal and performance scales):** SMD, -0.34 (95% CI, -1.01 to 0.34)	Insufficient
Withdrawals Due to Adverse Events	1 RCT[335] (n=40) 26 weeks	Mild to severe	0% vitamin E vs. 15% rivastigmine (ARD, -15% [95% CI, -32 to 2]; RR, 0.14 [95% CI, 0.01 to 2.6])	Insufficient

ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognition; ARD=absolute risk difference; CATD=Clinical Alzheimer's-type Dementia; CI=confidence interval; MMSE=Mini-Mental State Examination; RCT=randomized controlled trial; RR=risk ratio; SMD=standardized mean difference; WAIS=Wechsler Adult Intelligence Scale

Variation in Outcomes by Participant or Drug Characteristics

Last, no studies reported on whether the comparative effects of vitamin E and rivastigmine varied as a function of participant characteristics, or by drug dose, duration or delivery route. Appendix Tables G.13-G.17 provide provides detailed evidence tables and strength of evidence for key comparisons and outcomes.

Saffron Extract Versus Memantine

Baseline Study Characteristics

One trial (n=68) evaluated the comparative effectiveness of saffron extract (*Crocus sativus* L.) versus memantine to decrease cognitive decline in adults with moderate to severe CATD.[332] Participants met DSM-IV dementia criteria and NINCDS-ADRDA criteria for CATD. The mean baseline MMSE score was 11.2. Mean participant age was 78 years, and 57 percent were male. Participants were assigned to receive either saffron extract (15 mg/day dried extract of *C. sativus* L. for one month, then 30 mg/day for the remaining 11 months) (n=34) or memantine (10 mg/day for one month, then 20 mg/day for the remaining 11 months) (n=34). Appendix Tables G.13-G.17 provide provides evidence tables, summary ROB assessments, and strength of evidence for key comparisons and outcomes.

Outcomes

Table 8.8 summarizes primary comparative effectiveness and harms results for saffron extract versus memantine. For comparative effectiveness, evidence was insufficient to draw conclusions about between treatment differences for brief cognitive tests commonly used as individual stand-alone tests or clinical impression of change, but no studies reported data on brief

multidomain batteries, domain level cognitive tests, function, quality of life, staging, or change in patient residence to a different level of independence.

For harms, saffron extract and memantine did not statistically differ for risk of somnolence (2.9% vs. 8.8%, RR, 0.33 [95% CI, 0.04 to 3.0]) or confusion (2.9% vs. 2.9%, RR, 1.0 [95% CI, 0.7 to 15.3]). In addition, one patient in each treatment group died during the 12-month trial (2.9% vs. 2.9%, RR, 1.0 [95% CI, 0.7 to 15.3]). No studies reported data on serious adverse events, withdrawals due to adverse events, falls, extrapyramidal symptoms, or stroke.

Table 8.8. Summary of findings for primary outcomes: saffron extract versus memantine

Domain	# Studies/ Design (n Analyzed) Timing	CATD Population	Findings (Incidence, Change from Baseline)	Strength of Evidence
Cognition-Brief Stand-Alone Tests	1 RCT[332] (n=68) 12 months	Moderate to severe	**Mean MMSE change:** SMD, -0.28 (95% CI, -0.79 to 0.23) **Mean SCIRS change:** SMD, 0.22 (95% CI, -0.29 to 0.73)	Insufficient
Clinical Impression of Change	1 RCT[332] (n=68) 12 months	Moderate to severe	**Mean FAST change:** SMD, -0.03 (95% CI, -0.53 to 0.48)	Insufficient

CATD=Clinical Alzheimer's-type Dementia; CI=confidence interval; FAST=Functional Assessment Staging Tool; MMSE=Mini-Mental State Examination; RCT=randomized controlled trial; SCIRS=Severe Cognitive Impairment Rating Scale; SMD=standardized mean difference

Variation in Outcomes by Participant or Drug Characteristics

Last, no studies reported data on whether the comparative effects of saffron extract and memantine varied as a function of participant characteristics, or by drug dose, duration or delivery route. Appendix Tables G.13-G.17 provide provides detailed evidence tables and strength of evidence for key comparisons and outcomes.

Additional Drug Versus Drug Comparisons

Key Message

- In older adults with CATD, evidence was insufficient from all other eligible studies that compared different prescription drugs versus each other due to high ROB.

Eligible Studies

We identified 10 additional publications of nine unique trials that compared different prescription drugs with each other for treatment of CATD and reported on outcomes of cognition, function, quality of life, global staging, clinical impression of change, or harms.[227, 256, 261, 328, 329, 335, 339-341] These included five trials that compared rivastigmine with donepezil,[328, 329, 335, 339, 342] two of which also compared rivastigmine with galantamine,[328, 329] one trial that compared add-on memantine combined with continued donepezil versus increased dose donepezil,[227] and three that evaluated additional combinations.[256, 261, 341] However, all were rated high ROB and excluded from analyses. The most common reasons for the high ROB ratings were high attrition bias[256, 261, 328, 329, 339, 340, 342] and high performance bias.[227, 328, 329, 335, 340, 341] Appendix Tables G.18-G.19 provide ROB assessments and study characteristics for these high-risk-of-bias studies.

Chapter 9. Key Question 6: Prescription Drugs Versus Placebo for Behavioral and Psychological Symptoms of Dementia

Antipsychotics Versus Placebo and Antipsychotic Dose Comparisons

Key Messages

- In older adults with clinical Alzheimer's-type dementia (CATD) and behavioral and psychological symptoms of dementia (BPSD), evidence for antipsychotics compared with placebo showed:
    - Insufficient evidence for reducing agitation, aggression, or psychosis at 2 weeks or longer.
    - No evidence for disinhibited sexual behavior, depression, anxiety, general behavior, quality of life, or caregiver outcomes.
    - Insufficient evidence for serious adverse events or withdrawals due to adverse events.
- In older adults with CATD and BPSD, evidence for antipsychotic dosage comparisons showed insufficient evidence for standard- compared with low-dose haloperidol for all efficacy and harms outcomes.

Eligible Studies

We identified 20 eligible publications reporting 16 unique trials (n=4,235) that compared the efficacy of antipsychotics versus placebo for treating BPSD in adults with CATD.[343-358] Among unique trials, twelve were excluded from our analyses because of high overall risk of bias (ROB), in all cases including attrition bias and often including selection or performance bias.[343-345, 347, 349-353, 355, 357-363] The four remaining trials, with low or medium overall ROB, were analyzed. We identified one pooled analysis of six trials, but did not extract it because most of the individual trials included had high ROB or were ineligible.[364] Appendix Tables H.1-H.9 provide evidence tables, summary ROB assessments, and strength of evidence for key comparisons and outcomes.

Baseline Study Characteristics

Characteristics of the 522 participants enrolled in the four analyzed studies are shown in Table 9.1. All studies required participants to have dementia, such as defined by criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM), and possible or probable Alzheimer's disease, most often as defined by criteria from the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders NINCDS-ADRDA.[5]

One trial required participants to have agitation, enrolled participants with a mean Severe Impairment Battery (SIB) score of 64 (possible range 0-152) and mean Cohen-Mansfield Agitation Inventory (CMAI) score of 58, and randomized participants to quetiapine (n=31) or placebo (n=31) for 26 weeks. Quetiapine was dosed up to 25 to 50 mg twice daily for 12 weeks,

then 50 mg twice daily through week 26, but we only analyzed results for 6 weeks because of high ROB for later results. [346] This trial also included a rivastigmine arm (n=31), and comparisons between rivastigmine and placebo are detailed in Chapter 6. Results comparing rivastigmine and quetiapine were rated as high ROB due to high attrition and were not analyzed.

The second trial required participants to have hallucinations or delusions, enrolled participants with mild to severe CATD (mean Mini-Mental State Exam [MMSE] score of 14 [study range 6 to 24]) and a mean Neuropsychiatric Inventory (NPI) score of 40, and randomized participants to aripiprazole 2 to 15 mg daily (n=106) or placebo (n=102) for 10 weeks.[348]

The third trial enrolled 71 participants with moderate to severe CATD (mean modified MMSE score of 19 [possible range 0 to 57]) and delusions, hallucinations, or disruptive behavior, , and randomized them to standard dose haloperidol (2 to 3 mg daily), low dose haloperidol (0.5 to 0.75 mg daily), or placebo for 6 weeks. A subsequent crossover phase did not meet eligibility for our review and was not analyzed.[354]

The fourth trial required participants to have severe psychosis, defined as a score $\geq$4 on either the hallucinations or delusions subscales of the Neuropsychiatric Inventory-Nursing Home Version (NPI-NH), or a combined score of $\geq$6, and have symptoms judged to require treatment with an antipsychotic medication.[356, 365] Participants were nursing home residents, and were randomized to 34 mg pimavanserin daily (n=90) or placebo (n=91) for 12 weeks. Efficacy was measured after 6 weeks. Most analyses were reported for a smaller subgroup of participants (n=57) with particularly severe psychosis, defined as NPI-NH scores ≥12.

No studies specified whether participants received a prior psychosocial intervention and if it was unsuccessful, nor whether study participants received a concomitant psychosocial intervention during the trial, although one required that participants have symptoms that required treatment with an antipsychotic medication.[365]

Table 9.1. Baseline characteristics of antipsychotic versus placebo trials

Characteristic	N, Mean, or % (Study Range)	Trials Reporting, N
Number of participants enrolled	522 (62 to 208)	4
Age, mean	81 (72 to 86)	4
Race – white, %	77 (56 to 98)	2
Residence, Community dwelling, %	53 (0 to 100)	4
Residence, Care Home, %	47 (0 to 100)	4
Men, %	28 (18 to 35)	4
Severity of CATD	NA	NA
Severe, %	12 (n=62)	1
Any (mild, moderate, or severe), %	88 (n=460)	3
MMSE, baseline mean*	12 (10 to 14)	2
Behavioral symptoms	NA	NA
NPI, mean	37 (33 to 40)	2
CMAI, mean	57.8 (NA)	1

CATD=clinical Alzheimer's-type dementia; CMAI=Cohen-Mansfield Agitation Inventory; MMSE=Mini-Mental State Exam; NA=not applicable; NPI=Neuropsychiatric Inventory

*A third study (n=71) reported a mean baseline score of 19 in the modified MMSE (possible scoring range 0-57).

Outcomes

Table 9.2 summarizes the primary efficacy and harms results between antipsychotic medications and placebo. For efficacy, among patients with CATD and agitation, aggression, or psychosis, results for psychosis outcomes between antipsychotics and placebo was inconsistent and insufficient to draw conclusions. Evidence also was insufficient to draw conclusions about

differences between antipsychotics and placebo for agitation and aggression. No studies in this patient population reported data on disinhibited sexual behavior at 2 weeks or longer, or depression, anxiety, general behavior, patient quality of life, caregiver distress, caregiver burden, caregiver depression, or caregiver quality of life at 24 weeks or longer.

For harms, evidence was insufficient to draw conclusions about differences between any individual antipsychotic and placebo for serious adverse events or withdrawals due to adverse events. One trial reported no statistical difference between pimavenserin and placebo for falls (23% vs. 23%, p not reported).[356] In a second trial somnolence and injurious falls each were reported in 8 percent of participants assigned aripiprazole, while somnolence was reported in 1 percent and injurious falls were reported in 5 percent of the placebo group (p-values not reported).[348] Two trials reported data on motor abnormalities. The first reported that standard-dose haloperidol and placebo did not statistically differ for extrapyramidal symptoms (p=0.08) or for Treatment Emergent Symptoms Scale change scores (p not reported),[354] and the second reported no statistical differences between aripiprazole and placebo for change in extrapyramidal symptoms (Simpson-Angus Scale) (0.71 vs. 0.03; p=0.11), or in two measures of tardive dyskinesia (Abnormal Involuntary Movement Scale: -0.13 vs. -0.01, p=0.62; Barnes Akathisia Rating Scale: -0.09 vs. -0.06, p=0.47).[348] Mortality was reported in three trials, with one reporting no statistical difference between quetiapine and placebo (6% vs. 0%, p-value not reported), [346] a second reporting no statistical difference between aripiprazole and placebo (4% vs. 0%, p-value not reported),[348] and a third reporting no statistical difference between pimavenserin and placebo (4% vs. 4%, p-value not reported).[356] No eligible trials reported data on confusion or stroke.

Appendix Tables H.1-H.9 provide detailed evidence tables and assessments of strength of evidence for key comparisons and outcomes

Table 9.2. Summary of findings for primary outcomes:* antipsychotic versus placebo

Domain	# Studies/ Design (n Analyzed) Timing	CATD Population	Findings (Incidence, Change from Baseline)	Strength of Evidence
Agitation	3 RCT (n=314) 6 weeks	With agitation/disruptive behavior with or without psychosis (42%), [346, 354] or with psychosis (58%)[365]	**Likelihood ≥25% improved BSSD-Psychomotor Agitation score:** *Standard-dose haloperidol:* 55% vs. 30% placebo (ARD, 25% [95% CI, -5% to 55%]; RR, 1.83 [95% CI, 0.84 to 3.99]; 1 trial, n=40) [354] *Low-dose haloperidol:* 25% vs. 30% placebo (ARD, -5% [95% CI, -33% to 23%]; RR, 0.83 [95% CI, 0.30 to 2.29]; 1 trial, n=40) [354] **Mean BSSD-Psychomotor Agitation score change†:** *Standard-dose haloperidol:* SMD, -0.59 (95% CI, -1.22 to 0.05); 1 trial, n=40[354] *Low-dose haloperidol:* SMD, 0.12 (95% CI, -0.50 to 0.74); 1 trial, n=40[354] **Mean CMAI change†:** *Quetiapine:* SMD, 0.26 (95% CI, -0.27 to 0.79); 1 trial, n=62[346] **Mean CMAI-SF Total Score change:** *Pimavanserin:* SMD, 0.04 (95% CI, -0.27 to 0.35); 1 trial, n=181[365] **Mean CMAI-SF Verbally Agitated Behavior score change:** *Pimavanserin:* SMD, -0.05 (95% CI, -0.36 to 0.27); 1 trial, n=181[365]	Insufficient

Domain	# Studies/ Design (n Analyzed) Timing	CATD Population	Findings (Incidence, Change from Baseline)	Strength of Evidence
			Mean NPI-NH Agitation/Aggression score change: *Pimavanserin:* SMD, -0.18 (95% CI, -0.50 to 0.13); 1 trial, n=181[365]	
Aggression	2 RCT (n=252) 6 weeks	With agitation/disruptive behavior with or without psychosis (28%),[354] or with psychosis (72%)[365]	**Mean BSSD-Physical Aggressiveness score change†:** *Standard-dose haloperidol:* SMD, -0.40 (95% CI, -1.03 to 0.23); 1 trial, n=40[354] *Low-dose haloperidol:* SMD, -0.04 (95% CI, -0.66 to 0.58); 1 trial, n=40[354] **Mean BPRS-Hostile-Suspiciousness score change†:** *Standard-dose haloperidol:* SMD, -0.42 (95% CI, -1.05 to 0.21); 1 trial, n=40[354] *Low-dose haloperidol:* SMD, -0.23 (95% CI, -0.85 to 0.39); 1 trial, n=40[354] **Mean CMAI-SF Aggressive Behavior score change:** *Pimavanserin:* SMD, 0.12 (95% CI, -0.20 to 0.43); 1 trial, n=181[365]	Insufficient
Psychosis	3 RCT (n=460) 6 weeks (standard- and low-dose haloperidol,[354] pimavanserin[365] to 10 weeks (aripiprazole)[348]	With agitation/disruptive behavior with or without psychosis (61%),[348, 354] or with psychosis (39%)[365]	**Likelihood ≥25% improved BPRS-Psychosis score:** *Standard-dose haloperidol:* 60% vs. 30% placebo (ARD, 30% [95% CI, 1% to 59%]; RR, 2.00 [95% CI, 0.94 to 4.27]; 1 trial, n=40) [354] *Low-dose haloperidol:* 30% vs. 30% placebo (ARD, 0% [95% CI, -28 to 28]; RR 1.00 [95% CI, 0.39 to 2.58]; 1 trial, n=40) [354] **Likelihood ≥25% improved SADS-PD score:** *Standard-dose haloperidol:* 55% vs. 25% placebo (ARD, 30% [95% CI, 1% to 59%]; RR, 2.20 [95% CI, 0.93 to 5.18]; 1 trial, n=40) [354] *Low-dose haloperidol:* 35% vs. 25% placebo (ARD, 10% [95% CI, -18 to 38]; RR 1.40 [95% CI, 0.53 to 3.68]; 1 trial, n=40) [354] **Likelihood 100% improved NPI-NH Psychosis score:** *Pimavanserin:* 12.6% vs. 9.9%; ARD, 2.7% [95% CI, -7 to 12]; RR, 1.28 [95% CI, 0.56 to 2.93]; 1 trial, n=178[356] **Likelihood ≥75% improved NPI-NH Psychosis score:** *Pimavanserin:* 27.6% vs. 16.5%; ARD, 11.1% [95% CI, -1 to 23]; RR, 1.67 [95% CI, 0.94 to 2.97]; 1 trial, n=178[356] **Likelihood ≥50% improved NPI-NH Psychosis score:** *Pimavanserin:* 50.6% vs. 34.1%; ARD, 16.5% [95% CI, 2 to 31]; RR, 1.48 [95% CI, 1.04 to 2.11]; 1 trial, n=178[356] **Likelihood ≥30% improved NPI-NH Psychosis score:** *Pimavanserin:* 55.2% vs. 37.4%; ARD, 17.8% [95% CI, 3 to 32]; RR, 1.48 [95% CI, 1.07 to 2.05]; 1 trial, n=178[356] **Likelihood ≥20% improved NPI-NH Psychosis score** *Pimavanserin:* 58.6% vs. 46.2%; ARD, 12.5% [95% CI, -2 to 27]; RR, 1.27 [95% CI, 0.96 to 1.69]; 1 trial,	Insufficient

Domain	# Studies/ Design (n Analyzed) Timing	CATD Population	Findings (Incidence, Change from Baseline)	Strength of Evidence
			n=178[356] **Mean BPRS-Psychosis score change†:** *Standard-dose haloperidol:* -2.0 vs. -0.85 placebo, p<0.02; 1 trial, n=40[354] *Low-dose haloperidol:* -0.85 vs. -0.85 placebo, p=NR; 1 trial, n=40[354] *Aripiprazole:* -1.93 vs. -1.27 placebo, p=0.029; 1 trial, n=208[348] **Mean BPRS-Core score change†:** *Aripiprazole:* -3.9 vs. -2.7 placebo, p=0.042; 1 trial, n=208[348] **Mean SADS-PD change†:** *Standard-dose haloperidol:* -3.35 vs. -1.85 placebo, p=NR; 1 trial, n=40[354] *Low-dose haloperidol:* -1.60 vs. -1.85 placebo, p=NR; 1 trial, n=40[354] **Mean NPI-Psychosis score change†:** *Aripiprazole:* -6.55 vs. -5.52, p=0.169; 1 trial, n=208[348] **Mean NPI-NH-Psychosis score change†:** *Pimavanserin:* SMD, -0.30 (95% CI, -0.59 to -0.01); 1 trial, n=181[365]	
SAE	3 RCTs (n=451) 6 weeks (quetiapine[346]), 10 weeks (aripiprazole[348]), or 12 weeks (pimavenserin[365])‡	With psychosis (86%)[348, 365] or agitation (14%)[346]	*Quetiapine:* 0% vs. 3% placebo, p=NR; 1 trial, n=62[346] *Aripiprazole:* 15% vs. 9% placebo, p=NR; 1 trial, n=208[348] *Pimavanserin:* 17% vs. 11% placebo; ARD, 6% [95% CI, -4 to 16]; RR, 1.52 (95% CI, 0.72 to 3.20); 1 trial, n=181[356, 365]	Insufficient
Withdrawals Due to Adverse Events	2 RCTs (n=389) 10 weeks (aripiprazole)[348] to 12 weeks (pimavenserin[365])‡	With psychosis	*Aripiprazole:* 9% vs. 7% placebo, p=NR; 1 trial, n=208[348] *Pimavanserin:* 9% vs. 12% placebo; ARD, -3% [95% CI, -12 to 6]; RR, 0.74 (95% CI, 0.31 to 1.74); 1 trial, n=181[356, 365]	Insufficient

ARD=absolute risk difference; BPRS=Brief Psychiatric Rating Scale; BSSD=Behavioral Syndromes Scale for Dementia; CATD=clinical Alzheimer's-type dementia; CI=confidence interval; CMAI=Cohen-Mansfield Agitation Inventory; CMAI-SF=Cohen-Mansfield Agitation Inventory-Short Form; NNTB=number needed to treat to produce 1 additional benefit; NNTH=number needed to treat to produce 1 additional harm; NPI=Neuropsychiatric Inventory; NPI-NH= Neuropsychiatric Inventory-Nursing Home; NR=not reported; RCT=randomized controlled trial; RR=relative risk; SADS=Schedule for Affective Disorders and Schizophrenia; SAE=serious adverse events; SMD=standardized mean difference

*No studies reported data on disinhibited sexual behavior at 2 weeks or longer, or depression, anxiety, general behavior, quality of life or on caregiver distress, caregiver burden, caregiver depression, or caregiver quality of life at 24 weeks or longer.

†Lower scores are in the direction of improved behavior for the following scales: CMAI, BPRS-Core, BPRS-Psychosis, BPRS-Hostile suspiciousness, SADS-PD, NPI-Psychosis, NPI-NH Psychosis, BSSD-Physical aggressiveness, and BSSD-Psychomotor agitation.

‡This trial reported efficacy through 6 weeks, but harms through 12 weeks.

Variation in Outcomes by Participant Characteristics

In one 6-week trial of pimavanserin compared with placebo in individuals with CATD and psychosis, prespecified secondary and exploratory subgroup analyses were reported for the 57 participants with the most pronounced psychosis (31% of total participants).[365] Results showed

that in this subgroup, pimavanserin had a higher likelihood than placebo of ≥20% improvement on the NPI-NH Psychosis score (96.3% vs. 53.3%, p<0.01), ≥30% improvement (88.9% vs. 43.3%, p<0.01), ≥50% improvement (77.8% vs. 43.3%, p=0.08), and ≥75% improvement (40.7% vs. 16.7%, p=0.038), but not a higher likelihood of 100% improvement (11.1% vs. 10.0%, p=0.884). Participants in this subgroup assigned to pimavanserin compared with placebo also had statistically significantly larger improvements for change in NPI-NH Delusions and Hallucinations scores, but not for any agitation, aggression, or other BPSD outcome measures. However, the study did not evaluate whether any of these results differed as a function of severity of baseline psychosis symptoms. No studies reported whether treatment efficacy of antipsychotics on BPSD varied as a function of other patient characteristics.

Antipsychotic Dosage Comparisons

As detailed above, one trial in patients with CATD and disruptive behavior with or without psychosis (n=71) compared standard-dose haloperidol (2 to 3 mg daily) with low-dose haloperidol (0.5 to 0.75 mg daily).[354]

For agitation (Behavioral Syndromes Scale for Dementia [BSSD] subscale on psychomotor agitation), the proportion of participants with ≥25 percent improvement in agitation scores was 55 percent for standard-dose haloperidol and 25 percent for low-dose haloperidol (p<0.06), but differences in mean agitation change scores between the standard (-1.0) and low-dose (-0.1) haloperidol dose groups were not directly compared.

For aggression, standard- and low-dose haloperidol did not statistically differ for mean change on either Brief Psychiatric Rating Scale (BPRS)-Hostile-suspiciousness (standardized mean difference [SMD], -0.20 [95% confidence intervals (CI), -0.82 to 0.42]) or BSSD-Physical aggressiveness (SMD, -0.36 [95% CI, -0.98 to 0.27]).

For psychosis, standard- and low-dose haloperidol did not statistically differ for likelihood of at least 25 percent improvement in either BPRS-Psychosis score (60% vs. 30%; relative risk [RR], 2.00 [95% CI, 0.94 to 4.27]) or Schedule for Affective Disorders and Schizophrenia-Parkinson's Disease (SADS-PD) score (55% vs. 35%; RR, 1.57 [95% CI, 0.77 to 3.22]). Standard dose haloperidol was associated with a marginally statistically larger mean reduction in the SADS-PD ([SMD, -0.68 [95% CI, -1.32 to -0.04]) but not for the BPRS-Psychosis (SMD, -0.45 [95% CI, -1.08 to 0.17]).

No studies compared whether treatment efficacy varied as a function of antipsychotic duration or delivery route.

Antidepressants Versus Placebo

Key Messages

- In older adults with CATD and agitation or aggression, evidence for antidepressants compared with placebo showed:
    - Insufficient evidence for agitation or psychosis.
    - No evidence for aggression, depression, anxiety, general behavior, or quality of life.
    - Insufficient evidence about serious adverse events or withdrawals due to adverse events.

- In older adults with CATD and depression, evidence for antidepressants compared with placebo showed:
    - No difference in depression, general behavior, or quality of life (all low strength of evidence [SOE]).
    - No evidence for agitation, aggression, psychosis, disinhibited sexual behavior, or anxiety.
    - Insufficient evidence about serious adverse events, but no evidence for withdrawals due to adverse events.

Eligible Studies

We identified six eligible publications of five unique trials that compared antidepressants with placebo for treating BPSD in patients with CATD.[366-371] One of these trials was excluded from our analysis for high ROB.[370] The four remaining trials were analyzed. All evaluated the efficacy and harms of selective serotonin reuptake inhibitor (SSRI) treatment and one also evaluated a tetracyclic antidepressant. Appendix Tables H.10-H.17 provide evidence tables, summary ROB assessments, and strength of evidence for key comparisons and outcomes.

We identified no eligible trials that evaluated the efficacy or harms of serotonin-norepinephrine reuptake inhibitors (SNRIs) (e.g., venlafaxine, duloxetine), tricyclic or tetracyclic antidepressants (TCAs or TeCAs) other than mirtazapine (e.g., amitriptyline), serotonin modulators (e.g., trazodone), or norepinephrine-dopamine reuptake inhibitors (NDRIs) (e.g., bupropion) for treating BPSD in patients with CATD.

Baseline Study Characteristics

Characteristics of the 836 participants enrolled in the four analyzed trials are shown in Table 9.3. All studies required participants to have probable CATD according to NINCDS-ADRDA clinical criteria.[5] The mean baseline NPI score of 32.5 suggested moderate behavioral disturbance.

In one study, participants with baseline agitation (n=186) were randomized to receive citalopram titrated to 30 mg/day (exceeding the current maximum recommended dose of 20 mg/day) (n=94) or placebo (n=92) for 9 weeks.[366, 367] A second trial randomized participants with moderate CATD and at least one behavioral or psychological symptom who were receiving memantine up to 20 mg daily to either add-on citalopram 30 mg daily (n=40) or placebo (n=40) for 12 weeks.[371] A third trial randomized participants with untreated depression to sertraline (target dose 150 mg/day) (n=107), mirtazapine (45 mg/day) (n=108), or placebo (n=111) for 39 weeks.[368] A fourth trial randomized participants with agitation or aggression who had received donepezil 5 to 10 mg/day for 8 weeks and continued to have behavioral symptoms (including NPI score >5) to sertraline (target dose 200 mg/day) (n=124) versus placebo (n=120) for an additional 12 weeks; all trial participants were assigned to continue donepezil.[369] No studies specified whether participants received or failed a prior psychosocial intervention, and only one specified that all study participants received a concomitant psychosocial intervention during the trial.[366, 367]

Table 9.3. Baseline characteristics of antidepressant versus placebo trials

Characteristic	N, Mean, or % (Study Range)	Trials Reporting, N
Number of participants enrolled	836 (80 to 326)	4
Age, mean	76 (71 to 80)	4
Race – white, %	83 (65 to 93)	2
Residence, Community dwelling*, %	89 (n=522)	3
Residence, Long-term care*, %	11 (n=70)	2
Men, %	45 (29 to 59)	4
Alzheimer's disease severity	NA	NA
Moderate, %	10 (n=80)	1
Any, %	90 (n=756)	3
MMSE, mean	16.8 (15.0 to 18.5)	4
Behavioral symptoms	NA	NA
NPI, mean	32.5 (26.9 to 37.3)	4
CMAI, mean	27.8 (26.6 to 28.2)	2
CSDD, mean	12.9 (12.5 to 13.6)	1

CMAI=Cohen-Mansfield Agitation Inventory; CSDD=Cornell scale for depression in dementia; MMSE=Mini-Mental State Exam; NA=not applicable; NPI=Neuropsychiatric Inventory

*Results are reported for the three trials that reported on residence; one trial (n=244) reported no information about residence.

Outcomes

Table 9.4 summarizes primary efficacy and harms results for antidepressants versus placebo. For efficacy, among patients with CATD and agitation or aggression, results for change in agitation and psychosis outcomes between antidepressants and placebo were mixed and evidence was judged insufficient to draw conclusions about any between group differences. No studies in this patient population reported data comparing antidepressants and placebo on outcomes of aggression or disinhibited sexual behavior. Among study participants with CATD and depression, low strength evidence showed no difference between antidepressants and placebo for patient depression, general behavior, or patient-reported or caregiver-reported patient quality of life. In individuals with CATD and agitation or aggression, citalopram compared with placebo was associated with a statistically borderline greater improvement in caregiver distress as measured by the NPI Caregiver Distress Scale (SMD, -0.71 [95% CI, -1.41 to 0.0]; 2 trials).[366, 367, 371] However, antidepressants and placebo did not statistically differ for change in caregiver burden in one trial reporting (sertraline vs. placebo in participants receiving open-label donepezil).[369] In individuals with CATD and depression, antidepressants and placebo did not statistically differ for caregiver quality of life or caregiver burden (mirtazapine or sertraline vs. placebo).[368] No studies reported data on patient anxiety or caregiver depression.

For harms, evidence from three trials collectively was insufficient to draw conclusions about differences between individual antidepressants and placebo for risk of serious adverse events or withdrawals due to adverse events, though one trial reported a statistically significantly higher total number of severe serious adverse events with mirtazapine or sertraline compared with placebo (p=0.03).[368] In the only trial reporting these outcomes, citalopram and placebo did not statistically differ for risk of confusion (76.7% vs. 83.7%, p=0.24), somnolence (52.2% vs. 48.8%, p=0.65)[366, 367] or falls (16.7% vs. 11.6%, p=0.34).[366, 367] For mortality, one trial reported no deaths in the citalopram group and one death in the placebo group,[366, 367] while a second trial reported that five deaths each occurred in sertraline, mirtazapine, and placebo arms, respectively.[368] No studies reported data on extrapyramidal symptoms or stroke.

Appendix Tables H.10-H.17 provide detailed evidence tables and strength of evidence for key comparisons and outcomes.

Table 9.4. Summary of findings for primary outcomes:* antidepressant versus placebo

Domain	# Studies/ Design (n Analyzed) Timing	CATD Population	Findings (Incidence, Change from Baseline)	Strength of Evidence
Agitation	3 RCT (n=508) 9 weeks (citalopram 30 mg/d† without memantine) to 12 weeks (citalopram 30 mg/d† with memantine, sertraline)	With agitation or aggression	**Likelihood unchanged/improved mADCS-CGIC:** *Citalopram (no memantine):* 88% vs. 79% placebo (ARD, 9% [95% CI, -2% to 21%]; RR, 1.12 [95% CI, 0.98 to 1.28]; 1 trial, n=186)[366, 367] **Likelihood improved mADCS-CGIC:** *Citalopram (no memantine):* 69% vs. 51% placebo (ARD, 18% [95% CI, 3% to 33%]; RR, 1.36 [95% CI, 1.05 to 1.75]; 1 trial, n=186)[366, 367] **Likelihood moderately/markedly improved mADCS-CGIC:** *Citalopram (no memantine):* 40% vs. 26% placebo (ARD, 14% [95% CI, -0.5% to 28%]; RR, 1.52 [95% CI, 0.97 to 2.40]; 1 trial, n=186)[366, 367] **Mean CMAI change:** *Citalopram (no memantine):* SMD, -0.41 (95% CI, -0.72 to -0.11); 1 trial, n=18[366, 367] **Mean CMAI-C change:** *Sertraline:* SMD, -0.06 (95% CI, -0.32 to 0.19); 1 trial, n=244[369] **Mean NBRS-A change:** *Citalopram (no memantine):* SMD, -0.33 (95% CI, -0.63 to -0.02); 1 trial, n=186[366, 367] **Mean NPI-A change:** *Citalopram (no memantine):* SMD, -0.24 (95% CI, -0.54 to 0.06); 1 trial, n=186[366, 367] **Mean NPI agitation/aggression subscale change:** *Citalopram (with memantine):* SMD, 0.67 (95% CI, 0.22 to 1.13); 1 trial, n=80[371]	Insufficient
Psychosis	2 RCT (n=266) 9 weeks (citalopram 30 mg/d† without memantine) to 12 weeks (citalopram 30 mg/d† with memantine)	With agitation	**Likelihood 100% reduced NPI delusion domain:** *Citalopram (no memantine):* 41% vs. 15% placebo (ARD, 26% [95% CI, 6 to 45]; RR, 2.7 [95% CI, 1.2 to 6.1]; 1 trial, n=78) [366, 367] **Likelihood ≥50% reduced NPI delusion domain:** *Citalopram (no memantine):* 54% vs. 38% placebo (ARD, 15% [95% CI, -7% to 37%]; RR, 1.4 [95% CI, 0.9 to 2.3]; 1 trial, n=186) [366, 367] **Mean change in prevalence of nonzero NPI hallucination domain score at 9 weeks:** *Citalopram (no memantine):* -6% vs. -7% placebo, p=NR; 1 trial, n=186) [366, 367] **Mean NPI hallucinations subscale change:** *Citalopram (with memantine):* SMD, -0.05 (95% CI, -0.49 to 0.39); 1 trial, n=80[371] **Mean NPI delusions subscale change:** *Citalopram (with memantine):* SMD, 0.12 (95% CI, -0.32 to 0.57); 1 trial, n=80[371]	Insufficient
Depression	1 RCT (n=326) 39 weeks	With depression	**Mean CSDD at 39 weeks:** *Mirtazapine:* No difference vs. placebo (SMD, -0.14 [95% CI, -0.45 to 0.17]; 1 trial, n=219) [368] *Sertraline:* No difference vs. placebo (SMD, 0.08 [95% CI, -0.24 to 0.40]; 1 trial, n=218) [368]	Low

Domain	# Studies/ Design (n Analyzed) Timing	CATD Population	Findings (Incidence, Change from Baseline)	Strength of Evidence
General Behavior	2 RCT (n=404) 12 weeks (citalopram 30 mg/d† with memantine) to 39 weeks (mirtazapine or sertraline)	With at least one BPSD (citalopram with memantine); or with depression (mirtazapine or sertraline)	**Mean NPI change:** *Citalopram (with memantine):* 6.95 vs. 3.38 placebo (with memantine), p<0.001; 1 trial, n=80[371] **Mean NPI score at 39 weeks:** *Mirtazapine:* No difference vs. placebo (SMD, 0.13 [95% CI, -0.18 to 0.44]; 1 trial, n=219) [368] *Sertraline:* No difference vs. placebo (SMD, -0.10 [95% CI, -0.42 to 0.22]; 1 trial, n=218) [368]	**With at least one BPSD**: Insufficient **With depression**: Low
Quality of Life	1 RCT (n=326) 39 weeks	With depression	**Mean patient-rated DEMQOL at 39 weeks:** *Mirtazapine:* No difference (SMD, 0.00 [95% CI, -0.31 to 0.31]; 1 trial, n=219) [368] *Sertraline:* No difference (SMD, -0.14 [95% CI, -0.46 to 0.18]; 1 trial, n=218) [368] **Mean carer-rated DEMQOL at 39 weeks:** *Mirtazapine:* No difference (SMD, 0.26 [95% CI, -0.05 to 0.57]; 1 trial, n=219) [368] *Sertraline:* No difference (SMD, 0.20 [95% CI, -0.13 to 0.52]; 1 trial, n=218)[368] **Mean patient-rated EQ5D at 39 weeks:** *Mirtazapine:* No difference (SMD, -0.05 [95% CI, -0.36 to 0.27]; 1 trial, n=219) [368] *Sertraline:* No difference (SMD, -0.17 [95% CI, -0.49 to 0.15]; 1 trial, n=218) [368] **Mean carer-rated EQ5D at 39 weeks:** *Mirtazapine:* No difference (SMD, -0.06 [95% CI, -0.37 to 0.26]; 1 trial, n=219) [368] *Sertraline:* No difference (SMD, -0.01 [95% CI, -0.33 to 0.31]; 1 trial, n=218) [368]	Low
SAE	2 RCT* (n=512) 9 weeks (citalopram 30 mg/d† without memantine) to 39 weeks (mirtazapine or sertraline)	With agitation or depression	**Total SAE:** *Citalopram (no memantine):* 8 vs. 7 placebo, p=NR; 1 trial, n=186) [366, 367] *Mirtazapine:* 14 vs. 15 placebo, p=NR; 1 trial, n=219[368] *Sertraline:* 12 vs. 15 placebo, p=NR; 1 trial, n=218) [368] **Total Severe SAE:** *Mirtazapine:* 10 vs. 3 placebo; 1 trial, n=219[368] *Sertraline:* 8 vs. 3 placebo (p=0.03 for collective antidepressant group vs. placebo; 1 trial, n=218) [368]	Insufficient
Withdrawals Due to Adverse Events	2 RCT (n=430) 9 weeks (citalopram 30 mg/d† without memantine) to 20 weeks (sertraline)	With agitation or aggression	*Citalopram (no memantine):* 14% vs. 14% placebo, p=NR; 1 trial, n=186[366, 367] *Sertraline:* 12% vs. 12% placebo, p=NR; 1 trial, n=244[369]	Insufficient

ARD=absolute risk difference; CATD=clinical Alzheimers's type dementia; CSDD=Cornell scale for depression in dementia; CI=confidence interval; CMAI=Cohen-Mansfield Agitation Inventory; CMAI-C=Cohen-Mansfield Agitation Inventory-Community; DEMQOL=Dementia Quality of Life; EQ5D=EuroQol 5D; mADCS-CGIC=modified Alzheimer Disease Cooperative Study-Clinical Global Impression of Change; NBRS=Neurobehavioral Rating Scale; NBRS-A=Neurobehavioral Rating Scale-agitation subscale; NNTB=number needed to treat to produce 1 additional benefit; NPI=Neuropsychiatric Inventory; NPI-A=Neuropsychiatric Inventory-agitation subscale; NR=not reported; SAE=serious adverse events; SMD=standardized mean difference

*A third trial (n=80) randomized participants receiving memantine to add-on citalopram or add-on placebo and reported that treatment groups did not differ for serious adverse events but provided no data.[371]
†The citalopram dosing of up to 30 mg/day evaluated in these trials exceeds the current maximum recommended dose of 20 mg/day.

Variation in Outcomes by Participant or Drug Characteristics

In a trial that separately compared sertraline and mirtazapine with placebo, authors reported that efficacy findings did not differ in subgroup analyses stratified by baseline depression severity (Cornell Scale for Depression in Dementia score 8 to 11 vs. ≥12).[368] In a second trial, in participants treated with open-label donepezil for 8 weeks, there was no difference in caregiver burden between those randomized to added sertraline versus added placebo for an additional 12 weeks (SMD, -0.19 [95% CI, -0.57 to 0.18]) in a subgroup with moderate to severe baseline BPSD. [369] However, no results were reported for the subgroup without moderate-to-severe symptoms at baseline and no test of interaction was reported for whether the effect of treatment significantly varied by baseline BPSD severity category. The trial did not report subgroup results for agitation, aggression, psychosis, disinhibited sexual behavior, or for at least 24 weeks followup of depression, anxiety, general behavior, or quality of life.

No studies assessed whether treatment efficacy of any individual antidepressant varied as a function of dose, duration, or delivery route.

Donepezil Versus Placebo

Key Messages

- In older adults with CATD and agitation, evidence for donepezil compared with placebo showed:
    - No difference for agitation (low SOE).
    - No evidence for aggression, psychosis, disinhibited sexual behavior, depression, anxiety, general behavior, quality of life, serious adverse events, or withdrawals due to adverse events.

Eligible Studies

We identified one eligible study (n=272) comparing the efficacy of donepezil versus placebo for treating agitation in dementia.[372] Agitation and harms outcomes were medium ROB and were extracted. Other reported outcomes of interest were high ROB due to high attrition and were not extracted or analyzed. Appendix Tables H.18-H.21 provide evidence tables, ROB assessment, and strength of evidence assessment.

We identified no eligible trials that evaluated the efficacy or harms of other cholinesterase inhibitors for treatment of BPSD in individuals with CATD and BPSD.

Baseline Study Characteristics

Characteristics of the 272 study participants are shown in Table 9.5. Participants had probable CATD by NINCDS-ADRDA clinical criteria; clinical agitation defined by baseline CMAI score >38 and causing distress to the participant and moderate management problems for caregivers; age >39 years; lived in a residential care facility (94%) or with a caregiver in the community; had not responded to a prior psychosocial program for agitation; and no current treatment with neuroleptic agents or cholinesterase inhibitors. [372] Inclusion criteria did not

address baseline cognition. Participants initially were randomized to donepezil up to 10 mg daily, risperidone, or placebo for 12 weeks, but the risperidone arm was eliminated because of regulatory concern about safety of antipsychotics for treatment of behavioral symptoms in dementia. [373] The trial did not specify whether study participants received a concomitant psychosocial intervention during the trial.

Table 9.5. Baseline characteristics of donepezil versus placebo trials

Characteristic	N, Mean, or %	Trials Reporting, N
Number of participants enrolled	272	1
Age, mean	85	1
Race – white, %	97	1
Men, %	16	1
Severity of CATD not specified, %	100	1
SMMSE, baseline mean	8.2	1
Behavioral symptoms, baseline	NA	NA
NPI, mean	23.7	1
CMAI, mean	61.6	1

CATD=clinical Alzheimers's type dementia; CMAI=Cohen-Mansfield Agitation Inventory; NA=not applicable; NPI=Neuropsychiatric Inventory; SMMSE=Standardized Mini-Mental State Exam.

Outcomes

Table 9.6 summarizes primary efficacy and harms results for donepezil versus placebo. For efficacy, low strength evidence showed no difference between treatments for change in agitation, but no studies reported data on aggression, psychosis, or disinhibited sexual behavior at 2 weeks or longer, or on depression, anxiety, or quality of life at 24 weeks or longer. Although this study reported data on general behavior and on caregiver distress at 24 weeks or longer, these results were high ROB due to high attrition and were not extracted or analyzed.

For harms, falls occurred in 1.6 percent of the donepezil group compared with 1.5 percent of the placebo group, stroke occurred in 0.8 percent of the donepezil group compared with none of the placebo group, and death occurred in 2.3 percent of the donepezil group versus 3.1 percent of the placebo group. However, no studies reported data on serious adverse events, withdrawals due to adverse events, confusion, somnolence, or extrapyramidal symptoms.

Table 9.6. Summary of findings for primary outcomes: donepezil versus placebo

Domain	# Studies/ Design (n Analyzed) Timing	CATD Population	Findings (Incidence, Change from Baseline)	Strength of Evidence
Agitation	1 RCT[372] (n=221) 12 weeks	With agitation	**Likelihood ≥30% improved CMAI score:** No difference (19.5% donepezil vs. 20.4% placebo; ARD, -1 [95% CI, -11 to 10]; NNTH, 100 [95% CI, NNTH 9 to ∞ NNTB 10], RR, 0.96 [95% CI, 0.56 to 1.62]) **Mean CMAI change:** No difference (SMD, 0.00, [95% CI, -0.25 to 0.24])	Low

ARD=absolute risk difference; CATD=Clinical Alzheimers's-type Dementia; CI=confidence intervals; CMAI=Cohen-Mansfield Agitation Inventory; NNTB=number needed to treat to produce 1 additional benefit; NNTH=number needed to treat to produce 1 additional harm; RCT=randomized controlled trial; RR=relative risk; SMD=standardized mean difference

Variation in Outcomes by Participant or Drug Characteristics

Last, no studies reported data on whether the efficacy of donepezil versus placebo varied as a function of participant characteristics, or by drug dose, duration or delivery route. Tables H.19-H.22 provide provides detailed evidence tables and strength of evidence for key comparisons and outcomes.

Anticonvulsants Versus Placebo

Key Messages

- In older adults with CATD and BPSD, evidence for the anticonvulsant divalproex sodium compared with placebo showed:
    - Insufficient evidence for agitation.
    - No evidence for aggression, psychosis, disinhibited sexual behavior, depression, anxiety, general behavior, quality of life, serious adverse events, or withdrawals due to adverse events.

Eligible Studies

We identified one eligible publication of one unique trial that compared the anticonvulsant, divalproex, with placebo for BPSD outcomes or harms in adults with CATD and BPSD.[374] The study was medium ROB and was analyzed. Appendix Tables H.22-H.25 provide evidence tables, ROB assessment, and strength of evidence assessment.

We identified no eligible trials that evaluated the efficacy or harms of other anticonvulsants or mood stabilizers for treatment of BPSD in patients with CATD and BPSD.

Baseline Study Characteristics

Characteristics of the 153 study participants are shown in Table 9.7. Participants had probable CATD by NINCDS-ADRDA clinical criteria; agitation lasting at least 2 weeks; age >49 years; lived in a residential care facility; were at least ambulatory with a walking aid; were medically stable; and had a baseline MMSE score between 4 and 24. Baseline agitation was defined as a Brief Psychiatric Rating Scale (BPRS) score >14 and a score >2 on select BPRS items (tension, hostility, uncooperativeness, excitement). Participants were randomized to divalproex sodium targeted to 750 mg daily versus placebo for 6 weeks. Participants could continue stable doses of medications prescribed before the trial, but the only psychotropic medications permitted during the trial were zolpidem or lorazepam as needed for severe agitation or sleep induction. The study did not specify whether participants received or failed a prior psychosocial intervention, nor whether participants received a concomitant psychosocial intervention during the trial

Table 9.7. Baseline characteristics of anticonvulsant versus placebo trials

Characteristic	N, Mean, or %	Trials Reporting, N
Number of participants enrolled	153	1
Age, years, mean	86	1
Race – white, %	92	1
Residence -- Care Home, %	100	1
Men, %	31	1

Characteristic	N, Mean, or %	Trials Reporting, N
CATD severity – any (mild, moderate or severe), %	100	1
MMSE, baseline mean	10.7	1
Behavioral symptoms	NA	1
BPRS, mean	33.7	1
BPRS agitation score, mean	8.3	1
CMAI, mean	36.5	1

BPRS=Brief Psychiatric Rating Scale; CATD=Clinical Alzheimer's-type Dementia; CMAI=Cohen-Mansfield Agitation Inventory; MMSE=Mini-Mental State Exam; NA=not applicable

Outcomes

Table 9.8 summarizes primary efficacy and harms results for divalproex versus placebo. For efficacy, evidence was insufficient about between group differences in change in agitation, but no studies reported data on aggression, psychosis, or disinhibited sexual behavior at 2 weeks or longer, or on depression, anxiety, quality of life, or caregiver outcomes at 24 weeks or longer. Although this study reported on general behavior, followup for this outcome was less than 24 weeks, so data were not extracted or analyzed.

For harms, falls occurred in 21 percent of the divalproex group compared with 17 percent of the placebo group (p=0.54), and one death occurred in divalproex group. No studies reported data on serious adverse events, withdrawals due to adverse events, confusion, somnolence, or extrapyramidal symptoms.

Table 9.8. Summary of findings for primary outcomes: divalproex versus placebo

Domain	# Studies/Design (n Analyzed) Timing	CATD Population	Findings (Incidence, Change from Baseline)	Strength of Evidence
Agitation	1 RCT[374] (n=128) 6 weeks	With agitation, living in residential care facility	**Mean BPRS change:** SMD, -0.12 (95% CI, -0.44 to 0.21) **Mean CMAI change:** SMD, -0.21 (95% CI, -0.54 to 0.11)	Insufficient

BPRS=Brief Psychiatric Rating Scale; CATD=clinical Alzheimer's-type dementia; CI=confidence interval; CMAI=Cohen-Mansfield Agitation Inventory; RCT=randomized controlled trial; SMD=standardized mean difference

Variation in Outcomes by Participant or Drug Characteristics

Last, no studies reported data on whether the efficacy and harms of divalproex versus placebo varied as a function of patient characteristics, or by drug dose, duration or delivery route. Appendix Tables H.22-H.25 provide detailed evidence tables and strength of evidence for key comparisons and outcomes.

Other Prescription Drugs Versus Placebo

Key Messages

- In older adults with CATD and BPSD, evidence for other prescription drugs compared with placebo was insufficient to draw conclusions about their efficacy and harms.

Eligible Studies

We identified four additional eligible trials that compared prescription drugs with placebo for treatment of BPSD in adults with CATD and BPSD. These included two trials that compared memantine with placebo (n=522),[258, 375] and two that compared estrogen with placebo (n=41).[376, 377] All were assessed as high ROB and outcomes were not extracted or analyzed. The most common reasons for high ROB were attrition bias,[375, 376] performance bias,[258, 377] and reporting bias.[258, 377] Appendix Tables H.26-H.29 provide study characteristics and ROB assessments for these two high-risk-of-bias trials.

We identified no eligible trials that compared benzodiazepines anxiolytics, other anxiolytics or cannabinoids with placebo for treatment of BPSD in adults with CATD and BPSD.

Chapter 10. Key Question 7: Supplements Versus Placebo for Behavioral and Psychological Symptoms of Dementia

Key Messages

- In older adults with clinical Alzheimer's-type dementia (CATD) and behavioral and psychological symptoms of dementia (BPSD):
    - Evidence was insufficient for the traditional Japanese herbal mixture, Yokukansan, versus placebo for agitation, aggression, psychosis, serious adverse events, or withdrawals due to adverse events.
    - There was no evidence for any supplements versus placebo for disinhibited sexual behavior or quality of life, and no evidence at 24 weeks or longer for depression, anxiety, or general behavior.

Eligible Studies

We identified one eligible publication of one unique trial that compared efficacy of supplements with placebo for BPSD outcomes in adults with CATD and BPSD.[378] This trial had low risk of bias (ROB).

Baseline Study Characteristics

Participants (n=145) had probable CATD by clinical criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM) III or National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders (NINCDS-ADRDA); baseline Mini-Mental State Exam (MMSE) 1-26; Neuropsychiatric Inventory Brief Questionnaire Form (NPI-Q) score >4; and sum of NPI-Q agitation/aggression and irritability subcategory scores >2.[378] Mean participant age was 78 years, 58 percent were female, and 97 percent were community dwelling. Race was not reported. Mean baseline MMSE and NPI-Q scores were 19.4 and 9.5, respectively. Participants were randomized to Yokukansan 7.5 grams/day (n=70) or placebo (n=75) for 4 weeks. Yokukansan dose could be decreased to 5.0 grams/day based on tolerability and response.

Outcomes

For efficacy, there was no statistically significant difference between Yokukansan and placebo for change in general behavior (NPI-Q scores) (-2.3 vs. -2.0, p=0.523) or in NPI-Q subcategory scores, such as the Agitation/Aggression, Delusion, Hallucination, and Disinhibition subscales (no data reported). Evidence was considered insufficient to draw conclusions about between group differences for all these outcomes. No studies reported data on disinhibited sexual behavior at 2 weeks or longer, or on depression, anxiety, quality of life, or caregiver outcomes at 24 weeks or longer.

For harms, evidence was insufficient to draw conclusions about between treatment group differences in serious adverse events (2 Yokukansan participants vs. 1 placebo participant) or withdrawals due to adverse events (1 participant in each treatment group), and no studies reported data on confusion, somnolence, falls, extrapyramidal symptoms, stroke, or mortality.

Appendix I provides detailed evidence tables and strength of evidence for key comparisons and outcomes.

Variation in Outcomes by Participant or Drug Characteristics

In *post hoc* analyses, treatment efficacy was compared between Yokukansan and placebo in subgroups defined by MMSE <20, age <74 years, moderate to severe agitation/aggression defined by baseline NPI-Q subcategory score >2, and baseline hallucinations. In participants scoring below 20 on the baseline MMSE (n=73), treatment groups did not significantly differ for NPI-Q total scores (p=0.086), but participants assigned Yokukansan had a greater decrease than placebo in the NPI-Q Agitation and Aggression Subscale (-0.68 vs. -0.22, p=0.007). In participants <74 years old (n=35), Yokukansan resulted in a greater decrease in the NPI-Q agitation and aggression subscale than placebo (-0.94 vs. -0.5, p=0.049). In participants with baseline moderate to severe agitation/aggression (n=91), Yokukansan was associated with a greater decrease in the NPI-Q Agitation and Aggression Subscale than placebo (p=0.050). Finally, in participants with baseline hallucinations (n=20), those assigned Yokukansan had a greater decrease in NPI-Q scores than those assigned placebo (p=0.019). No adjustments for multiple comparisons or tests for interaction were reported.

No studies reported whether differences in treatment efficacy and harms between Yokukansan and placebo varied as a function of Yokukansan dose, duration, or delivery route.

Chapter 11. Key Question 8: Prescription Drug Treatment Versus Other Active Treatment for Behavioral and Psychological Symptoms of Dementia

Key Messages

- In older adults with clinical Alzheimer's-type dementia (CATD) and behavioral and psychological symptoms of dementia (BPSD), evidence for prescription drugs compared with other prescription drugs showed:
- For sertraline versus mirtazapine in individuals with mild to moderate CATD and depression:
    - Insufficient evidence for depression, general behavior, quality of life, or serious adverse events.
    - No evidence for agitation, aggression, psychosis, disinhibited sexual behavior, anxiety, or withdrawals due to adverse events.
- For memantine compared with continued antipsychotics in individuals with moderate to severe CATD receiving antipsychotics:
    - Insufficient evidence for agitation, general behavior, or serious adverse events.
    - No evidence for aggression, psychosis, disinhibited sexual behavior, anxiety, quality of life, or withdrawals due to adverse events.

Eligible Studies

We identified 12 eligible publications reporting 12 unique trials that directly compared effectiveness of different prescription drugs for treatment of BPSD in patients with CATD.[331, 346, 347, 352, 353, 355, 360, 368, 379-382] Ten trials were assessed as high risk of bias (ROB) and excluded from analysis. Two remaining trials were rated medium ROB and included in our analysis.[331, 368]

Sertraline Versus Mirtazapine

Baseline Study Characteristics

One trial enrolled 215 participants with probable or possible CATD defined by the clinical criteria of the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders (NINCDS-ADRDA), and depression defined by Cornell Scale for Depression in Dementia (CSDD) score $\geq$8.[368] All participants were receiving old-age psychiatry services from UK National Health Service centers and 14 percent lived in care homes. Mean participant age was 79 years, and 70 percent were female. Mean Mini-Mental State Exam (MMSE) score was 18.0, suggesting mild to moderate CATD severity. Mean Neuropsychiatric Inventory (NPI) and CSDD scores were 28.4 and 12.6, respectively. Participants were randomized to sertraline up to 150 mg/day or mirtazapine 45 mg/day for 39 weeks for treatment of depression. Appendix J provides detailed evidence tables, summary ROB assessments, and strength of evidence for key comparisons and outcomes.

Outcomes

Table 11.1 summarizes primary comparative effectiveness and harms outcomes. For comparative effectiveness, evidence was insufficient to draw conclusions about differences between sertraline and mirtazapine for depression, general behavior, or quality of life, and no data were reported for agitation, aggression, psychosis or disinhibited sexual behavior at 2 weeks or longer, or for anxiety at 24 weeks or longer. For caregiver outcomes, sertraline and mirtazapine did not statistically differ at 39 weeks for caregiver burden[383] (standardized mean difference [SMD], 0.21 [95% confidence intervals (CI), -0.11 to 0.54]), caregiver general health questionnaire (GHQ-12) (SMD, 0.22 [95% CI, -0.11 to 0.55]), caregiver general quality of life mental component score (SF-12 MCS) (SMD, 0.04 [95% CI, -0.29 to 0.37]), or caregiver general quality of life physical component score (SF-12 PCS) (SMD, -0.12 [95% CI, -0.45 to 0.21]).[368]

For harms, evidence was insufficient to draw conclusions about differences between sertraline and mirtazapine for serious adverse events. Five deaths were reported for each treatment group, but no studies reported data on withdrawals due to adverse events, somnolence, confusion, falls, extrapyramidal symptoms or stroke.

Table 11.1. Summary of findings for primary outcomes: sertraline versus mirtazapine

Domain	# Studies/ Design (n Analyzed) Timing	CATD Population	Finding (Incidence, Change From Baseline)	Strength of Evidence
Depression	1 RCT[368] (n=215) 39 weeks	Mild to moderate with depression	**Mean CSDD score at 39 weeks:** SMD, 0.23 [95% CI, -0.10 to 0.56])	Insufficient
General Behavior	1 RCT[368] (n=215) 39 weeks	Mild to moderate with depression	**Mean NPI score at 39 weeks:** SMD, 0.23 (95% CI, -0.09 to 0.56)	Insufficient
Quality of Life	1 RCT[368] (n=215) 39 weeks	Mild to moderate with depression	**Mean DEMQOL score at 39 weeks:** SMD, -0.14 (95% CI, -0.47 to 0.19) **Mean DEMQOL-proxy score at 39 weeks:** SMD, -0.07 (95% CI, -0.40 to 0.26) **Mean Self-rated EQ5D at 39 weeks:** SMD, -0.07 (95% CI, -0.40 to 0.26) **Mean Carer-rated EQ5D at 39 weeks:** SMD, 0.04 (95% CI, -0.29 to 0.37)	Insufficient
SAE	1 RCT[368] (n=215) 39 weeks	Mild to moderate with depression	Authors reported no difference between treatment groups, but provided no data	Insufficient

CATD=Clinical Alzheimer's-type Dementia; CI=confidence intervals; CMAI=Cohen-Mansfield Agitation Inventory; CSDD=Cornell Scale for Depression in Dementia; DEMQOL=Dementia Quality of Life; EQ5D=EuroQol 5D; NPI=Neuropsychiatric Inventory; RCT=randomized controlled trial; SAE=serious adverse events; SMD=standardized mean difference

Variation in Outcomes by Participant or Drug Characteristics

Efficacy findings were reported to not differ in subgroup analyses stratified by baseline depression severity (CSDD score 8 to 11 vs. $\geq$12).[368] No studies reported whether differences in treatment efficacy and harms between sertraline and mirtazapine varied as a function of participant characteristics or drug dose, duration, or delivery route.

Memantine Versus Antipsychotics

Baseline Study Characteristics

One trial enrolled 199 participants with probable or possible CATD defined by NINCDS-ADRDA clinical criteria who were living in care homes in the UK or Norway and already were receiving an antipsychotic. [331] Mean participant age was 83 years, and 69 percent were female. Mean MMSE score was 8, suggesting moderate to severe CATD. Mean NPI and Cohen-Mansfield Agitation Inventory (CMAI) scores were 17.6 and 51.4, respectively. Participants were randomized to antipsychotic continuation (risperidone 0.5 mg, olanzapine 5 mg, quetiapine 50 mg, or haloperidol 0.5 mg, once or twice daily as needed) or memantine (10-20 mg/day) for 24 weeks.

Outcomes

Table 11.2 summarizes primary comparative effectiveness and harms outcomes. For comparative effectiveness, evidence was insufficient to draw conclusions about differences between memantine and antipsychotics for agitation or general behavior, and no data were reported for aggression, psychosis or disinhibited sexual behavior at 2 weeks or longer, or for depression or anxiety at 24 weeks or longer.

For harms, evidence was insufficient to draw conclusions about differences between memantine and antipsychotics for serious adverse events. In the memantine group, there were no strokes and 9 percent of participants died, compared to the antipsychotic group with 2.5 percent incidence of stroke and 4 percent mortality. No studies reported data on withdrawals due to adverse events, somnolence, confusion, falls or extrapyramidal symptoms.

Table 11.2. Summary of findings for primary outcomes:* memantine versus antipsychotics

Domain	# Studies/ Design (n Analyzed) Timing	CATD Population*	Findings (Incidence, Change From Baseline)	Strength of Evidence
Agitation	1 RCT[331] (n=164) 24 weeks	Moderate to severe	**Mean CMAI score at 24 weeks:** SMD, 0.28 (95% CI, -0.02 to 0.59)	Insufficient
General Behavior	1 RCT[331] (n=164) 24 weeks	Moderate to severe	**Likelihood ≥30% worsened mean NPI score at 24 weeks:** 39.2% memantine vs. 29.6% antipsychotics (ARD, 9.6% [95% CI, -5 to 24]; OR, 1.99 [95% CI, 1.17 to 3.40]) (post hoc analysis) **Mean NPI score at 24 weeks:** SMD, 0.22 (95% CI, -0.08 to 0.53)	Insufficient
SAE	1 RCT[331] (n=164) 24 weeks	Moderate to severe	**Total SAE:** 18 memantine vs. 25 antipsychotics, p=NR	Insufficient

ARD=absolute risk difference; CATD=Clinical Alzheimer's-type Dementia; CI=confidence intervals; CMAI=Cohen-Mansfield Agitation Inventory; NPI=Neuropsychiatric Inventory; NR=not reported; OR=odds ratio; RCT=randomized controlled trial; SAE=serious adverse events; SMD=standardized mean difference

Variation in Outcomes by Participant or Drug Characteristics

No studies reported data on whether comparative effectiveness and harms between memantine and antipsychotics varied as a function of patient characteristics, or drug dose, duration, or delivery route.

Chapter 12. Discussion

Overview

How accurate are brief cognitive tests for identifying clinical Alzheimer's-type dementia (CATD) in individuals with suspected cognitive impairment? Brief cognitive tests alone cannot diagnose CATD. However, this review found that among individuals with suspected cognitive impairment, many of these tests are highly sensitive and specific for case finding, and appear more accurate for distinguishing CATD from normal cognition than for distinguishing CATD from mild cognitive impairment (MCI) or distinguishing mild CATD from normal cognition. Therefore, these tests may help providers decide which patients warrant a more comprehensive diagnostic evaluation. Brief cognitive tests may also provide a less burdensome way than comprehensive neuropsychological testing to objectively document cognitive impairment when patients have already undergone an appropriate cognitive history and have evidence of functional impairment.

Which brief cognitive tests, test combinations, and test cut points are best for distinguishing between CATD, MCI, and normal cognition in individuals with suspected cognitive impairment? We found few direct comparisons of different tests and cut points within studies, and different studies rarely compared the same test cut points. However, results from this review suggest that in individuals with suspected cognitive impairment, brief instruments commonly used as individual stand-alone tests, brief multidomain batteries, and, among domain-level tests typically part of a larger battery, memory, and verbal fluency tests may have the most potential for distinguishing between CATD, normal cognition and MCI. Within these test categories, the individual tests with the most available accuracy data were clock drawing and Mini-Mental Status Exam (MMSE) among the tests commonly used as individual stand-alone tests, Dementia Rating Scale (DRS) for brief multidomain batteries, list learning delayed recall and retention for memory tests, and semantic (category) fluency for language. However, the optimal version and cut point for each of these tests is uncertain. Test combinations may be more accurate for distinguishing between diagnostic categories than individual tests, but the additional administration time may not be feasible in primary care settings.

What is the evidence that brief, web-based cognitive tests can accurately distinguish between CATD, MCI, and normal cognition? Our review identified no eligible studies that evaluated the classification accuracy of web-based cognitive testing, alone or in comparison to a different testing approach. Though the Cogstate Brief Battery evaluated in this review is available for web-based administration, the web version was not used in the reported study.

Does the classification accuracy of brief cognitive tests for CATD vary based on participant characteristics, and should different tests and cut points be used in different individuals? In clinical practice, cognitive tests administered as part of a neuropsychological test battery are normed for age, gender, and education. Norms for brief cognitive tests also vary by these factors. However, the small set of studies that examined whether classification accuracy of brief cognitive tests varies by participant characteristics reported that accuracy did not vary by age, sex, race/ethnicity, or education. These studies were likely too small to rule out such associations and inadequate for concluding whether or not different cut points should be used for classifying between CATD and normal cognition or MCI in different clinical populations. By

comparison, sensitivity was consistently high for distinguishing participants with moderate CATD from normal cognition, and lower for distinguishing between mild CATD and normal cognition. These findings suggest that brief cognitive testing may be sufficient to categorize more moderately impaired patients, but insufficient to categorize more mildly impaired patients. For the latter group, inconclusive brief cognitive testing may warrant followup with more comprehensive neuropsychological testing and possibly specialty referral.

Are there harms of brief cognitive testing for CATD? We identified no studies that reported data on harms of brief cognitive testing for CATD. We also found no such data in prior systematic reviews of brief cognitive testing for CATD published since 2013. Nevertheless, potential harms following brief cognitive testing that incorrectly classifies someone as having CATD (false positive) include stigma from being incorrectly labeled with CATD and harms of unnecessary interventions (e.g., restrictions on independence, physical or psychological harms of further diagnostic testing, medication adverse effects). Potential harms following brief cognitive testing that incorrectly fails to identify CATD (false negative) include psychological distress from unexplained symptoms and lack of appropriate interventions (e.g., future planning, taking safety precautions, initiation of medications).

In individuals with CATD, which brain imaging test, cerebrospinal fluid (CSF) test, or combination is most accurate for distinguishing Alzheimer's disease (AD) from non-AD dementia? Our review could not determine which brain imaging test is most accurate for distinguishing neuropathologically-confirmed AD from non-AD dementia, or from individual types of non-AD dementia, because the only study that compared different brain imaging tests (amyloid positron emission tomography [PET] plus computed tomography [CT] versus amyloid PET alone) reported no data.[4] However, single studies suggested that amyloid PET and fluorodeoxyglucose (FDG)-PET may increase classification accuracy when added to clinical evaluation compared with clinical evaluation only. By comparison, in two studies, single-photon emission computed tomography (SPECT) added to clinical evaluation had lower sensitivity and higher specificity than clinical evaluation alone, and no studies compared magnetic resonance imaging (MRI) medial temporal atrophy (MTA) plus clinical evaluation versus clinical evaluation alone.

Evidence regarding whether certain individual CSF tests or combinations of CSF tests are better than others for distinguishing neuropathologically-confirmed AD from non-AD is inconclusive. Three eligible studies directly compared accuracy of selected CSF biomarkers. Collectively, they suggested that abnormally phosphorylated tau (p-tau), the Aβ42/p-tau ratio, and the t-tau/Aβ42 ratio may be more accurate and beta amyloid 42 (Aβ42) and total tau (t-tau) may be less accurate. Analyses comparing CSF tests for distinguishing between AD and individual types of non-AD showed different patterns. However, all cut points for defining abnormal versus normal CSF biomarker levels were specific to individual studies and virtually none were validated in other studies.

A 2018 systematic review reported much greater diagnostic accuracy for Aβ42, Aβ42/p-tau, and Aβ42/t-tau ratio.[17] That review was conducted to provide the evidence base to support Alzheimer's Association appropriateness criteria on the accuracy of CSF testing for AD. Using an autopsy reference, authors reported sensitivity ranging from 0.89 to 0.92 and specificity ranging from 0.82 to 0.88. However, their analysis focused on the ability of CSF markers to distinguish AD from patients without dementia, for which testing performance would be

expected to be higher. Our analyses, in contrast, examined the ability of CSF markers to distinguish AD from non-AD dementias in patients with CATD.

In patients with CATD, how likely are brain imaging or CSF tests to add to a clinical evaluation by correcting an incorrect clinical diagnosis between AD and non-AD dementia? In two studies, SPECT plus clinical evaluation had lower sensitivity and higher specificity than clinical evaluation alone. By comparison, in one study (with AD prevalence of 74 percent and clinical diagnostic accuracy for distinguishing AD from non-AD dementia of 80 percent), amyloid PET increased diagnostic accuracy to 98 percent by correctly reclassifying 92 percent of clinical false negatives, while falsely reclassifying 4 percent of clinical true positives. In a second study (with AD prevalence of 57 percent, and clinical diagnostic accuracy for distinguishing between AD and non-AD of 68 percent), FDG-PET increased diagnostic accuracy to 80 percent, due to small reductions in both clinical false negatives and clinical false positives. This second study showed that FDG-PET also modestly increased accuracy distinguishing between AD and frontotemporal lobar degeneration (FTLD) when added to a clinical evaluation. However, the gains in diagnostic accuracy with amyloid PET and FDG-PET reported in research studies may not be achievable in clinical settings. One reason is that the high prevalence of AD in research studies may have increased diagnostic vigilance and test sensitivity. Second, in clinical settings, both individuals with and without AD dementia may be more likely to have multiple etiologies and thus be harder to distinguish. Third, it is not likely that image interpretation in clinical settings will be able to rely on the consensus of multiple readers (five in the amyloid PET study and two in the FDG-PET study).

The recent IDEAS study on amyloid PET brain imaging was not included in this review because biomarker testing was not compared with a neuropathological reference standard.[384] Nevertheless, its findings are pertinent to the discussion about the feasibility of testing outside of research settings and the potential for test results to change clinical diagnoses and subsequent clinical management. IDEAS enrolled 11,409 Medicare beneficiaries with dementia or MCI of uncertain etiology after they had completed a comprehensive evaluation by a dementia specialist (most based in private practice). For eligibility, AD must have been a diagnostic consideration and knowledge of amyloid PET status must have been expected to alter diagnosis and management. Amyloid PET imaging was performed in accredited imaging facilities and scans were interpreted by imaging specialists following approved reading methodologies. Prior to imaging, AD was the leading suspected etiology in 83 percent of participants with dementia and 73 percent of those with MCI, and 59 percent of participants with dementia were taking AD drugs compared with 35 percent of those with MCI. Amyloid PET results were rated positive in 70.1 percent of participants with dementia and 55.3 percent of those with MCI. Among individuals with previously suspected AD, based on amyloid PET imaging, the suspected etiological diagnosis changed to non-AD in 32.6 percent (2,860 of 8,770), whereas among individuals with previously suspected non-AD, the suspected etiological diagnosis changed to AD in 45.5 percent (1,201 of 2,639). Reclassification results were not reported separately for participants with dementia versus MCI. Results also were not compared to a neuropathological reference. Clinical management (use of AD drugs, use of non-AD drugs, or counseling about safety or future planning) changed within 90 days after amyloid PET in 63.5 percent of participants with dementia and 60.2 percent of participants with MCI. These changes included large increases in AD drug use after positive amyloid PET results in both patients with AD and MCI, and small reductions in AD drug use after negative amyloid PET results. However, the

ability to attribute clinical management changes to amyloid PET results was limited by the lack of a non-PET control group and inclusion only of participants for whom amyloid PET results were expected to alter management. In addition, clinical management was not evidence-based (many patients with MCI or with negative amyloid PET results were treated with AD drugs) and the association of amyloid PET evaluation with clinical outcomes was not examined.

By comparison, SPECT combined with clinical evaluation in two studies did not appear to increase classification accuracy compared with clinical evaluation alone. Further, in one study, clinical evaluation alone and MRI medial temporal atrophy alone had similar diagnostic accuracy and no studies directly compared MRI plus clinical evaluation versus clinical evaluation alone.

Only one eligible study reported data on the diagnostic accuracy of CSF testing added to clinical evaluation compared with clinical evaluation alone. In this study, clinical evaluation had a sensitivity of 0.80 and specificity of 0.80 for distinguishing between neuropathologically-confirmed AD and FTLD. However, a regression model including CSF Aβ42 and p-tau levels measured using a Luminex assay had a sensitivity of 0.98 and specificity of 0.93. CSF testing improved accuracy primarily by reclassifying participants who were incorrectly classified by clinical evaluation as having FTLD. To a lesser extent, CSF testing improved accuracy by reclassifying participants who were incorrectly classified by clinical evaluation as having AD. However, CSF testing also falsely reclassified 3 percent of participants who were correctly classified by clinical evaluation. Authors also created a regression model of CSF markers using results from an enzyme-linked immunosorbent assay (ELISA), but did not report how this affected classification accuracy compared with clinical evaluation.

Does the classification accuracy of brain imaging or CSF tests for AD vary based on patient characteristics, and should different tests and cut points be used in different populations? Available data appears inadequate to guide targeting of different brain imaging or CSF tests, or use of different test cut points for classification of patients between AD and non-AD dementias in different populations. We found little information in eligible studies about whether accuracy of brain imaging or CSF tests for distinguishing autopsy-confirmed AD from non-AD varies based on study participant characteristics, including by age, race/ethnicity, sex or CATD severity. One study reported similar sensitivity and specificity for FDG-PET between participants with milder versus more severe cognitive impairment. A second study reported that SPECT diagnostic accuracy did not vary by age at dementia symptom onset, MMSE score, disease duration, or interval between imaging and death. However, no studies reported tests of interaction for potential subgroup differences, or whether accuracy of any brain imaging test differed by other participant characteristics. For CSF testing, one study reported that classification accuracy of t-tau levels for distinguishing autopsy-confirmed AD from non-AD did not vary by age or sex. Otherwise, no studies reported on whether classification accuracy of brain imaging or CSF tests or the optimal test cut points vary by participant characteristics.

In patients with CATD, how likely are prescription drugs to prevent worsening of cognition and function, how likely are they to improve these outcomes, and how long will any benefits last? Trials of about 6 months showed benefits for cholinesterase inhibitors compared with placebo regardless of baseline CATD severity. However, average differences for cognition and function between treatment groups were small, with standardized mean differences generally between 0.20 to 0.40 for cognition and about 0.20 for function. Responder analyses showed that compared with placebo, for approximately every 5 to 9 participants assigned

cholinesterase inhibitors, one additional individual was stable at 6 months on a brief multidomain cognitive battery (ADAS-Cog) or a global change measure (Clinician's Interview-Based Impression of Change with caregiver input [CIBIC-Plus] or Clinical Global Impression of Improvement [CGIC]). Further, for approximately every 5 to 13 participants assigned cholinesterase inhibitors compared with placebo, one additional individual was improved at 6 months on ADAS-Cog (≥4-point improvement), CIBIC-Plus or CGIC. Whether improvements meeting these thresholds are clinically meaningful is unclear. Data on moderate or marked improvement for cognition or function were not reported and moderate or marked improvement on the global change measure was rare and no more likely with cholinesterase inhibitor treatment than placebo. Because no eligible cholinesterase inhibitor trials with low or medium risk of bias reported efficacy outcomes beyond 6 months, it is uncertain whether any benefits compared with placebo are sustained beyond this duration. For memantine, one trial suggested that compared with placebo, for approximately every six participants who were taking a cholinesterase inhibitor and were assigned add-on memantine compared with placebo, one additional individual improved on a global measure of change. However, this trial did not report responder analyses for cognition or function and no other eligible memantine trials reported responder analyses for any efficacy outcomes. Similar to the cholinesterase inhibitor results, it is unclear whether the 6-month improvement in this single outcome compared with placebo is clinically meaningful and whether there are any sustained benefits beyond 6 months.

In patients with CATD, how likely are supplements to prevent worsening of cognition and function, how likely are they to improve these outcomes, and how long will any benefits last? Available evidence was mostly insufficient about whether supplements are more effective or safe than placebo for treatment of patients with CATD, let alone about the magnitude or duration of any benefits. Among eligible trials with low or medium risk of bias, compared with placebo, omega-3 fatty acids did not improve cognition and the nutritional drink Souvenaid® did not improve function. Although single trials showed statistically significant benefit for at least one cognitive outcome for melatonin, choline alfoscerate, and the combination of omega-3 fatty acid and alpha lipoic acid, respectively, strength of evidence for these three treatments was insufficient. We found additional eligible trials that compared gingko biloba, acetyl-l-carnitine, vitamin E, ginseng, curcumin, lecithin, and other supplements versus placebo, but all were rated as having high risk of bias (ROB), most often due to high attrition. Therefore, evidence from these trials was a priori considered insufficient and was not analyzed. We found no eligible studies for Prevagen (apoaequorin), huperzine or phosphatidylserine.

Our findings are mostly consistent with those reported in prior systematic reviews. A 2000 Cochrane review on lecithin reported no clear benefit for AD,[39] a 2003 Cochrane review on acetyl-l-carnitine for AD suggested that isolated favorable findings for cognition were likely due to chance in the context of many other negative results,[385] and a 2009 Cochrane review concluded that evidence for whether gingko improved cognition or function compared to placebo in people with AD was inconsistent and unreliable.[386] In addition, a 2016 Cochrane review on omega-3 fatty acids in patients with mild to moderate AD found no convincing evidence of a benefit compared with placebo in trials of 6 to 18 months for cognition, function, staging, or quality of life. [387] However, our findings differed from those in a 2017 Cochrane review on vitamin E.[388] We excluded a moderately sized (n=304), long-term trial of vitamin E versus placebo due to high ROB from high attrition (41% death, withdrawal, or loss to followup at 4 years; analyzed by a longitudinal repeated-measures mixed-effects model assuming missing at

random). In contrast, the prior review, for which this was the only trial with extractable data in individuals with CATD, rated its attrition bias as low, stating that missing data were balanced across groups.[300] This trial reported that among individuals with mild to moderate AD, participants assigned vitamin E for 6 to 48 months had a small improvement in function compared with placebo, but that treatments did not differ for cognition or serious adverse events.

In patients with CATD, how do prescription drugs and supplements compare for effects on cognition, function, behavioral and psychological symptoms of dementia (BPSD), and safety? We identified several eligible trials that directly compared supplements with prescription drugs for treatment of individuals with CATD. Respectively, these trials compared gingko biloba to donepezil, gingko biloba to rivastigmine, saffron extract to donepezil, vitamin E to donepezil, vitamin E to memantine, and Yishen Huazhuo decoction group to donepezil. For all these comparisons, evidence was judged insufficient to draw conclusions about relative differences for cognition, function, and safety, and none of the trials reported on BPSD. Although evidence from direct comparisons is insufficient, indirect evidence from placebo controlled trials suggests supplements may be less effective but is less clear regarding safety. Compared with placebo, cholinesterase inhibitors modestly improved cognition and function, while possibly increasing serious adverse events and withdrawals due to adverse events. Memantine inconsistently improved cognition in individuals with moderate to severe CATD when added to a cholinesterase inhibitor, but did not improve function. However, supplements compared with placebo either showed no difference in efficacy (Souvenaid®, omega-3 fatty acids), or insufficient evidence about efficacy and safety (e.g., gingko biloba, ginseng, curcumin, vitamin E, resveratrol).

In patients with CATD, is there evidence to support targeting different prescription drugs or supplements to different patients for cognition and function outcomes? Limited trial data indicate that memantine may have a small benefit in individuals with moderate to severe CATD, but not in those with mild to moderate CATD. Trials of memantine compared with placebo did not stratify results by baseline CATD severity, but those limited to study participants with moderate to severe CATD showed inconsistent improvement in cognition, while those that enrolled patients with mild to moderate CATD showed no benefit in cognition or function. Cholinesterase inhibitors compared with placebo showed small improvements in cognition and function in both participants with mild to moderate and moderate to severe CATD. Three cholinesterase inhibitor trials reported that efficacy compared with placebo, or of high- versus standard-dose donepezil (i.e., 23 mg/day vs. 10 mg/day), may be greater in participants with lower compared with higher baseline MMSE. However, these findings were based on *post hoc* analyses, no tests for interaction were performed, and they may be due to chance. One trial reported that omega-3 fatty acids were no better than placebo in any of several groups defined by baseline MMSE. No eligible studies reported results stratified by age, race/ethnicity or sex.

In patients with CATD and BPSD, how effective are prescription drugs and supplements for agitation, aggression, and psychosis, and how long do benefits last? In eligible trials of individuals with CATD and BPSD of at least 2 weeks duration, antipsychotics and the antidepressant citalopram statistically significantly improved a minority of BPSD outcomes compared with placebo. However, due in part to imprecise and inconsistent results, evidence about the efficacy of these treatments for these outcomes was insufficient to draw

conclusions. For antipsychotics, data were limited to small trials with little statistical power. One 6-week trial reported moderate-sized improvements in two agitation measures with standard-dose haloperidol compared with placebo, but neither of these differences was statistically significant and standard-dose haloperidol and placebo did not differ for either of two aggression measures. In another 6-week trial, quetiapine and placebo did not differ for agitation. Two antipsychotic trials showed inconsistent effects for psychosis, with statistically significant improvement in one of four measures for standard-dose haloperidol after 6 weeks, and in two of three measures for aripiprazole after 10 weeks. No evidence addressed the effects of antipsychotics on these outcomes beyond 10 weeks. For antidepressants, citalopram compared with placebo statistically significantly improved four of seven agitation measures after 9 weeks. Citalopram compared with placebo also statistically significantly improved one of five measures for psychosis. However, both citalopram trials evaluated a dose of 30 mg/day that exceeds the current maximum recommended dose of 20 mg/day. The effects of the this lower dose on BPSD outcomes is unknown. In people receiving open-label cholinesterase inhibitor, sertraline compared with placebo did not improve agitation. No eligible trials with low or medium risk of bias compared different antipsychotics, different antidepressants, or antipsychotics with antidepressants and reported data on agitation, aggression, or psychosis.

Trials investigating donepezil, divalproex sodium, and the traditional Japanese herbal mixture, Yokukansan, for 4 to 12 weeks collectively, reported no statistically significant improvements in agitation, aggression, or psychosis. Evidence was mostly insufficient to draw conclusions about these findings. Two trials of memantine for BPSD were rated high ROB and not analyzed. In one trial in which individuals living in care homes and receiving antipsychotics were randomized to either continue antipsychotics or switch to memantine, treatments did not statistically differ for agitation after 24 weeks, but evidence was graded insufficient.

In patients with CATD and BPSD, how well do prescription drugs and supplements work for treating disinhibited sexual behavior? Antipsychotics, selective serotonin reuptake inhibitor (SSRI) antidepressants, and less often hormones are sometimes used in clinical practice to treat disinhibited sexual behavior in patients with CATD and BPSD. However, no eligible trials with low or medium ROB reported on the effects of antipsychotics, SSRIs, other prescription drugs, or supplements on disinhibited sexual behavior. One small trial (n=14) compared estrogen versus placebo for 4 weeks and reported on sexual aggressiveness as a secondary outcome, but was rated high ROB and therefore not analyzed. Although trials in individuals with CATD and BPSD provide insufficient strength evidence about differences in risk of harms compared with placebo, trials in broader populations suggest potential risks of somnolence, confusion, falls, fractures, stroke, mortality, and other adverse outcomes. Given these potential harms, and the absence of evidence from eligible trials for benefits (not the same as definitive evidence that there is no benefit), use of these treatments for disinhibited sexual behavior in patients with CATD may not be warranted.

Which patients with CATD and BPSD are most likely to experience improvements in BPSD or harms from drug treatments? No eligible studies in individuals with CATD and BPSD reported on whether differences in BPSD or harms vary by participant characteristics.

In patients with CATD and BPSD, how do prescription drugs and nondrug treatments compare for BPSD outcomes and safety? Current guidelines for managing BPSD in patients

with CATD recommend nondrug interventions as first line therapy.[24] However, a 2016 AHRQ report found that psychosocial interventions were not superior to usual care for managing agitation and aggression.[25] Our review found insufficient evidence about the comparative effectiveness of drug treatment and nondrug interventions for BPSD in patients with CATD and BPSD because no eligible trials addressed this question. We also found little indirect evidence. Eleven trials compared prescription drugs with placebo for BPSD. However, only one reported that enrolled patients must have had an inadequate response to a prior psychosocial intervention, and one reported that all participants in both treatment groups received a concomitant psychosocial intervention during the drug trial. Both tested the question of whether prescription medication improved BPSD beyond the uncertain benefit of psychosocial intervention.

AD is a qualifying condition for medical marijuana in many U.S. States, but what are the efficacy and safety of cannabinoids in patients with CATD? We identified no eligible trials of cannabinoids lasting at least 2 weeks for outcomes of agitation, aggression, psychosis, or disinhibited sexual behavior, or at least 24 weeks for cognition, function, and other efficacy outcomes and harms in individuals with CATD. Therefore, evidence was insufficient to draw conclusions about the efficacy or safety of cannabinoids for treatment of CATD and more specifically for treatment of BPSD in patients with CATD. Future trials are needed to examine the scientific evidence on the efficacy and harms of cannabinoids for these indications.

Applicability

This review aimed to evaluate the accuracy of brief cognitive tests for distinguishing CATD from normal cognition and MCI among individuals with suspected cognitive impairment (i.e., case finding). By intent, this review did not evaluate the role of formal neuropsychological testing for clinical diagnosis of CATD. This review also did not address the accuracy of brief cognitive tests for predicting future clinical progression to CATD or for distinguishing CATD from other types of dementia, though accuracy distinguishing between different types of dementia would be expected to be lower than that for distinguishing CATD from either normal cognition or MCI. We calculated true positive, false positive, true negative and false negative rates by applying the sensitivity and specificity reported in each analyzed study to its prevalence of CATD, normal cognition and MCI. These rates may not be generalizable to populations with a lower CATD prevalence or greater variability in the causes of cognitive impairment. In addition, participants in studies of brief cognitive testing were younger (mean 73 to 74 years) than many who present with suspected cognitive impairment in typical clinical settings, potentially limiting generalizability to these older patients. In the minority of cognitive testing studies that reported race, most participants were white; therefore, generalizability of study findings to other race/ethnic groups is unknown.

This review aimed to evaluate the accuracy of brain imaging and CSF tests to distinguish autopsy-confirmed AD from non-AD in individuals with CATD. Our review did not examine the accuracy of these biomarker tests to distinguish AD from either normal cognition or MCI, and excluded studies that used a biomarker as the reference gold standard rather than autopsy. This review also did not address the accuracy of biomarker tests for predicting clinical progression to AD over time. In the minority of studies that reported race, most participants were white; therefore, generalizability of study findings to other race/ethnic groups is unknown. Because studies examining biomarker classification accuracy included mostly participants whose symptoms began in their early 60s to early 70s, who were followed for years in research settings,

and had low life expectancy after biomarker collection to limit the time interval between testing and autopsy, applicability to patients in better health, with later onset disease, and earlier in their disease course may be limited. This is in part because abnormalities detected by these tests and neuropathology may be less earlier in the disease course. In addition, studies examining the classification accuracy of brain imaging and CSF tests compared to a neuropathological reference sometimes used methods not feasible in clinical settings (e.g., complex analytical techniques for scan interpretation, gradings based on the consensus of multiple readers). Also, studies did not use standardized imaging techniques, assays, and cut points to categorize normal versus abnormal test results. The applicability of study findings on the accuracy of brain imaging and CSF tests for AD also may be limited because many of these biomarker tests may not be easily available in typical clinical settings--though the IDEAS study suggested that amyloid PET imaging at least may be accessible to dementia specialists outside of academic research settings. Further, CSF tests are invasive, and the association of all these biomarker test results with clinical patient outcomes is unknown.

It was the aim of the review on CATD drug treatment efficacy and harms to apply to older adults with CATD in typical clinical settings whose clinical dementia is not secondary solely to traumatic brain injury, frontotemporal dementia (FTD), Parkinson's disease, Lewy body disease (LBD), stroke, or another non-AD etiology. Therefore, review findings may not apply to populations with these non-AD causes of dementia. Because few drug treatment trials reported data on race or ethnicity and those enrolled predominately white participants, the applicability of review findings to other racial or ethnic groups is unknown. Also, comorbidity was infrequently reported, so applicability of results to patients with multiple comorbid conditions is unknown. In addition, this review does not address the question of stopping drug treatment for CATD towards the end of life or the efficacy and harms of acute drug treatment for BPSD.

Limitations

The first limitation of this review on brief cognitive tests and biomarker tests is that it did not identify eligible studies that linked test accuracy to patient or caregiver outcomes, including cognitive, functional, psychological, quality of life and others. Moreover, eligible studies did not report on the association of these tests with process outcomes like changes in drug or nondrug management, including lifestyle changes or changes in life planning that may or may not affect patient or caregiver outcomes. Although the IDEAS study reported on changes in management, it is likely the frequency of management changes investigators reported after amyloid PET testing exceeded what would be expected in typical clinical practice. This is both because participating clinicians expected to change management following the test and a substantial portion of the management changes made were not evidence based (e.g., starting AD drug treatment in patients with MCI).

Evidence on the accuracy of brief cognitive tests for distinguishing CATD from normal cognition and MCI in patients with suspected cognitive impairment was limited in several ways. Many studies had small sample sizes. There were few eligible studies in this population for most individual cognitive tests, fewer of test combinations, and none for several common tests (e.g., Mini-Cog, St. Louis University Mental Status [SLUMS], Telephone Interview for Cognitive Status [TICS], Cambridge Neuropsychological Test Automated Battery [CANTAB]) or for any web-based tests. Studies on the classification accuracy of these and other brief cognitive tests were excluded for various reasons, including non-English test administration, not completing a diagnostic evaluation in many participants who completed brief cognitive testing, not using a

acceptable definition for CATD (e.g., basing it only on a single cognitive test). [389]Evidence on the accuracy of brief cognitive tests also was limited because studies used variable standards to define CATD, MCI and normal cognition, none defined CATD using National Institute on Aging-Alzheimer's Association (NIA-AA) clinical criteria,[15] and none directly compared whether test classification accuracy varied as a function of which definitions were used. Cognitive test studies also used variable test scoring metrics and most often used cut points for distinguishing normal from abnormal that were defined from the analyzed cohort rather than being prespecified. Test performance was assessed when distinguishing CATD from MCI or NC, and is expected to be less accurate when distinguishing CATD from any other cause of cognitive impairment.

Limitations of biomarker classification studies included that there were few brain imaging and CSF biomarker studies with autopsy-confirmed reference standards, and none for blood tests. Many biomarker studies were limited by small sample sizes. Biomarker studies were methodologically heterogeneous, with sources of heterogeneity including composition of non-AD comparison groups, interval between biomarker collection and autopsy, methods of image acquisition or CSF assay and analysis, autopsy reference standards, and use of test cut points unique to their individual study cohorts. Biomarker studies also were limited because many study participants with biomarker measures did not complete autopsy and weren't included in analyses, potentially introducing a selection bias. Further, no eligible biomarker studies evaluated accuracy of MRI hippocampal atrophy, CT, tau PET, or functional magnetic resonance imaging (fMRI) brain imaging; Aß42/Aß40 ratio or neurofilament light protein CSF tests; or of any blood tests compared to a reference standard of autopsy-confirmed AD. Few studies examined the classification accuracy of test combinations.

In both cognitive and biomarker test accuracy studies, the high prevalence of CATD and AD, respectively, could have increased diagnostic vigilance and led to sensitivity results higher than what would be expected in typical clinical populations,[390] even those in whom CATD is suspected. Where reported, most participants in these studies were white, and little data evaluated whether accuracy varied by patient characteristics. Lastly, no cognitive testing studies or brain imaging or CSF testing studies reported data on clinical patient outcomes and only a few brain imaging or CSF testing studies reported on harms.

There are several limitations of the evidence on the efficacy and harms of CATD drug treatments. Few trials examined individual drug treatments, especially for supplements, BPSD treatments, and for prescription drugs when results were stratified by CATD severity. Many trials were limited by small sample size and short follow-up times, resulting in low statistical power for even somewhat common events and large mean differences between groups. For example, only 14 total deaths occurred in the 451 participants in the three eligible antipsychotic trials that reported mortality. This review limited prescription drug classes evaluated for cognition and function to cholinesterase inhibitors and memantine, and prescription drug classes evaluated for BPSD to cholinesterase inhibitors, memantine, antipsychotics, antidepressants, anxiolytics, antiepileptics/mood stabilizers, hormonal agents, and cannabinoids. Consequently, dextromethorphan-quinidine for treatment of individuals with CATD and agitation was not included, though one phase 2 trial suggests it may improve agitation, aggression and some caregiver measures compared with placebo.[391] By design, this review required studies of cognition and function to be at least 24 weeks in length, and studies of agitation, aggression, and psychosis to be at least 2 weeks in length. Trials reporting only on shorter-term treatment effects were excluded. Few included trials were longer than 26 weeks, so longer-term drug effects were

unclear. Because trial populations were predominately white, generalizability to other racial/ethnic groups is uncertain. Few studies directly compared different drug treatments. Few trials reported results for CATD staging, individual cognitive domains, quality of life, or caregiver outcomes, and no eligible studies without high ROB reported results for disinhibited sexual behavior. Harms reporting was poor. For example, no eligible antipsychotic trials reported data on incident stroke. Many eligible trials were excluded from analyses due to high ROB, often because of high attrition, especially trials longer than 26 weeks and some that compared two active treatments. In at least one example, a trial we rated high ROB and excluded from analysis was not rated high ROB and was analyzed in a prior systematic review; this highlighted the potential sensitivity of systematic review results to the details of eligibility criteria. Many studies analyzed results using methods of accounting for missing data that may overestimate treatment benefit. It was difficult to interpret the relevance of small between-group differences in continuous outcomes, and most studies did not report data on between-group differences in the likelihood of experiencing clinically important treatment effects (i.e., responder analyses). Few trials evaluated whether treatment efficacy and harms varied by participant characteristics. Last, because we analyzed studies grouped by participant CATD severity and graded SOE for treatment effects within these severity categories, it is possible that SOE grades would have been different in cases when lumping studies regardless of baseline CATD severity may have been clinically reasonable (e.g., for harms).

Future Research

Brief Cognitive Testing for CATD in Adults With Suspected Cognitive Impairment

Future research should use the most updated available standardized criteria to clinically define participants with CATD and MCI, and should define normal cognition based on a formal cognitive evaluation rather than from participant self-report. Studies should evaluate the case finding accuracy of brief cognitive tests commonly used as individual stand-alone tests that are commonly used or promoted for use in clinical practice, but for which we identified few or no eligible studies in older adults with suspected cognitive impairment. Tests with few eligible studies included the Montreal Cognitive Assessment (MoCA), and tests with no eligible studies included the Mini-Cog, SLUMS, TICS, CANTAB, and web-based tests. Small sample sizes limited the precision of many studies evaluating the accuracy of brief cognitive tests for CATD, and limited their ability to evaluate whether results differed by participant characteristics. Therefore, future studies should be larger and should prespecify analyses to examine whether results differ as a function of characteristics like age, race/ethnicity, sex, and education. Prior studies have almost exclusively evaluated the accuracy of cut points derived to maximize performance within their study cohort and rarely evaluated the accuracy of prespecified raw or demographically normed cut points. Future studies should validate cut points derived in prior studies so that cut points can be externally validated and generalized across populations. Future studies should compare the accuracy of different individual cognitive tests and their combinations in the same study populations, to help identify the best test or combination of tests for maximizing classification accuracy and feasibility in typical clinical settings. Studies should systematically collect data on psychological and other harms of cognitive testing. Studies should also, directly or through modeling, evaluate whether brief cognitive testing of patients with

suspected cognitive impairment affects drug and nondrug treatment decisions and, more importantly, affects patient and caregiver outcomes.

Biomarker Testing for AD in Adults With CATD

Future research about the accuracy of biomarkers for distinguishing AD from non-AD dementias in patients with CATD should compare brain imaging, CSF and blood biomarker accuracy with autopsy-confirmed AD. Among participants with collected biomarkers, studies should compare characteristics between participants with and without available autopsy data. This may help to better identify potential selection or attrition biases in studies using autopsy as a reference standard. Research should examine how biomarker accuracy varies as a function of the duration between biomarker collection and autopsy. Doing so would improve understanding about the strengths and limitations of using biomarkers as surrogates for brain autopsy. Studies should evaluate how accuracy of biomarkers for AD and non-AD dementias vary as a function of which neuropathological criteria are used. Future studies should evaluate the accuracy of biomarkers for which we identified no eligible studies (e.g., MRI hippocampal atrophy, CT MTA, tau PET, and fMRI for brain imaging; Aß42/Aß40 ratio and neurofilament light protein for CSF; and blood biomarkers). Studies should report information about participant clinical diagnosis. Such information would make it possible to directly examine how often clinical diagnoses are correctly and incorrectly reclassified based on biomarker testing. Studies should standardize imaging and assay analytic methods and rating criteria that are feasible to implement in typical clinical settings. Studies should externally validate cut points for optimally distinguishing AD from non-AD dementias across populations, including in typical clinical populations. Studies should compare different individual and combined brain imaging and CSF tests in the same population, and evaluate whether test accuracy varies by participant characteristics (e.g., age, sex, race/ethnicity, education). Studies should systematically collect data on potential psychological and physical harms of biomarker testing. Lastly, directly or through modeling, controlled studies should evaluate whether biomarker testing affects drug and nondrug treatment decisions and alters clinically important patient and caregiver outcomes.

Drug Treatment for CATD

Future trials investigating drug treatment for CATD should be large enough to detect the likelihood of response to treatment as defined for clinically important cognitive, functional, and global outcome measures. Trials should routinely report on patient quality of life and caregiver outcomes and investigate all treatment efficacy and harms outcomes beyond 6 months to increase applicability to clinic populations who may be treated for years. Trials should enroll more diverse participants, including nonwhites, and should pre-specify analyses with sufficient statistical power to examine whether treatment effects are modified by patient characteristics, including age, sex, race/ethnicity, baseline CATD severity, baseline BPSD severity, and living setting. Trials should evaluate certain treatments (including at various doses approved by the Food and Drug Administration [FDA]) for which some data suggest the possibility of clinically meaningful benefits, but for which the strength of evidence is insufficient or low at best, such as antipsychotics and antidepressants for agitation and psychosis. Antipsychotics and antidepressants should be directly compared for treatment of BPSD. Future BPSD trials also should directly compare drug and nondrug treatment strategies, and drug trials should specify whether participants receive a concomitant psychosocial intervention. Future BPSD drug trials should be longer in order to better establish the evidence for long-term efficacy and safety.

Supplements should be subjected to rigorous trial examination, both for efficacy and safety compared with placebo, and for comparative effectiveness and safety compared with and as an adjunct to FDA approved prescription drugs. Future drug trials for BPSD, which likely will continue to target agitation, aggression, and psychosis, should also prespecify disinhibited sexual behavior, depression, and anxiety as secondary efficacy outcomes.

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Abbreviations

7MS	7 Minute Screen
AAFP	American Academy of Family Physicians
Aß	beta amyloid
ADCS-ADL	Alzheimer Disease Cooperative Study–Activities of Daily Living
ACP	American College of Physicians
AD	Alzheimer's dementia
ADAS-Cog	Alzheimer's Disease Assessment Scale-Cognition
ADAS-CogA	ADAS-Cog with additional attention item
ADCS-CGIC	Alzheimer's Disease Cooperative Study—Clinical Global Impression of Change
ADL	activities of daily living
AE	adverse events
AHRQ	Agency for Healthcare Research & Quality
ALS	amyotrophic lateral sclerosis
AMSTAR	A Measurement Tool to Assess Systematic Reviews
APOE	apolipoprotein E
APP	amyloid precursor protein
ARD	absolute risk difference
AUC	area under the curve
BADLS	Bristol Activities of Daily Living Scale
BCRS	Brief Cognitive Rating Scale
BEHAVE-AD	Behavioral Pathology in Alzheimer's Disease Rating Scale
BNT	Boston Naming Test
BPRS	Brief Psychiatric Rating Scale
BPSD	behavioral and psychological symptoms of dementia
BrADL	Bristol Activities of Daily Living scale
BSSD	Behavioral Syndromes Scale for Dementia
BVRT	Benton Visual Retention Test
CANTAB	Cambridge Neuropsychological Test Automated Battery
CASI	Cognitive Abilities Screening Instrument
CATD	clinical Alzheimer's-type dementia
CBB	Cogstate Brief Battery
CCT	controlled clinical trial
CDR	Clinical Dementia Rating
CDR-SOB	Clinical Dementia Rating-Sum of Boxes
CDT	Clock Drawing Test
CENTRAL	Cochrane Central Register of Controlled Trials

CER	Comparative Effectiveness Review
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CGI-2	Clinical Global Impression item 2
CGIC	Clinical Global Impression of Improvement
CI	confidence intervals
CIBIC	Clinician's Interview-Based Impression of Change
CIBIC-Plus	Clinician's Interview-Based Impression of Change-Plus Caregiver Input
CJD	Creutzfeld-Jakob disease
CMAI	Cohen-Mansfield Agitation Inventory
CMBT	Computerized Memory Battery Test
COWAT	Controlled Oral Word Association Test
CPT	Continuous Performance Test
CSF	cerebrospinal fluid
CSDD	Cornell scale for depression in dementia
CT	computed tomography
CVD	cardiovascular disease
CVLT	California Verbal Learning Test
DAD	Disability Assessment for Dementia
DEMQOL	Dementia Quality of Life
DEMQOL-proxy	Caregiver reported DEMQOL
DKEFS	Delis-Kaplan Executive Function System
DLB	dementia with Lewy bodies
DRS	Dementia Rating Scale
DTI	diffusion tensor imaging
DSM	Diagnostic and Statistical Manual of Mental Disorders
DWR	DemTect[81] Delayed Word Recall Test
ELISA	enzyme-linked immunosorbent assay
EPC	Evidence-based Practice Center
EQ5D	EuroQOL 5D
FAST	Functional Assessment Staging Tool
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
fMRI	functional magnetic resonance imaging
FN	false negative
FOME	Fuld Object Memory Evaluation
FP	false positive
FTD	frontotemporal dementia
FTLD	frontotemporal lobar degeneration

GDS	global deterioration scale
GHQ-12	general health questionnaire
GPGT	Graphic Pattern Generation Test
HIS	Hachinski Ischemic Scale
HVLT	Hopkins Verbal Learning Test
IADL	instrumental activities of daily living
ICD	International Classification of Disease
ISLT	CogState International Shopping List Test
KI	Key Informant
KQ	Key Question
LBD	Lewy body disease
LM	Logical Memory
LOCF	last observation carried forward
MCAS	Minnesota Cognitive Acuity Screen
MCI	mild cognitive impairment
MD	mean difference
MDS-ADL	Minimum Data Set Activities of Daily Living
MENFIS	Mental Function Impairment Scale
MIS	Memory Impairment Screen
MMRM	mixed methods repeated measures
MMSE	Mini-Mental State Exam
MoCA	Montreal Cognitive Assessment
MRI	magnetic resonance imaging
MTA	medial temporal lobe atrophy
NA	not applicable
NAB	Neuropsychological Assessment Battery
NBRS	Neurobehavioral Rating Scale
NBRS-A	Neurobehavioral Rating Scale agitation subscale
NDRI	norepinephrine-dopamine reuptake inhibitor
NfL	neurofilament light protein
NIA	National Institute on Aging
NIA-AA	National Institute on Aging-Alzheimer's Association
NIA-AA ABC	National Institute on Aging-Alzheimer's Association (Amyloid, Braak, CERAD)
NIA-Reagan	National Institute on Aging and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association

NMDA	N-methyl-D-aspartate
NPH	normal pressure hydrocephalus
NPI	Neuropsychiatric Inventory
NPI-A	Neuropsychiatric Inventory-agitation subscale
NPI-NH	Neuropsychiatric Inventory-Nursing Home Version
NPI-Q	Neuropsychiatric Inventory Brief Questionnaire Form
NR	not reported
OR	odds ratio
OTC	over-the-counter
PD	Parkinson's disease
PDS	Progressive Deterioration Scale
PET	positron emission tomography
PICOTS	Populations, interventions, comparators, outcomes, timing, and settings
PLPH	post-lumbar puncture headaches
PO	oral
PSP	progressive supranuclear palsy
p-tau	abnormally phosphorylated tau
QOL	quality of life
QUADAS	Quality Assessment tool for Diagnostic Accuracy Studies
RAVLT	Rey Auditory Verbal Learning Test
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RCFT	Rey-Oosterrieth Complex Figure Test
RCT	randomized clinical trial
ROB	risk of bias
ROC	receiver operating characteristic
RR	risk ratio
SADS	Schedule for Affective Disorders and Schizophrenia
SAE	serious adverse event
SCA	spinocerebellar ataxia
SCIRS	Severe Cognitive Impairment Rating Scale
SD	standard deviation
SEADs	Supplemental Evidence and Data for Systematic Reviews
SF-12	mental quality of life
SIB	Severe Impairment Battery
SLUMS	St. Louis University Mental Status
SKT	Syndrom Kurz Test
SMD	standardized mean difference
SNRI	serotonin-norepinephrine reuptake inhibitor

SOE	strength of evidence
SPECT	single-photon emission computed tomography
SR	systematic review
SSRI	selective serotonin reuptake inhibitor
STMS	Short Test of Mental Status
TCA	tricyclic antidepressant
TDP-43	TAR DNA-binding protein 43
TeCA	tetracyclic antidepressant
TEP	Technical Expert Panel
TICS	Telephone Interview for Cognitive Status
TMT	Trail Making Test
TN	true negative
TOO	Task Order Officer
TOVA	Tests of Variables of Attention
TP	true positive
TR	topic refinement
t-tau	total tau
VaD	vascular dementia
VR	Visual Reproduction
WAIS	Wechsler Adult Intelligence Scale
WCST	Wisconsin Card Sorting Test
WMD	weighted mean difference
WMS	Wechsler Memory Scales
ZBI	Zarit Burden Interview

Appendix Table of Contents

Appendix A. Search Strategy

Electronic Literature Search Strategies for Key Question 1: Cognitive Tests for Diagnosing Clinical CATD

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)
Search Strategy:

---

1 *Alzheimer Disease/
2 alzheimer*.ti.
3 mild cognitive impairment.ti.
4 MCI.ti.
5 or/1-4
6 exp Neuropsychological Tests/
7 screen*.ti.
8 test*.ti.
9 detect*.ti.
10 battery.ti.
11 assess*.ti.
12 validat*.ti.
13 tool*.ti.
14 instrument*.ti.
15 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16 5 and 15
17 15 and 16
18 limit 17 to "diagnosis (best balance of sensitivity and specificity)"
19 limit 18 to english language
20 limit 19 to (addresses or autobiography or bibliography or biography or case reports or clinical conference or comment or congresses or dataset or dictionary or directory or editorial or "expression of concern" or festschrift or interactive tutorial or interview or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or video-audio media or webcasts)
21 19 not 20

Database: Embase Classic+Embase
Search Strategy:

---

1 alzheimer*.ti.
2 mild cognitive impairment.ti.
3 MCI.ti.
4 or/1-3
5 exp Neuropsychological Tests/
6 screen*.ti.

7 test*.ti.
8 detect*.ti.
9 battery.ti.
10 assess*.ti.
11 validat*.ti.
12 tool*.ti.
13 instrument*.ti.
14 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15 4 and 14
16 limit 15 to "diagnosis (best balance of sensitivity and specificity)"
17 limit 16 to english language
18 limit 17 to conference abstracts
19 17 not 18
20 limit 19 to (book or book series or trade journal)
21 19 not 20
22 limit 21 to (books or "book review" or chapter or conference abstract or "conference review" or editorial or letter or note or patent or short survey or tombstone)
23 21 not 22
24 limit 23 to (embryo <first trimester> or infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)
25 23 not 24

Database: PsycINFO
Search Strategy:
---
1 alzheimer*.ti.
2 mild cognitive impairment.ti.
3 MCI.ti.
4 or/1-3
5 screen*.ti.
6 test*.ti.
7 detect*.ti.
8 battery.ti.
9 assess*.ti.
10 validat*.ti.
11 tool*.ti.
12 instrument*.ti.
13 exp neuropsychological assessment/
14 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15 4 and 14
16 diagnos*.ti.
17 sensitivity.ti,ab.
18 specificity.ti,ab.
19 exp diagnosis/
20 16 or 17 or 18 or 19
21 15 and 20

22 limit 21 to english language
23 limit 22 to (abstract collection or bibliography or chapter or "column/opinion" or "comment/reply" or dissertation or editorial or encyclopedia entry or interview or letter or obituary or poetry or publication information or review-book or review-media or review-software & other or reviews)
24 22 not 23
25 limit 24 to (100 childhood <birth to age 12 yrs> or 120 neonatal <birth to age 1 mo> or 140 infancy <2 to 23 mo> or 160 preschool age <age 2 to 5 yrs> or 180 school age <age 6 to 12 yrs> or 200 adolescence <age 13 to 17 yrs>)
26 24 not 25

Electronic Literature Search Strategies for Key Question 2: Biomarker Tests for Diagnosing Pathologically Confirmed CATD

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R)
Search Strategy:
---
1 Alzheimer Disease/
2 alzheimer*.ti,ab.
3 Dementia/
4 Cognition Disorders/
5 Cognitive Dysfunction/
6 MCI.ti,ab.
7 mild cognitive impairment.ti,ab.
8 or/1-7
9 BIOMARKERS/
10 Neuroimaging/
11 exp Hematologic Tests/
12 Cerebrospinal Fluid/
13 exp Magnetic Resonance Imaging/
14 exp Positron-Emission Tomography/
15 exp Tomography, Emission-Computed, Single-Photon/
16 CT.ti,ab.
17 computed tomography.ti,ab.
18 PET.ti,ab.
19 positron emission.ti,ab.
20 imag*.ti,ab.
21 neuroima*.ti,ab.
22 single photon.ti,ab.
23 SPECT.ti,ab.
24 magnetic resonance.ti,ab.
25 MRI.ti,ab.

26 (blood or plasma or serum).ti,ab.
27 or/9-26
28 Alzheimer Disease/dg [Diagnostic Imaging]
29 exp Alzheimer Disease/di [Diagnosis]
30 exp Cognitive Dysfunction/di [Diagnostic Imaging]
31 exp Cognitive Dysfunction/di [Diagnosis]
32 Cognition Disorders/dg [Diagnostic Imaging]
33 exp Cognition Disorders/di [Diagnosis]
34 or/28-33
35 8 and 27
36 34 or 35
37 exp AUTOPSY/
38 autops*.ti,ab.
39 neuropath*.ti,ab.
40 histopath*.ti,ab.
41 postmortem.ti,ab.
42 Braak.ti,ab.
43 37 or 38 or 39 or 40 or 41 or 42
44 36 and 43
45 limit 44 to "diagnosis (best balance of sensitivity and specificity)"
46 limit 45 to english language
47 limit 46 to (addresses or autobiography or bibliography or biography or case reports or dataset or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or video-audio media or webcasts)
48 46 not 47
49 limit 48 to yr="2012 -Current"
50 11 or 26
51 48 and 50
52 49 or 51
****

Database: Embase Classic+Embase
Search Strategy:
---
1 Alzheimer Disease/
2 alzheimer*.ti,ab.
3 Dementia/
4 Cognition Disorders/
5 Cognitive Dysfunction/
6 MCI.ti,ab.
7 mild cognitive impairment.ti,ab.
8 or/1-7
9 BIOMARKERS/
10 Neuroimaging/
11 exp Hematologic Tests/

12 Cerebrospinal Fluid/
13 exp Magnetic Resonance Imaging/
14 exp Positron-Emission Tomography/
15 exp Tomography, Emission-Computed, Single-Photon/
16 CT.ti,ab.
17 computed tomography.ti,ab.
18 PET.ti,ab.
19 positron emission.ti,ab.
20 imag*.ti,ab.
21 neuroima*.ti,ab.
22 single photon.ti,ab.
23 SPECT.ti,ab.
24 magnetic resonance.ti,ab.
25 MRI.ti,ab.
26 (blood or plasma or serum).ti,ab.
27 or/9-26
28 [Alzheimer Disease/dg [Diagnostic Imaging]]
29 exp Alzheimer Disease/di [Diagnosis]
30 exp Cognitive Dysfunction/di [Diagnostic Imaging]
31 exp Cognitive Dysfunction/di [Diagnosis]
32 [Cognition Disorders/dg [Diagnostic Imaging]]
33 exp Cognition Disorders/di [Diagnosis]
34 or/28-33
35 8 and 27
36 34 or 35
37 exp AUTOPSY/
38 autops*.ti,ab.
39 neuropath*.ti,ab.
40 histopath*.ti,ab.
41 postmortem.ti,ab.
42 Braak.ti,ab.
43 37 or 38 or 39 or 40 or 41 or 42
44 36 and 43
45 limit 44 to "diagnosis (best balance of sensitivity and specificity)"
46 limit 45 to english language
47 limit 46 to (addresses or autobiography or bibliography or biography or case reports or dataset or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or video-audio media or webcasts) [Limit not valid in Embase; records were retained]
48 46 not 47
49 limit 48 to yr="2012 -Current"
50 11 or 26
51 48 and 50
52 49 or 51

Electronic Literature Search Strategies for Key Questions 3-8: CATD Treatment

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)
Search Strategy:
---
1 exp Alzheimer Disease/
2 Dementia/
3 (dementia or alzheimer*).ti.
4 1 or 2 or 3
5 limit 4 to "therapy (best balance of sensitivity and specificity)"
6 limit 5 to english language
7 limit 6 to (addresses or autobiography or bibliography or biography or case reports or clinical conference or comment or comparative study or congresses or consensus development conference or consensus development conference, nih or dataset or dictionary or directory or editorial or evaluation studies or "expression of concern" or festschrift or government publications or guideline or historical article or interactive tutorial or interview or lectures or legal cases or legislation or letter or news or newspaper article or observational study or patient education handout or periodical index or personal narratives or portraits or "review" or "scientific integrity review" or validation studies or video-audio media or webcasts)
8 limit 7 to (adaptive clinical trial or clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or controlled clinical trial or randomized controlled trial)
9 6 not 7
10 8 or 9
11 limit 10 to ("all child (0 to 18 years)" or "adult (19 to 44 years)")
12 limit 11 to ("middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)")
13 10 not 11
14 12 or 13

Database: Embase Classic+Embase
Search Strategy:
---
1 exp *Alzheimer disease/
2 *dementia/
3 (alzheimer* or dementia*).ti.
4 1 or 2 or 3
5 limit 4 to english language
6 limit 5 to "therapy (best balance of sensitivity and specificity)"
7 limit 6 to "reviews (best balance of sensitivity and specificity)"
8 6 not 7
9 limit 8 to (embryo <first trimester> or infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)

10 limit 9 to (adult <18 to 64 years> or aged <65+ years>)
11 8 not 9
12 10 or 11
13 limit 12 to (book or book series or conference proceeding or trade journal)
14 12 not 13
15 limit 14 to conference abstracts
16 14 not 15
17 limit 16 to (abstract report or books or "book review" or chapter or conference abstract or "conference review" or editorial or letter or note or patent or reports or "review" or short survey or tombstone)
18 16 not 17
19 limit 18 to (amphibia or ape or bird or cat or cattle or chicken or dog or "ducks and geese" or fish or "frogs and toads" or goat or guinea pig or "hamsters and gerbils" or horse or monkey or mouse or "pigeons and doves" or "rabbits and hares" or rat or reptile or sheep or swine) (355)
20 18 not 19

Database: PsycINFO
Search Strategy:
---
1 exp *ALZHEIMER'S DISEASE/
2 *dementia/
3 (dementia* or alzheimer*).ti.
4 1 or 2 or 3
5 limit 4 to "therapy (best balance of sensitivity and specificity)"
6 limit 5 to (childhood <birth to 12 years> or adolescence <13 to 17 years>)
7 limit 6 to adulthood <18+ years>
8 5 not 6
9 7 or 8
10 limit 9 to animal
11 9 not 10
12 limit 11 to (100 childhood <birth to age 12 yrs> or 120 neonatal <birth to age 1 mo> or 140 infancy <2 to 23 mo> or 160 preschool age <age 2 to 5 yrs> or 180 school age <age 6 to 12 yrs> or 200 adolescence <age 13 to 17 yrs> or 320 young adulthood <age 18 to 29 yrs> or 340 thirties <age 30 to 39 yrs>)
13 limit 12 to (360 middle age <age 40 to 64 yrs> or "380 aged <age 65 yrs and older>" or "390 very old <age 85 yrs and older>")
14 11 not 12
15 13 or 14
16 limit 15 to (abstract collection or bibliography or chapter or clarification or "column/opinion" or "comment/reply" or dissertation or editorial or encyclopedia entry or interview or letter or obituary or poetry or publication information or review-book or review-media or review-software & other or reviews)
17 15 not 16
18 limit 17 to ("0200 book" or "0240 authored book" or "0280 edited book" or "0300 encyclopedia" or "0400 dissertation abstract")
19 17 not 18

20 limit 19 to english language
21 limit 20 to "therapy (maximizes specificity)"

Appendix B. Risk of Bias Assessment Decision Aid

Selection Bias

Definition

Systematic differences between baseline characteristics of the groups that arise from self-selection of treatments, physician-directed selection of treatments, or association of treatment assignments with demographic, clinical, or social characteristics. Good randomization produces study groups that are likely comparable for known and unknown risk factors, removes investigator bias in allocation, and allow the most valid statistical inference in comparing outcomes between groups. In randomized studies, whether there is bias in allocation of study participants to treatment groups is a function both of whether the methods of randomization are good AND whether randomization successfully achieved a balance between treatment groups in risk factors or prognostic covariates.

Assessment Guidance

OPTION 1: The study reports that it was randomized.

Clear Methodology: The study used a randomization method such as random numbers table, computer-generated random number producing algorithm, blocked randomization, stratified randomization, adaptive randomization (e.g., minimization).

Unclear Methodology: Study reports that allocation/assignment was randomized but gives no further detail.

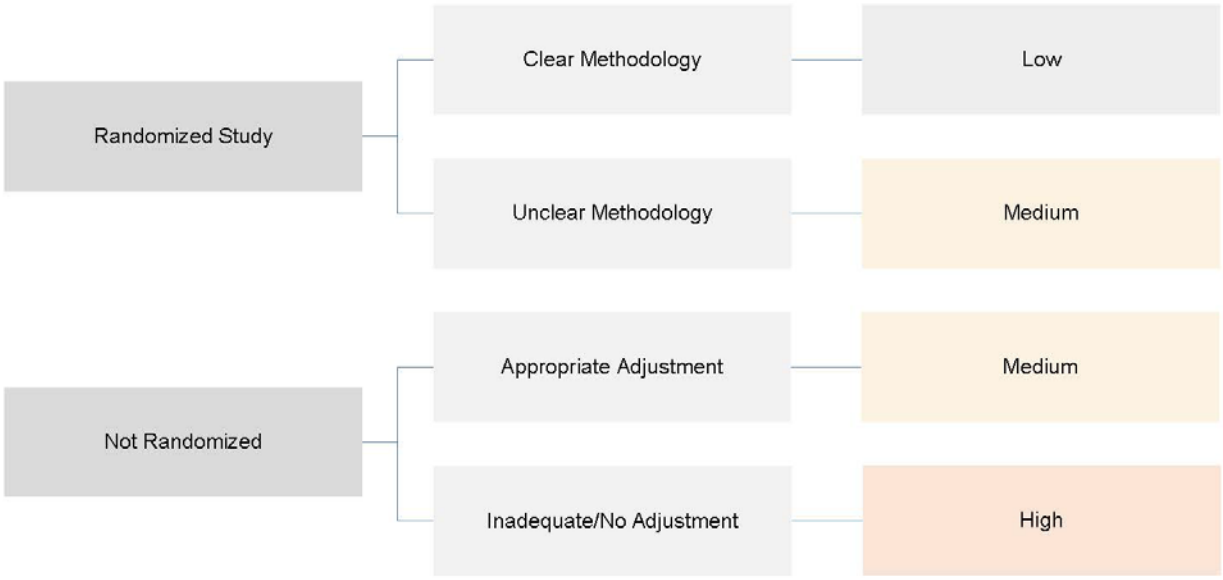
OPTION 2: Study is not randomized (for treatment efficacy outcomes, CCTs are the only eligible nonrandomized study design).

Study uses systematic allocation of treatment by investigator: Systematic and predictable investigator allocation of treatment assignment (e.g., alternation, based on day of week, based on the month of birthday).

Study should use an appropriate statistical adjustment (propensity score, instrumental variable, multivariate).

Figure B.1 shows decision options for selection bias.

Figure B.1. Selection bias assessment guidance



Attrition

Definition

Loss of participants from the study, potential systematic differences in that loss to follow-up, and how losses were accounted for in the results (e.g., incomplete follow-up, differential attrition). Those who drop out of the study or who are lost to follow-up may be systematically different from those who remain in the study. Attrition bias can potentially change the collective (group) characteristics of the relevant groups and their observed outcomes in ways that affect study results by confounding and spurious associations. **Overall attrition** refers to attrition in all groups combined for a given outcome comparison and timepoint. **Differential attrition** refers to the absolute difference between groups in attrition for a given outcome comparison and timepoint.

Assessment Guidance

*Studies that have long-term outcomes that are 5 years and longer should be assessed on a case-by-case basis.

OPTION 1: Study has low overall attrition (<10%). Reasons for incomplete/missing data should be adequately explained.

OPTION 2: Study has moderate overall attrition (10 to 20%). Reasons for incomplete/missing data should be adequately explained and authors should attempt to address attrition in their analysis. Analysis should be done with appropriate method, noting that this may help explain the size and direction of the potential bias, but they don't eliminate the bias. Last valued carried forward is not an appropriate adjustment. Some imputation methods might be appropriate (to be evaluated on a case-by-case basis).

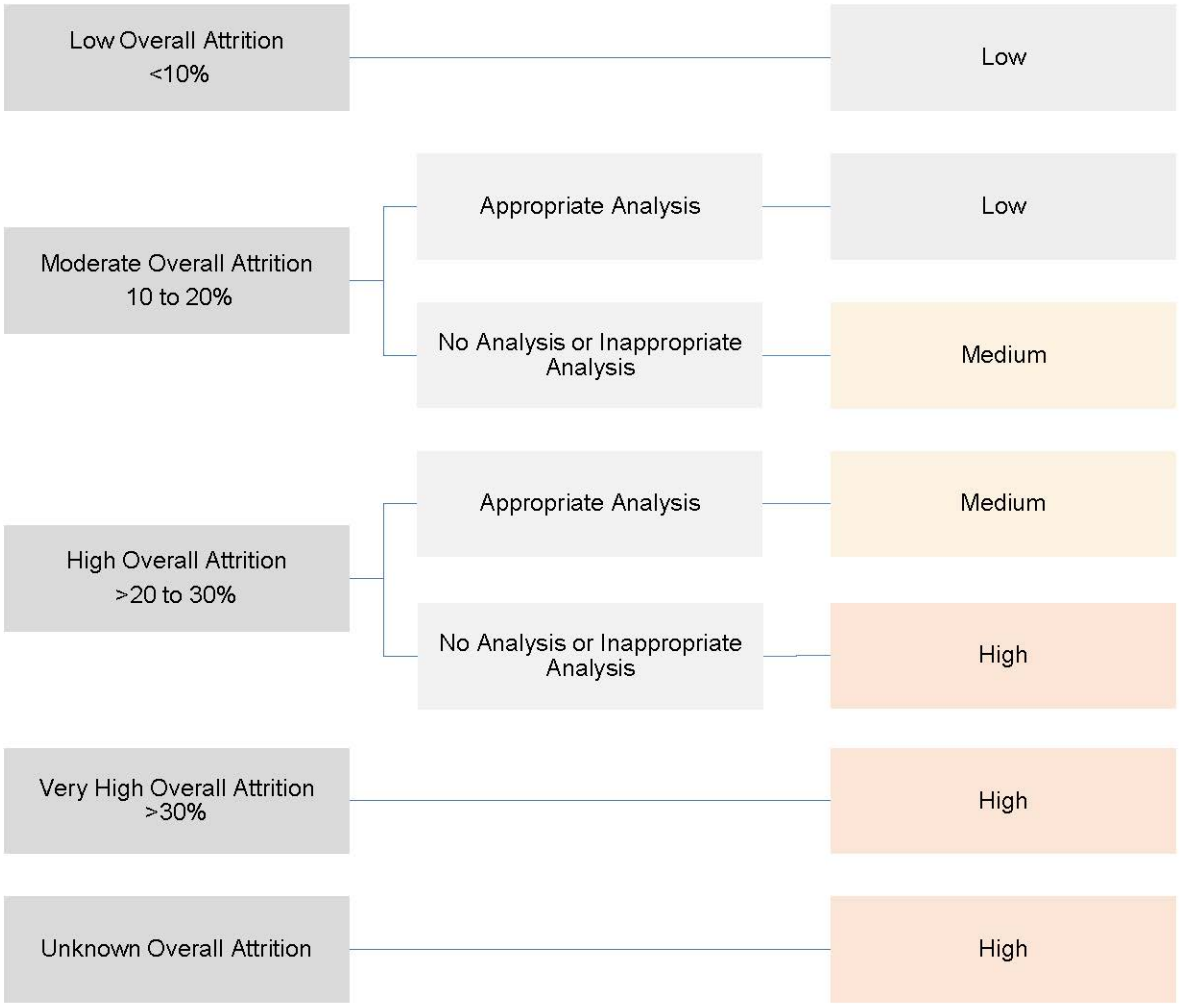
OPTION 3: Study has high overall attrition (>20 to 30%) Reasons for incomplete/missing data should be adequately explained and authors should to address attrition in their analysis with an appropriate method. This reduces, but does not eliminate, the risk of attrition bias. Last valued carried forward is not an appropriate adjustment. Some imputation methods might be appropriate (to be evaluated on a case-by-case basis).

OPTION 4: Study has very high overall attrition (>30%) Authors may attempt to address attrition in their analysis, but the risk of attrition bias is high.

OPTION 5: Reporting of attrition by study arm is inadequate. It is unclear how many participants have been lost in each group. Risk of attrition bias is high.

Figure B.2 shows decision options for attrition bias.

Figure B.2. Attrition assessment guidance



Performance Bias

Definition

Systematic differences in the care provided to participants and protocol deviation. Examples include contamination of the control group with the exposure or intervention, unbalanced provision of additional interventions or co-interventions, difference in co-interventions, and inadequate blinding of providers and participants. **Intention-to-Treat Principle (ITT) is** when the study counts events in all randomized participants according to their treatment assignment, regardless of whether they received assigned treatment. It does not exclude participants from analysis for nonadherence, protocol deviations, withdrawal, or anything else that happens after randomization. To exclude such participants undercuts the benefit of randomization in minimizing selection bias. **Modified ITT (mITT)** is where analyses exclude randomized participants who did not receive any of their assigned treatment. This is not strictly ITT, but is accepted as such by the FDA in evaluating drug trials for approval.

Assessment Guidance

Guidelines for assessing performance bias are detailed in Appendix Tables B.1 and B.2.

Appendix Table B.1. Assessment guidance for performance bias

Domain	Assessment	Options
1. ITT/Adjustment of Known Confounders	**OPTION 1A:** Study is an RCT. Check if study uses ITT or modified ITT.	-Yes -No -Unclear/Not Reported
	OPTION 1B: Study is a CCT. Check for adjustment of known confounders. **Adequate adjustment** includes adjustment for at least age, sex, and baseline cognition. **Partially adequate adjustment** adjusts for 1 or 2 of these potential confounder categories. **Inadequate adjustment** does not adjust for any of these potential confounder categories.	-Adequate -Partially Adequate -Inadequate
2. Participant Blinding	For all studies, check to see if participant blinding is described in text.	Yes
		No
		Unclear

Appendix Table B.2. Overall performance rating for performance bias assessment

Overall Performance Rating	**Low** = ITT or adequate adjustment of confounders. Participants are blinded.	**Medium** = Unclear ITT or partially adequate adjustment of confounders. Participant blinding is unclear or not described.	**High** = No ITT or inadequate adjustment of known confounders.

Detection Bias

Definition

Systematic differences in outcomes assessment among groups being compared, including systematic misclassification of the exposure or intervention, covariates, or outcomes because of variable definitions and timings, diagnostic thresholds, recall from memory, inadequate assessor blinding, and faulty measurement techniques. Erroneous statistical analysis might also affect the validity of effect estimates.

Assessment Guidance

Guidelines for assessing detection bias are detailed in Appendix Tables B.3 and B.4.

Appendix Table B.3. Assessment guidance for detection bias

Assessment	Options
1. Check if outcome assessors were blinded to treatment assignment.	-Yes -No -Unclear

Assessment	Options
2. Check if studies used validated, reliable, outcomes measure and that the groups assessed using comparable outcome measures. **Please flag the test for the team if you are unsure if a test is validated or think that the measure is based on unconfirmed self-report.**	-Yes -No -Unclear

Appendix Table B.4. Overall performance rating for detection bias assessment

Overall Performance Rating	**Low** = 2 Yes OR 1 Yes, 1 Unclear	**Medium** = All unclear	**High** = At least 1 No

Reporting Bias

Definition

Systematic differences between reported and unreported findings (e.g., differential reporting of outcomes or harms, incomplete reporting of study findings). Reporting bias includes selective analysis (e.g., study combines intervention groups or adjusts planned analysis without explanation).

Assessment Guidance

- Check if all outcomes reported in the methods section reported in the result section and vice versa (Appendix Table B.5).
- If study indicates that additional information is available in a separate protocol, protocol papers should be checked to ensure no relevant information is missed.

Appendix Table B.5. Assessment guidance for reporting bias

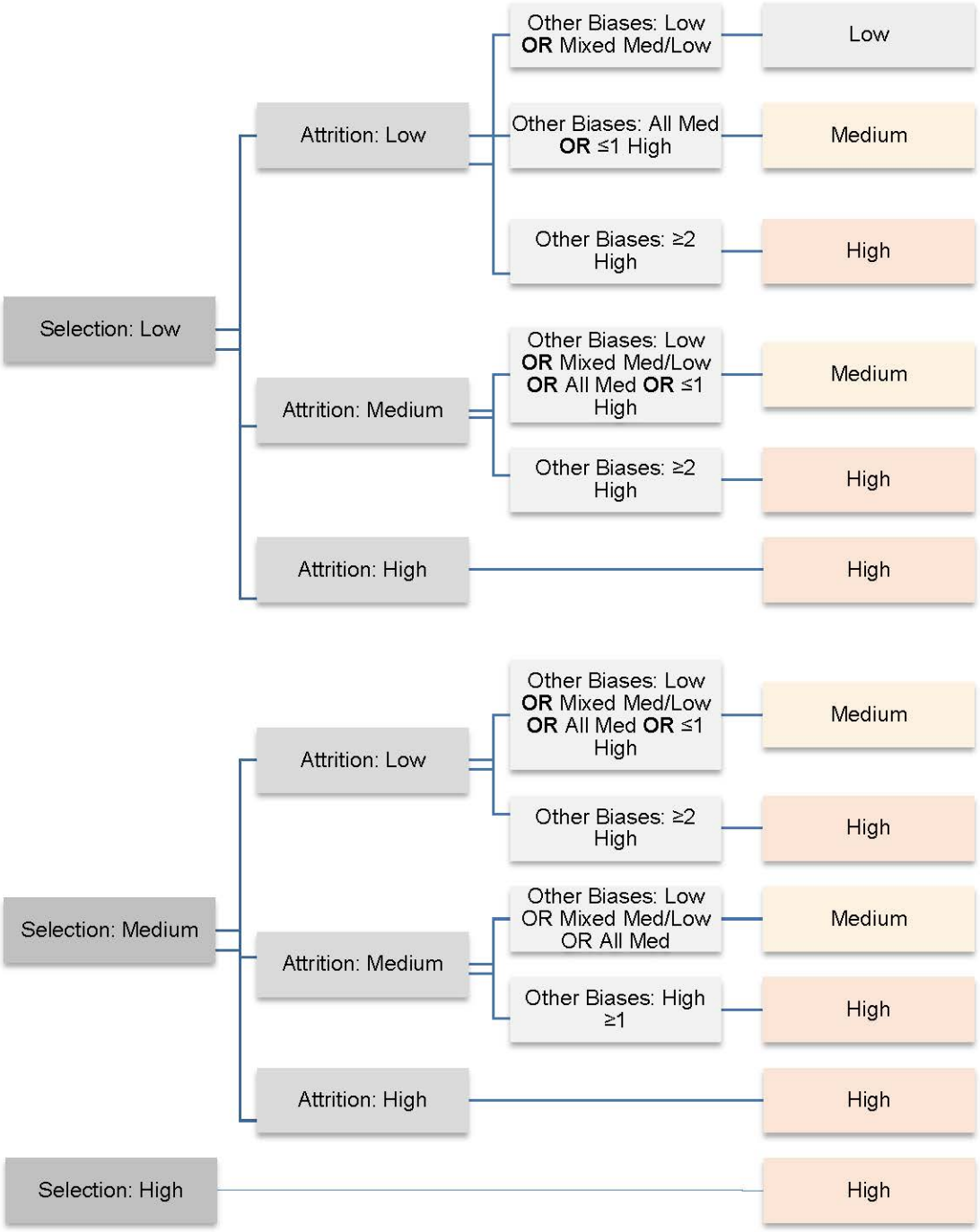
Assessment	Options	Rating
Check if all outcomes are reported without selective analysis?	Yes	Low
	No	High
	Unclear	Medium

Overall Risk of Bias Assessment

Assessment Guidance

Overall risk of bias is determined by reviewer, or team, consensus. Figure B.3 provides a guide for how to rate overall risk of bias, based on the assessment of each individual domain. Reviewers should use this guide when making judgements about overall risk of bias. However, there may be cases where deviation from this guide is necessary and appropriate. For clarification and transparency, reviewers should provide a brief written justification for these deviations.

Figure B.3. Overall risk of bias assessment guidance



Appendix C. Key Question 1: Accuracy, Comparative Accuracy, and Harms of Cognitive Tests for Identifying CATD

Appendix Table C.1. QUADAS-2 Risk of bias assessment for studies of classification accuracy of brief cognitive tests

Study	Risk of Bias: Patient Selection *(0=low, 1=high or unclear)*	Risk of Bias: Index Test *(0=low, 1=high or unclear)*	Risk of Bias: Reference Standard *(0=low, 1=high or unclear)*	Risk of Bias: Flow and Timing *(0=low, 1=high or unclear)*	Applicability Concerns: Patient Selection *(0=low, 1=high or unclear)*	Applicability Concerns: Index Test *(0=low, 1=high or unclear)*	Applicability Concerns: Reference Standard *(0=low, 1=high or unclear)*	Total Score	ROB Rating
Ashendorf 2008[1]	0	1	1	1	0	0	0	3	Medium
Bondi 1993[2]	1	1	1	0	0	0	0	3	Medium
Brodaty 1997[5]	1	1	1	0	0	0	0	3	Medium
Brown 2009[6]	1	0	0	1	0	0	0	2	Medium
Buschke 1999[7]	0	0	1	0	0	0	0	1	Low
Cahn 1997[8]	0	1	0	0	0	0	0	1	Low
Cahn 1995[9]	0	1	0	1	0	0	0	2	Medium
Cahn 1996[10]	0	1	0	1	0	0	0	2	Medium
Canning 2004[11]	1	1	0	0	0	0	0	2	Medium
Cerhan 2002[12]	1	1	0	1	0	0	0	3	Medium
Chandler 2005[13]	1	1	1	0	0	0	0	3	Medium
Chapman 2010[14]	1	1	1	0	0	0	0	3	Medium
Clark 2010[15]	1	0	1	0	0	0	0	2	Medium
Clark 2014[16]	1	1	1	0	0	0	0	3	Medium
Coen 1996[17]	1	1	1	1	0	0	0	4	High
Connor 2005[18]	1	1	1	0	0	0	0	3	Medium
De Jager 2003[19]	0	1	0	1	0	0	0	2	Medium
Elamin 2016[20]	0	1	1	0	0	0	0	2	Medium
Esteban-Santillas 1998[21]	1	1	0	1	0	0	0	3	Medium
Ewers 2012[22]	1	1	1	1	0	0	0	4	High
Galasko 1990[23]	0	1	1	0	0	0	0	2	Medium
Gavett 2009[24]	0	1	0	1	0	0	0	2	Medium
Gomez 2006[25]	1	1	0	0	0	0	0	2	Medium

Study	Risk of Bias: Patient Selection *(0=low, 1=high or unclear)*	Risk of Bias: Index Test *(0=low, 1=high or unclear)*	Risk of Bias: Reference Standard *(0=low, 1=high or unclear)*	Risk of Bias: Flow and Timing *(0=low, 1=high or unclear)*	Applicability Concerns: Patient Selection *(0=low, 1=high or unclear)*	Applicability Concerns: Index Test *(0=low, 1=high or unclear)*	Applicability Concerns: Reference Standard *(0=low, 1=high or unclear)*	Total Score	ROB Rating
Grober 2008[26]	1	0	0	0	0	0	0	1	Low
Grober 2008[27]	1	0	0	0	0	0	0	1	Low
Hackett 2018[28]	1	1	1	1	0	1	0	5	High
Hollocks 2018[29]	0	1	1	0	0	0	0	2	Medium
Johnson 2003[30]	1	1	0	0	0	0	0	2	Medium
Kalbe 2004[31]	1	1	1	0	0	0	0	3	Medium
Knopman 1989[32]	1	1	0	0	0	0	0	2	Medium
Kuslansky 2002[33]	1	1	0	0	0	0	0	2	Medium
Kuslansky 2004[34]	1	1	0	0	0	0	0	2	Medium
Lange 2006[35]	1	0	1	0	0	0	0	2	Medium
Lee 1996[36]	1	0	0	0	0	0	0	1	Low
Logsdon 1989[37]	1	0	0	0	0	0	0	1	Low
Loewenstein 2001[38]	1	1	1	0	0	0	0	3	Medium
Mahoney 2005[39]	1	1	0	1	1	0	0	4	High
Maruff 2013[40]	1	1	0	1	0	0	0	3	Medium
Mathuranath 2000[41]	1	1	0	1	0	1	0	4	High
Mendez 1992[42]	1	1	1	0	0	0	0	3	Medium
Mendiondo 2003[43])	1	1	1	0	0	0	0	3	Medium
Millar 2017[44]	1	1	1	0	0	0	0	3	Medium
Monsch 1992[45]	1	1	0	0	0	0	0	2	Medium
Monsch 1995[46]	1	1	0	0	0	0	0	2	Medium
Montgomery 2017[47]	1	1	1	1	0	0	0	4	High
Morgan 2010[48]	1	1	0	1	0	0	0	3	Medium
Parsey 2011[49]	0	1	0	0	0	0	0	1	Low
Petersen 1994[50]	1	1	0	0	0	0	0	2	Medium
Quarmley 2017[51]	1	0	0	0	0	1	0	2	Medium
Roalf 2013[52]	1	1	1	1	0	0	0	4	High
Roalf 2017[53]	1	1	1	0	0	0	0	3	Medium

Study	Risk of Bias: Patient Selection *(0=low, 1=high or unclear)*	Risk of Bias: Index Test *(0=low, 1=high or unclear)*	Risk of Bias: Reference Standard *(0=low, 1=high or unclear)*	Risk of Bias: Flow and Timing *(0=low, 1=high or unclear)*	Applicability Concerns: Patient Selection *(0=low, 1=high or unclear)*	Applicability Concerns: Index Test *(0=low, 1=high or unclear)*	Applicability Concerns: Reference Standard *(0=low, 1=high or unclear)*	Total Score	ROB Rating
Salmon 2002[54]	0	1	0	1	0	0	1	3	Medium
Solomon 1998[55]	1	1	0	0	0	0	0	2	Medium
Springate 2014[56]	1	1	1	0	0	0	0	3	Medium
Storandt 1989[57]	1	1	0	0	0	0	0	2	Medium
Sunderaraman 2015[58]	1	1	0	1	0	0	0	3	Medium
Thompson 2011[59]	1	1	0	1	0	0	0	3	Medium
Tremont 2011[60]	1	1	0	0	0	0	0	2	Medium
Troster 199[61]	1	1	0	1	0	0	0	3	Medium
Trzepacz 2015[62]	1	1	1	0	0	0	0	3	Medium
Tuokko 1992[63]	1	1	1	0	0	0	0	3	Medium
Uhlmann 1991[64]	1	1	1	0	0	0	0	3	Medium
Welsh 1991[65]	0	1	0	1	0	0	0	2	Medium
Welsh 1992[66]	0	1	0	1	0	0	0	2	Medium
Wolf-Klein 1989[67]	0	1	0	1	0	0	1	3	Medium
Zainal 2016[68]	1	1	0	0	0	0	0	2	Medium

Appendix Table C.2. Classification accuracy results for brief cognitive tests designed as individual stand-alone tests in eligible studies with low-moderate risk of bias

Test/Test Type	Author Year	CATD N	Comp Group	Comp N	Score (Subgroup)	Cut point	SE	SP	PPV+	NPV+	CATD Base Rate
Brief Alzheimer Screen (BAS)	Mendiondo 2003[43]	171	NC	203	Weighted sum score	22	0.90	0.99	0.99	0.92	0.46
BAS	Mendiondo 2003[43]	171	NC	203	Weighted sum score	23	0.92	0.97	0.96	0.94	0.46
BAS	Mendiondo 2003[43]	503	NC	657	Weighted sum score	26	0.98	0.96	0.95	0.98	0.43
Brief Memory and Executive Test (BMET)	Hollocks 2017[29]	51	NC	51	Total score	13	0.86	1.00	1.00	0.88	0.50

Test/Test Type	Author Year	CATD N	Comp Group	Comp N	Score (Subgroup)	Cut point	SE	SP	PPV+	NPV+	CATD Base Rate
Clock Drawing	Cahn 1996[10]	42	NC	237	Qualitative CDT score	1*	0.81	0.68	0.31	0.95	0.15
Clock Drawing	Cahn 1996[10]	42	NC	237	Global CDT score	6	0.83	0.72	0.34	0.96	0.15
Clock Drawing	Esteban-Santillan 1998[21]	41	NC	39	Mendez CDIS gross	2	0.63	0.71	0.70	0.65	0.51
Clock Drawing	Esteban-Santillan 1998[21]	41	NC	39	Mendez CDIS numbers	10	0.15	0.97	0.84	0.52	0.51
Clock Drawing	Esteban-Santillan 1998[21]	41	NC	39	Mendez CDIS hands	2	0.12	1.00	1.00	0.52	0.51
Clock Drawing	Esteban-Santillan 1998[21]	41	NC	39	Mendez CDIS total	17	0.46	0.79	0.70	0.58	0.51
Clock Drawing	Lee 1996[36]	30	NC	30	Mendez CDIS total	18	0.73	0.77	0.76	0.74	0.50
Clock Drawing	Mendez 1992[42]	46	NC	26	Mendez CDIS total	19*	0.91	1.00	1.00	0.86	0.64
Clock Drawing	Lee 1996[36]	9	NC	30	Mendez CDIS total (very mild CATD)	18	0.44	0.77	0.36	0.82	0.23
Clock Drawing	Lee 1996[36]	17	NC	30	Mendez CDIS total (mild CATD)	18	0.82	0.77	0.67	0.88	0.36
Clock Drawing	Lee 1996[36]	4	NC	30	Mendez CDIS total (moderate CATD)	18	1.00	0.77	0.37	1.00	0.12
Clock Drawing	Cahn 1995[9]	45	NC	238	Rouleau copy	7	0.57	0.87	0.45	0.91	0.16
Clock Drawing	Esteban-Santillan 1998[21]	41	NC	39	Rouleau face	1	0.81	0.21	0.52	0.51	0.51
Clock Drawing	Esteban-Santillan 1998[21]	41	NC	39	Rouleau numbers	3	0.44	0.76	0.66	0.56	0.51
Clock Drawing	Esteban-Santillan 1998[21]	41	NC	39	Rouleau hands	3	0.93	0.58	0.70	0.89	0.51
Clock Drawing	Cahn 1995[9]	45	NC	238	Rouleau total	7	0.88	0.63	0.31	0.97	0.16
Clock Drawing	Cahn 1996[10]	42	NC	237	Rouleau total	7	0.88	0.63	0.30	0.97	0.15
Clock Drawing	Connor 2005[18]	50	NC	50	Rouleau total	7	0.74	0.88	0.86	0.77	0.50
Clock Drawing	Esteban-Santillan 1998[21]	41	NC	39	Rouleau total	9	0.93	0.42	0.63	0.85	0.51
Clock Drawing	Connor 2005[18]	20	NC	20	Rouleau total (mild CATD)	7	0.5	0.85	0.77	0.63	0.50
Clock Drawing	Connor 2005[18]	10	NC	50	Rouleau total (DRS 101-105)	7	0.9	0.88	0.60	0.98	0.17
Clock Drawing	Connor 2005[18]	10	NC	50	Rouleau total (DRS 106-110)	7	0.9	0.88	0.60	0.98	0.17
Clock Drawing	Connor 2005[18]	10	NC	50	Rouleau total (DRS 111-115)	7	0.8	0.88	0.57	0.96	0.17
Clock Drawing	Connor 2005[18]	10	NC	50	Rouleau total (DRS 116-120)	7	0.5	0.88	0.45	0.90	0.17
Clock Drawing	Connor 2005[18]	10	NC	50	Rouleau total (DRS 121-125)	7	0.5	0.88	0.45	0.90	0.17
Clock Drawing	Brodaty 1997[5]	28	NC	28	Shulman scale	3*	0.86	0.96	0.96	0.87	0.50
Clock Drawing	Brodaty 1997[5]	8	NC	28	Shulman scale (MMSE 24+)	3*	0.88	0.96	0.86	0.96	0.22

Test/Test Type	Author Year	CATD N	Comp Group	Comp N	Score (Subgroup)	Cut point	SE	SP	PPV+	NPV+	CATD Base Rate
Clock Drawing	Brodaty 1997[5]	20	NC	28	Shulman scale (MMSE <24)	3*	0.85	0.96	0.94	0.90	0.42
Clock Drawing	Lee 1996[36]	30	NC	30	Sunderland scale	5	0.67	0.97	0.96	0.75	0.50
Clock Drawing	Brodaty 1997[5]	28	NC	28	Sunderland scale	5	0.57	1.00	1.00	0.70	0.50
Clock Drawing	Brodaty 1997[5]	28	NC	28	Sunderland scale	8	0.79	0.93	0.92	0.82	0.50
Clock Drawing	Brodaty 1997[5]	8	NC	28	Sunderland scale (MMSE 24+)	5	0.38	1.00	1.00	0.85	0.22
Clock Drawing	Brodaty 1997[5]	8	NC	28	Sunderland scale (MMSE 24+)	8	0.63	0.93	0.72	0.90	0.22
Clock Drawing	Brodaty 1997[5]	20	NC	28	Sunderland scale (MMSE <24)	8	0.85	0.93	0.90	0.90	0.42
Clock Drawing	Lee 1996[36]	9	NC	30	Sunderland scale (very mild CATD)	5	0.33	0.97	0.77	0.83	0.23
Clock Drawing	Lee 1996[36]	17	NC	30	Sunderland scale (mild CATD)	5	0.77	0.97	0.94	0.88	0.36
Clock Drawing	Lee 1996[36]	4	NC	30	Sunderland scale (moderate CATD)	5	1.00	0.97	0.82	1.00	0.12
Clock Drawing	Tuokko 1992[63]	58	NC	62	Tuokko drawing	3*	0.86	0.92	0.91	0.88	0.48
Clock Drawing	Tuokko 1992[63]	58	NC	62	Tuokko setting	13	0.97	0.87	0.87	0.97	0.48
Clock Drawing	Tuokko 1992[63]	58	NC	62	Tuokko reading	13	0.85	0.92	0.91	0.87	0.48
Clock Drawing	Tuokko 1992[63]	58	NC	62	Tuokko combined score	2*	0.93	0.94	0.94	0.93	0.48
Clock Drawing	Connor 2005[18]	50	NC	50	Watson abbreviated	5*	0.52	0.84	0.76	0.64	0.50
Clock Drawing	Connor 2005[18]	20	NC	20	Watson abbreviated (mild CATD)	5*	0.40	0.80	0.67	0.57	0.50
Clock Drawing	Connor 2005[18]	10	NC	50	Watson abbreviated (DRS 101-105)	5*	0.60	0.84	0.43	0.91	0.17
Clock Drawing	Connor 2005[18]	10	NC	50	Watson abbreviated (DRS 106-110)	5*	0.60	0.84	0.43	0.91	0.17
Clock Drawing	Connor 2005[18]	10	NC	50	Watson abbreviated (DRS 111-115)	5*	0.60	0.84	0.43	0.91	0.17
Clock Drawing	Connor 2005[18]	10	NC	50	Watson abbreviated (DRS 116-120)	5*	0.60	0.84	0.43	0.91	0.17
Clock Drawing	Connor 2005[18]	10	NC	50	Watson abbreviated (DRS 121-125)	5*	0.20	0.84	0.20	0.84	0.17
Clock Drawing	Wolf-Klein 1989[67]	105	NC	109	Wolf-Klein abbreviated	5	0.75	0.94	0.93	0.80	0.49
Clock Drawing	Wolf-Klein 1989[67]	121	NC	130	Wolf-Klein scale	5	0.87	0.93	0.92	0.88	0.48
Clock Drawing	Brodaty 1997[5]	28	NC	28	Wolf-Klein scale	6	0.36	1.00	1.00	0.61	0.50
Clock Drawing	Brodaty 1997[5]	28	NC	28	Wolf-Klein scale	8	0.79	0.89	0.88	0.81	0.50
Clock Drawing	Connor 2005[18]	50	NC	50	Wolf-Klein scale	8	0.78	0.78	0.78	0.78	0.50
Clock Drawing	Brodaty 1997[5]	8	NC	28	Wolf-Klein scale (MMSE 24+)	6	0.13	1.00	1.00	0.80	0.22
Clock Drawing	Brodaty 1997[5]	8	NC	28	Wolf-Klein scale (MMSE 24+)	8	0.88	0.89	0.69	0.96	0.22
Clock Drawing	Brodaty 1997[5]	20	NC	28	Wolf-Klein scale (MMSE <24)	8	0.75	0.89	0.83	0.83	0.42

Test/Test Type	Author Year	CATD N	Comp Group	Comp N	Score (Subgroup)	Cut point	SE	SP	PPV+	NPV+	CATD Base Rate
Clock Drawing	Connor 2005[18]	20	NC	20	Wolf-Klein scale (mild CATD)	8	0.60	0.75	0.71	0.65	0.50
Clock Drawing	Connor 2005[18]	10	NC	50	Wolf-Klein scale (DRS 101-105)	8	0.90	0.78	0.45	0.98	0.17
Clock Drawing	Connor 2005[18]	10	NC	50	Wolf-Klein scale (DRS 106-110)	8	1.00	0.78	0.48	1.00	0.17
Clock Drawing	Connor 2005[18]	10	NC	50	Wolf-Klein scale (DRS 111-115)	8	0.80	0.78	0.42	0.95	0.17
Clock Drawing	Connor 2005[18]	10	NC	50	Wolf-Klein scale (DRS 116-120)	8	0.60	0.78	0.35	0.91	0.17
Clock Drawing	Connor 2005[18]	10	NC	50	Wolf-Klein scale (DRS 121-125)	8	0.60	0.78	0.35	0.91	0.17
Clock Drawing	Parsey 2011[49]	33	MCI	33	CLOX 1 modified Rouleau	11	0.58	1.00	1.00	0.70	0.50
Clock Drawing	De Jager 2003[19]	55	MCI	29	CLOX 1 total	11	0.76	0.72	0.84	0.61	0.65
Clock Drawing	De Jager 2003[19]	55	MCI	29	CLOX 2 copy	13	0.67	0.62	0.77	0.50	0.65
Mini-Mental State Exam (MMSE)	Chapman 2010[14]	55	NC	78	Total score	NR	0.56	0.88	0.77	0.74	0.41
MMSE	Kalbe 2004[31]	88	NC	97	Total score	21	0.92	0.86	0.86	0.92	0.48
MMSE	Kuslansky 2004[34]	57	NC	323	Total score	24	0.75	0.82	0.42	0.95	0.15
MMSE	Kuslansky 2004[34]	57	NC	323	Total score	25	0.88	0.70	0.34	0.97	0.15
MMSE	Chandler 2005[13]	95	NC	95	Total score	26	0.93	0.95	0.95	0.93	0.50
MMSE	Roalf 2017[53]	340	NC	138	Total score	27	0.94	0.96	0.98	0.87	0.71
MMSE	Galasko 1990[23]	24	NC	74	Total score (Mild CATD)	NR	0.79	0.99	0.95	0.94	0.24
MMSE	Galasko 1990[23]	50	NC	74	Total score (Moderate CATD)	23	1.00	0.99	0.98	1.00	0.40
MMSE	Uhlmann 1991[64]	23	NC	17	Total score (Middle School)	21	0.82	0.94	0.95	0.79	0.58
MMSE	Uhlmann 1991[64]	23	NC	17	Total score (Middle School)	24	1.00	0.59	0.77	1.00	0.58
MMSE	Uhlmann 1991[64]	33	NC	30	Total score (High school)	23	0.79	0.97	0.97	0.81	0.52
MMSE	Uhlmann 1991[64]	33	NC	30	Total score (High school)	24	0.88	0.79	0.82	0.86	0.52
MMSE	Uhlmann 1991[64]	53	NC	54	Total score (College+)	24	0.83	1.00	1.00	0.86	0.50
MMSE	Chandler 2005[13]	95	MCI	60	Total score	25	0.88	0.83	0.89	0.82	0.61
MMSE	Roalf 2017[53]	340	MCI	109	Total score	18	0.79	0.79	0.92	0.55	0.76
Memory Impairment Screen (MIS)	Buschke 1999[7]	39	NC	433	Total score	4	0.87	0.96	0.66	0.99	0.08
MIS	Kuslansky 2002[33]	28	NC	212	Total score	4	0.86	0.97	0.79	0.98	0.12

Test/Test Type	Author Year	CATD N	Comp Group	Comp N	Score (Subgroup)	Cut point	SE	SP	PPV+	NPV+	CATD Base Rate
MIS	Buschke 1999[7]		NC	433	Total score (Mild CATD)	4	0.79	0.96	NA	NA	NA
MIS	Buschke 1999[7]		NC	433	Total score (Moderate CATD)	4	0.95	0.96	NA	NA	NA
MIS	Kuslansky 2002[33]	4	NC	212	Total score (CDR 0.5)	4	0.75	0.97	0.32	1.00	0.02
MIS	Kuslansky 2002[33]	4	NC	212	Total score (CDR 0.5)	5	1.00	0.85	0.11	1.00	0.02
MIS	Kuslansky 2002[33]	16	NC	212	Total score (CDR 1.0)	4	0.81	0.97	0.67	0.99	0.07
MIS	Kuslansky 2002[33]	6	NC	212	Total score (CDR 2.0)	2	1.00	1.00	1.00	1.00	0.03
MIS	Kuslansky 2002[33]	6	NC	212	Total score (CDR 2.0)	4	1.00	0.97	0.49	1.00	0.03
MIS	Kuslansky 2002[33]	2	NC	212	Total score (CDR 3.0)	1	1.00	1.00	1.00	1.00	0.01
MIS	Kuslansky 2002[33]	2	NC	212	Total score (CDR 3.0)	2	1.00	1.00	1.00	1.00	0.01
MIS	Kuslansky 2002[33]	2	NC	212	Total score (CDR 3.0)	3	1.00	1.00	1.00	1.00	0.01
Montreal Cognitive Assessment (MoCA)	Quarmley 2017*[51]	231	NC	155	Total score	23	0.93	0.94	0.96	0.90	0.60
MoCA	Roalf 2017[53]	340	NC	138	Total score	22	0.94	1.00	1.00	0.87	0.71
MoCA	Roalf 2017[53]	340	NC	138	Total score – modified short version	10	0.96	0.91	0.96	0.90	0.71
MoCA	Roalf 2017[53]	340	MCI	109	Total score	24	0.76	0.78	0.92	0.51	0.76
MoCA	Roalf 2017[53]	340	MCI	109	Total score – modified short version	6	0.67	0.79	0.91	0.43	0.76
MoCA	Trzepacz 2015[62]	100	MCI	299	Total score	19	0.82	0.88	0.70	0.94	0.25
MoCA	Quarmley 2017*[51]	231	MCI	110	Total score	19	0.97	0.79	0.91	0.92	0.68
7 Minute Screen (7MS)	Solomon 1998[55]	60	NC	60	Total score	0.3, 0.7	1.00	1.00	1.00	1.00	0.50
7MS	Solomon 1998[55]	60	NC	60	Total score	0.1, 0.9	0.96	0.96	0.96	0.96	0.50
7MS	Solomon 1998[55]	30	NC	30	Total score (confirmation sample)	0.1, 0.9	0.92	0.96	0.96	0.92	0.50
7MS	Solomon 1998[55]	35	NC	60	Total score (MMSE 21+)	0.1, 0.9	0.98	0.98	0.97	0.99	0.37
7MS	Solomon 1998[55]		NC		Total score (MMSE 24+)	0.1, 0.9	0.98	1.00	NA	NA	NA
Minnesota Cognitive Acuity Screen (MCAS)	Tremont 2011[60]	50	aMCI	100	Total score	42.5	0.86	0.77	0.65	0.92	0.33

Test/Test Type	Author Year	CATD N	Comp Group	Comp N	Score (Subgroup)	Cut point	SE	SP	PPV+	NPV+	CATD Base Rate
Test Your Memory (TYM)	Brown 2009[6]	94	NC	282	Total score	42	0.93	0.86	0.69	0.97	0.25

Abbreviations: aMCI=amnestic mild cognitive impairment; BAS=Brief Alzheimer Screen; BMET=Brief Memory and Executive Test; CATD=Clinical Alzheimer's-type dementia; CDIS=clock drawing interpretation scale; CDT=clock drawing test; Comp=comparator; MCAS=Minnesota Cognitive Acuity Screen; MCI=Mild Cognitive Impairment; MIS=Memory Impairment Screen; MMSE=Mini-Mental State Exam; MoCA; Montreal Cognitive Assessment; NC=normal control; NR=not reported; NPV=negative predictive value; PPV=positive predictive value; SE=sensitivity; SP=specificity; TYM=Test Your Memory; 7MS=7 Minute Screen
*indicates that values equal to or higher than the specified cut point are associated with worse cognition
+indicates that some PPV and NPV values were back-calculated

Appendix Table C.3. Classification accuracy results for brief cognitive batteries in eligible studies with low-moderate risk of bias

Cognitive Battery	Author Year	CATD N	Comp Group	Comp N	Score (Subgroup)	Cut Point	SE	SP	PPV+	NPV+	CATD Base Rate
Dementia Rating Scale (DRS)	**Monsch 1995[46]**	254	NC	105	Total score	129	0.97	0.99	1.00	0.93	0.71
	Salmon 2002[54]	74	NC	74	Total score	132	0.96	0.92	0.92	0.96	0.50
	Monsch 1995[46]	254	NC	105	Construction score	5	0.73	0.70	0.85	0.52	0.71
	Monsch 1995[46]	254	NC	105	Memory score	21	0.93	0.98	0.99	0.85	0.71
	Monsch 1995[46]	254	NC	105	Attention score	35	0.71	0.84	0.91	0.54	0.71
	Monsch 1995[46]	254	NC	105	Initiation & Preservation score	33	0.93	0.94	0.97	0.85	0.71
	Monsch 1995[46]	254	NC	105	Conceptualization score	33	0.69	0.91	0.95	0.55	0.71
	Monsch 1995[46]	254	NC	105	Memory/Initiation & Preservation	x<0	0.98	0.98	0.99	0.95	0.71
	Monsch 1995[46]	44	NC	238	Memory/Initiation & Preservation	x<0	0.91	0.93	0.71	0.98	0.16
	Monsch 1995[46]	76	NC	105	Memory/Initiation & Preservation (mild CATD)	x<0	0.92	0.98	0.97	0.94	0.42
	Springate 2014[56]	49	MCI	98	Total Score	123	0.78	0.83	0.70	0.88	0.33
Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog)	**Zainal 2016[68]**	64	NC	125	Total Score (ADAS-Cog 11)	14*	0.81	1.00	1.00	0.91	0.34
	Zainal 2016[68]	64	NC	125	Total Score (ADAS-Cog 12)	21*	0.73	1.00	1.00	0.88	0.34
	Zainal 2016[68]	64	MCI	80	Total Score (ADAS-Cog 11)	12*	0.86	0.89	0.86	0.89	0.44
	Zainal 2016[68]	64	MCI	80	Total Score (ADAS-Cog 12)	21*	0.79	0.89	0.85	0.84	0.44

Cognitive Battery	Author Year	CATD N	Comp Group	Comp N	Score (Subgroup)	Cut Point	SE	SP	PPV+	NPV+	CATD Base Rate
Cogstate Brief Battery (CBB)	**Maruff 2013[40]**	42	NC	642	Learning/Working Memory	89	1.00	0.847	0.30	1.00	0.06
	Maruff 2013[40]	51	NC	659	Attention/Psychomotor	89	0.53	0.857	0.22	0.96	0.07
Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Neuropsychological Battery	**Chandler 2005[13]**	95	NC	95	CERAD Total Score	77	0.94	0.93	0.93	0.94	0.50
	Chandler 2005[13]	95	MCI	60	CERAD Total Score	68	0.80	0.81	0.87	0.72	0.61
Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)	**Morgan 2010[48]**	100	NC	100	Verbal Index	NR	0.88	0.82	0.83	0.87	0.50
	Morgan 2010[48]	100	NC	100	Visual Index	NR	0.86	0.77	0.79	0.85	0.50
	Morgan 2010[48]	100	NC	100	Verbal & Visual Indices	NR	0.92	0.79	0.81	0.91	0.50
	Morgan 2010[48]	100	MCI	38	Verbal Index	NR	0.61	0.71	0.85	0.41	0.72
	Morgan 2010[48]	100	MCI	38	Visual Index	NR	0.68	0.76	0.88	0.48	0.72
	Morgan 2010[48]	100	MCI	38	Verbal & Visual Indices	NR	0.66	0.75	0.87	0.45	0.72
Addenbrooke's Cognitive Examination Version Three (ACE-III)	**Elamin 2016[20]**	31	NC	28	Total score	88	0.97	0.96	0.97	0.96	0.53
Wechsler Memory Scales (WMS)	**Lange 2006[35]**	34	NC	34	WMS-III General Memory Index	5th percentile	0.94	0.97	0.97	0.94	0.50
	Lange 2006[35]	34	NC	34	WMS-III General Memory Index	10th percentile	0.97	0.91	0.92	0.97	0.50
	Lange 2006[35]	34	NC	34	WMS-III Immediate Memory Index	5th percentile	0.85	1.00	1.00	0.87	0.50
	Lange 2006[35]	34	NC	34	WMS-III Immediate Memory Index	10th percentile	0.94	0.94	0.94	0.94	0.50
	Lange 2006[35]	34	NC	34	WMS-III Delayed Memory Index	5th percentile	0.88	0.97	0.97	0.89	0.50

Cognitive Battery	Author Year	CATD N	Comp Group	Comp N	Score (Subgroup)	Cut Point	SE	SP	PPV+	NPV+	CATD Base Rate
	Lange 2006[35]	34	NC	34	WMS-III Delayed Memory Index	10th percentile	0.97	0.97	0.97	0.97	0.50
	Lange 2006[35]	34	NC	34	WAIS-III GAI, WMS-III IMI: simple difference	5th percentile	0.68	0.82	0.79	0.72	0.50
	Lange 2006[35]	34	NC	34	WAIS-III GAI, WMS-III IMI: simple difference	10th percentile	0.74	0.82	0.80	0.76	0.50
	Lange 2006[35]	34	NC	34	WAIS-III GAI, WMS-III IMI: GAI stratified difference	5th percentile	0.76	0.91	0.89	0.79	0.50
	Lange 2006[35]	34	NC	34	WAIS-III GAI, WMS-III IMI: GAI stratified difference	10th percentile	0.79	0.91	0.90	0.81	0.50
	Lange 2006[35]	34	NC	34	WAIS-III GAI, WMS-III IMI: predicted difference	5th percentile	0.79	0.94	0.93	0.82	0.50
	Lange 2006[35]	34	NC	34	WAIS-III GAI, WMS-III IMI: predicted difference	10th percentile	0.88	0.91	0.91	0.88	0.50
	Lange 2006[35]	34	NC	34	WAIS-III GAI, WMS-III GMI: simple difference	5th percentile	0.65	0.88	0.84	0.72	0.50
	Lange 2006[35]	34	NC	34	WAIS-III GAI, WMS-III GMI: simple difference	10th percentile	0.79	0.85	0.84	0.80	0.50
	Lange 2006[35]	34	NC	34	WAIS-III GAI, WMS-III GMI: GAI stratified difference	5th percentile	0.91	0.94	0.94	0.91	0.50
	Lange 2006[35]	34	NC	34	WAIS-III GAI, WMS-III GMI: GAI stratified difference	10th percentile	0.91	0.88	0.88	0.91	0.50
	Lange 2006[35]	34	NC	34	WAIS-III GAI, WMS-III GMI: predicted difference	5th percentile	0.91	0.89	0.89	0.91	0.50
	Lange 2006[35]	34	NC	34	WAIS-III GAI, WMS-III GMI: predicted difference	10th percentile	0.91	0.85	0.86	0.90	0.50

Cognitive Battery	Author Year	CATD N	Comp Group	Comp N	Score (Subgroup)	Cut Point	SE	SP	PPV+	NPV+	CATD Base Rate
	Lange 2006[35]	34	NC	34	WAIS-III GAI, WMS-III DMI: simple difference	5th percentile	0.44	0.88	0.79	0.61	0.50
	Lange 2006[35]	34	NC	34	WAIS-III GAI, WMS-III DMI: simple difference	10th percentile	0.53	0.85	0.78	0.64	0.50
	Lange 2006[35]	34	NC	34	WAIS-III GAI, WMS-III DMI: GAI stratified difference	5th percentile	0.74	0.94	0.93	0.78	0.50
	Lange 2006[35]	34	NC	34	WAIS-III GAI, WMS-III DMI: GAI stratified difference	10th percentile	0.88	0.85	0.85	0.88	0.50
	Lange 2006[35]	34	NC	34	WAIS-III GAI, WMS-III DMI: predicted difference	5th percentile	0.79	0.88	0.87	0.81	0.50
	Lange 2006[35]	34	NC	34	WAIS-III GAI, WMS-III DMI: predicted difference	10th percentile	0.88	0.88	0.88	0.88	0.50
Wechsler Adult Intelligence Scale (WAIS)	**Logsdon 1989**[37]	44	NC	54	WAIS-R Fuld Profile[69]	Fuld criteria (Y/N)	0.07	0.93	0.45	0.55	0.45

Abbreviations: ACE=Addenbrooke's Cognitive Examination; ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive; CATD=Clinical Alzheimer's-type dementia; CBB=Cogstate Brief Battery; CERAD=Consortium to Establish a Registry for Alzheimer's Disease; Comp=comparator; DMI=delayed memory index; DRS=Dementia Rating Scale; GAI=general ability index; GMI=General Memory Index; IMI=immediate memory index; MCI=mild cognitive impairment; NC=normal control; NR=not reported; NPV=negative predictive value; PPV=positive predictive value; RBANS= Repeatable Battery for the Assessment of Neuropsychological Status; SE=sensitivity; SP=specificity; WAIS=Wechsler Adult Intelligence Scale; WMS=Wechsler Memory Scale

*indicates that values equal to or higher than the specified cut point indicate CATD

+indicates that some PPV and NPV values were back-calculated

Appendix Table C.4. Classification accuracy results for memory tests in eligible studies with low-moderate risk of bias

Memory Test	Author Year	CATD N	Comp Group	Comp N	Score (Subgroup)	Cut Point	SE	SP	PPV+	NPV+	CATD Base Rate
List Learning Tests – Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog)	**Zainal 2016[68]**	64	NC	125	All Recall Trials & Recognition	14*	0.77	0.98	0.89	0.96	0.34
	Zainal 2016[68]	64	MCI	80	All Recall Trials & Recognition	14*	0.76	0.85	0.97	0.35	0.44
List Learning Tests – Consortium to Establish a Registry for Alzheimer's Disease (CERAD)	**Welsh 1991, 1992[65, 66]**	49	NC	49	Delayed Recall & Recognition	NR	1.00	0.92	0.92	0.89	0.50
	Welsh 1991, 1992[65, 66]	49	NC	49	List Trial 1 (Mild CATD)	2	0.41	0.96	0.91	0.62	0.50
	Welsh 1991, 1992[65, 66]	49	NC	49	List Trial 1 (Moderate CATD)	2	0.67	0.96	0.94	0.74	0.50
	Welsh 1991, 1992[65, 66]	49	NC	49	List Trial 1 (Severe CATD)	2	0.92	0.96	0.96	0.92	0.50
	Welsh 1991, 1992[65, 66]	49	NC	49	List Trial 2 (Mild CATD)	4	0.49	0.94	0.89	0.65	0.50
	Welsh 1991, 1992[65, 66]	49	NC	49	List Trial 2 (Moderate CATD)	4	0.74	0.94	0.93	0.78	0.50
	Welsh 1991, 1992[65, 66]	49	NC	49	List Trial 2 (Severe CATD)	4	0.96	0.94	0.94	0.96	0.50
	Welsh 1991, 1992[65, 66]	49	NC	49	List Trial 3 (Mild CATD)	5	0.41	0.98	0.95	0.62	0.50
	Welsh 1991, 1992[65, 66]	49	NC	49	List Trial 3 (Moderate CATD)	5	0.59	0.98	0.97	0.71	0.50
	Welsh 1991, 1992[65, 66]	49	NC	49	List Trial 3 (Severe CATD)	5	0.90	0.98	0.98	0.91	0.50
	Cahn 1995[9]	45	NC	238	Delayed Recall	4	0.88	0.84	0.51	0.97	0.16
	Chandler 2005[13]	95	NC	95	Delayed Recall	4	0.93	0.90	0.90	0.92	0.50
	Welsh 1991, 1992[65, 66]	49	NC	49	Delayed Recall (Mild CATD)	3	0.86	0.94	0.93	0.87	0.50
	Welsh 1991, 1992[65, 66]	49	NC	49	Delayed Recall (Moderate CATD)	3	0.96	0.94	0.94	0.96	0.50
	Welsh 1991, 1992[65, 66]	49	NC	49	Delayed Recall (Severe CATD)	3	0.96	0.94	0.94	0.96	0.50
	Cahn 1995[9]	45	NC	238	Savings, Retention	65%	0.88	0.82	0.48	0.97	0.16
	Welsh 1991, 1992[65, 66]	49	NC	49	Savings, Retention (Mild CATD)	47%	0.62	0.96	0.94	0.72	0.50
	Welsh 1991, 1992[65, 66]	49	NC	49	Savings, Retention (Moderate CATD)	47%	0.93	0.96	0.96	0.93	0.50
	Welsh 1991, 1992[65, 66]	49	NC	49	Savings, Retention (Severe CATD)	47%	0.82	0.96	0.95	0.84	0.50
	Cahn 1995[9]	45	NC	238	Recognition	17	0.60	0.91	0.56	0.92	0.16

Memory Test	Author Year	CATD N	Comp Group	Comp N	Score (Subgroup)	Cut Point	SE	SP	PPV+	NPV+	CATD Base Rate
	Welsh 1991, 1992[65, 66]	49	NC	49	Recognition Yes (Mild CATD)	9	0.39	0.96	0.91	0.61	0.50
	Welsh 1991, 1992[65, 66]	49	NC	49	Recognition Yes (Moderate CATD)	9	0.53	0.96	0.93	0.67	0.50
	Welsh 1991, 1992[65, 66]	49	NC	49	Recognition Yes (Severe CATD)	9	0.73	0.96	0.95	0.78	0.50
	Welsh 1991, 1992[65, 66]	49	NC	49	Recognition No (Mild CATD)	7	0.25	0.98	0.93	0.57	0.50
	Welsh 1991, 1992[65, 66]	49	NC	49	Recognition No (Moderate CATD)	7	0.32	0.98	0.94	0.59	0.50
	Welsh 1991, 1992[65, 66]	49	NC	49	Recognition No (Severe CATD)	7	0.48	0.98	0.96	0.65	0.50
	Cahn 1997[8]	38	NC	236	Intrusion proportion	0	0.37	0.85	0.28	0.89	0.14
	Welsh 1991, 1992[65, 66]	49	NC	49	% Intrusions (Mild CATD)	2 SDs**	0.33	0.94	0.85	0.58	0.50
	Welsh 1991, 1992[65, 66]	49	NC	49	% Intrusions (Moderate CATD)	2 SDs**	0.33	0.94	0.85	0.58	0.50
	Welsh 1991, 1992[65, 66]	49	NC	49	% Intrusions (Severe CATD)	2 SDs**	0.62	0.94	0.91	0.71	0.50
	Welsh 1991, 1992[65, 66]	49	NC	49	Intrusions Trial 1 (Mild CATD)	2 SDs**	0.14	0.96	0.78	0.53	0.50
	Welsh 1991, 1992[65, 66]	49	NC	49	Intrusions Trial 1 (Moderate CATD)	2 SDs**	0.16	0.96	0.80	0.53	0.50
	Welsh 1991, 1992[65, 66]	49	NC	49	Intrusions Trial 1 (Severe CATD)	2 SDs**	0.14	0.96	0.78	0.53	0.50
	Welsh 1991, 1992[65, 66]	49	NC	49	Intrusions Trial 2 (Mild CATD)	2 SDs**	0.33	0.78	0.60	0.54	0.50
	Welsh 1991, 1992[65, 66]	49	NC	49	Intrusions Trial 2 (Moderate CATD)	2 SDs**	0.27	0.78	0.55	0.52	0.50
	Welsh 1991, 1992[65, 66]	49	NC	49	Intrusions Trial 2 (Severe CATD)	2 SDs**	0.33	0.78	0.60	0.54	0.50
	Welsh 1991, 1992[65, 66]	49	NC	49	Intrusions Trial 3 (Mild CATD)	2 SDs**	0.20	0.94	0.77	0.54	0.50
	Welsh 1991, 1992[65, 66]	49	NC	49	Intrusions Trial 3 (Moderate CATD)	2 SDs**	0.35	0.94	0.85	0.59	0.50
	Welsh 1991, 1992[65, 66]	49	NC	49	Intrusions Trial 3 (Severe CATD)	2 SDs**	0.39	0.94	0.87	0.61	0.50
	Welsh 1991, 1992[65, 66]	49	NC	49	Intrusions Delayed Recall (Mild CATD)	2 SDs**	0.27	0.90	0.73	0.55	0.50
	Welsh 1991, 1992[65, 66]	49	NC	49	Intrusions Delayed Recall (Moderate CATD)	2 SDs**	0.26	0.90	0.72	0.55	0.50

Memory Test	Author Year	CATD N	Comp Group	Comp N	Score (Subgroup)	Cut Point	SE	SP	PPV+	NPV+	CATD Base Rate
	Welsh 1991, 1992[65, 66]	49	NC	49	Intrusions Delayed Recall (Severe CATD)	2 SDs**	0.18	0.90	0.64	0.52	0.50
	Chandler 2005[13]	95	MCI	60	Delayed Recall	2	0.81	0.68	0.80	0.69	0.61
List Learning Tests - Cogstate International Shopping List Test (ISLT)	**Thompson 2011**[59]	27	NC	156	Trials Total (at 95% specificity)	18	0.78	0.95	0.73	0.96	0.15
	Thompson 2011[59]	27	NC	156	Trials Total (at 90% specificity)	20	0.82	0.90	0.59	0.97	0.15
List Learning Tests - Delayed Word Recall (DWR)	**Knopman 1989**[32]	28	NC	55	Delayed Recall	2	0.89	0.98	0.96	0.95	0.34
List Learning Tests – DemTect	**Kalbe 2004**[31]	88	NC	97	Delayed Recall	NR	0.93	0.76	0.78	0.93	0.48
List Learning Tests – Hopkins Verbal Learning Test (HVLT)	**Kuslansky 2004**[34]	57	NC	323	Trials Total	14	0.92	0.75	0.39	0.98	0.15
	De Jager 2003[19]	55	MCI	29	Trials Total	15	0.91	0.69	0.85	0.80	0.65
List Learning Tests - Neuropsychological Assessment Battery (NAB)	**Gavett 2009**[24]	26	NC	98	List A Immediate Recall	35	0.69	1.00	1.00	0.92	0.21
	Gavett 2009[24]	26	NC	98	List A Immediate Recall	40	0.85	0.90	0.69	0.96	0.21
	Gavett 2009[24]	26	NC	98	List B Immediate Recall	35	0.35	1.00	1.00	0.85	0.21
	Gavett 2009[24]	26	NC	98	List B Immediate Recall	44	0.85	0.79	0.52	0.95	0.21
	Gavett 2009[24]	26	NC	98	List A Short Delay Recall	35	0.85	0.97	0.88	0.96	0.21
	Gavett 2009[24]	26	NC	98	List A Short Delay Recall	37	0.92	0.97	0.89	0.98	0.21
	Gavett 2009[24]	26	NC	98	List A Long Delay Recall	35	0.81	0.98	0.91	0.95	0.21
	Gavett 2009[24]	26	NC	98	List A Long Delay Recall	40	0.92	0.97	0.89	0.98	0.21
	Gavett 2009[24]	26	aMCI	29	List A Immediate Recall	30	0.58	0.86	0.79	0.70	0.47

Memory Test	Author Year	CATD N	Comp Group	Comp N	Score (Subgroup)	Cut Point	SE	SP	PPV+	NPV+	CATD Base Rate
	Gavett 2009[24]	26	aMCI	29	List A Immediate Recall	35	0.69	0.66	0.65	0.70	0.47
	Gavett 2009[24]	26	aMCI	29	List B Immediate Recall	35	0.35	0.90	0.76	0.61	0.47
	Gavett 2009[24]	26	aMCI	29	List B Immediate Recall	41	0.65	0.72	0.68	0.70	0.47
	Gavett 2009[24]	26	aMCI	29	List A Short Delay Recall	30	0.73	0.83	0.79	0.77	0.47
	Gavett 2009[24]	26	aMCI	29	List A Short Delay Recall	35	0.85	0.62	0.67	0.82	0.47
	Gavett 2009[24]	26	aMCI	29	List A Long Delay Recall	35	0.81	0.52	0.60	0.75	0.47
	Gavett 2009[24]	26	aMCI	29	List A Long Delay Recall	36	0.89	0.52	0.62	0.84	0.47
List Learning Tests - Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)	**Clark 2010**[15]	73	aMCI	44	Savings, Retention	29.9%	0.90	0.72	0.84	0.82	0.62
List Learning Tests – Free and Cued Selective Reminding Test (FCSRT)	**Grober 2008**[26]	35	NC	283	Free Recall	24	0.83	0.76	0.30	0.97	0.11
	Millar 2017[44]	64	NC	519	Free Recall	NR	0.91	0.73	0.29	0.99	0.11
	Grober 2008[26]	35	NC	283	Total Recall	44	0.71	0.94	0.59	0.96	0.11
Prose Recall – Wechsler Memory Scales (WMS) Logical Memory (LM)	**Johnson 2003**[30]	31	NC	47	Veridical Reproduction	NR	0.84	0.87	0.81	0.89	0.40
	Johnson 2003[30]	98	NC	82	Veridical Reproduction (very mild CATD)	NR	0.77	0.81	0.83	0.75	0.54
	Johnson 2003[30]	31	NC	47	Veridical & Gist Recall	NR	0.77	0.89	0.82	0.85	0.40
	Johnson 2003[30]	31	NC	47	Distortion of Text	NR	0.84	0.81	0.74	0.88	0.40
	Johnson 2003[30]	98	NC	82	Distortion of Text (very mild CATD)	NR	0.75	0.81	0.83	0.73	0.54
	Salmon 2002[54]	27	NC	27	Delayed Recall	9	0.87	0.89	0.89	0.87	0.50
	Millar 2017[44]	64	NC	519	Delayed Recall	NR	0.71	0.83	0.34	0.96	0.11

Memory Test	Author Year	CATD N	Comp Group	Comp N	Score (Subgroup)	Cut Point	SE	SP	PPV+	NPV+	CATD Base Rate
Prose Recall – Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)	**Clark 2010[15]**	73	aMCI	44	Savings, Retention	59.9%	0.85	0.55	0.76	0.69	0.62
Figure Recall - Wechsler Memory Scales (WMS) Visual Reproduction (VR)	**Cahn 1995[9]**	45	NC	238	Immediate Recall	8	0.90	0.79	0.45	0.98	0.16
	Cahn 1995[9]	45	NC	238	Delayed Recall	2	0.87	0.87	0.56	0.97	0.16
	Salmon 2002[54]	82	NC	82	Delayed Recall	3	0.87	0.86	0.86	0.87	0.50
	Cahn 1995[9]	45	NC	238	Savings, Retention	29%	0.74	0.93	0.67	0.95	0.16
	Cahn 1997[8]	38	NC	236	Figural Intrusions	1*	0.27	0.82	0.19	0.87	0.14
Other Memory Tests – The Placing Test	**De Jager 2003[19]**	40	MCI	28	Total	10	0.68	0.68	0.75	0.60	0.59
	De Jager 2003[19]	39	MCI	28	Objects	6	0.80	0.71	0.79	0.72	0.58
	De Jager 2003[19]	39	MCI	28	Faces	5	0.90	0.50	0.71	0.78	0.58
Other Memory Tests - Wechsler Memory Scales (WMS) Logical Memory (LM) + Visual Reproduction (VR)	**Troster 1993[61]**	58	NC	69	Savings, Retention	NR	0.88	0.99	0.99	0.91	0.46
Other Memory Tests - Fuld Object Memory	**Loewenstein 2001[38]**	268	NC	144	Trials Total (age 59-68)	19	0.93	1.00	NA	NA	0.65
	Loewenstein 2001[38]	268	NC	144	Trials Total (age 69-78)	17	0.94	1.00	NA	NA	0.65
	Loewenstein 2001[38]	268	NC	144	Trials Total (age 69-78)	18	0.94	1.00	NA	NA	0.65
	Loewenstein 2001[38]	268	NC	144	Trials Total (age 79-90)	18	0.95	0.94	NA	NA	0.65

Memory Test	Author Year	CATD N	Comp Group	Comp N	Score (Subgroup)	Cut Point	SE	SP	PPV+	NPV+	CATD Base Rate
Evaluation (FOME)											
Other Memory Tests – Process Dissociation Procedure	**Millar 2017**[44]	64	NC	519	Recollection Estimate	NR	0.77	0.86	0.40	0.97	0.11

Abbreviations: ADAS-Cog=Alzheimer's Disease Assessment Scale-cognitive subscale; aMCI=amnestic mild cognitive impairment; CERAD=Consortium to Establish a Registry for Alzheimer's Disease; CATD=Clinical Alzheimer's-type dementia; CogState ISLT= Cogstate International Shopping List Test; Comp=comparator; DRS=dementia rating scale; DWR=Delayed Word Recall; FCSRT=Free and Cued Selective Reminding Test; FOME=Fuld Object Memory Evaluation; HVLT= Hopkins Verbal Learning Test; LM=logical memory; MCI=mild cognitive impairment; NAB=Neuropsychological Assessment Battery; NC=normal control; NR=not reported; NPV=negative predictive value; PPV=positive predictive value; RBANS= Repeatable Battery for the Assessment of Neuropsychological Status; SD=standard deviation; SE=sensitivity; SP=specificity; WMS=Wechsler Memory Scale; VR=visual reproduction

*indicates that values equal to or higher than the specified cutpoint indicate CATD

**indicates 2 standard deviations below the control mean

+indicates that some PPV and NPV values were back-calculated

Appendix Table C.5. Classification accuracy results for executive tests in eligible studies with low-moderate risk of bias

Executive Test	Author Year	CATD N	Comp Group	Comp N	Score (Subgroup)	Cut point	SE	SP	PPV+	NPV+	CATD Base Rate
Trail Making Test (TMT) part B	**Cahn 1995**[9]	45	NC	238	Time (sec)	173*	0.87	0.88	0.58	0.97	0.16
	Salmon 2002[54]	87	NC	87	Time (sec)	131*	0.85	0.83	0.83	0.85	0.50
	Ashendorf 2008[1]	57	MCI	200	Time (z score)	-1.0	0.53	0.57	0.26	0.81	0.22
	Ashendorf 2008[1]	57	MCI	200	Errors	1 error*	0.72	0.41	0.26	0.84	0.22
	Ashendorf 2008[1]	57	MCI	200	Errors (1) AND Time (-1.0 z)	1*, -1 z	0.44	0.67	0.27	0.81	0.22
	Ashendorf 2008[1]	57	MCI	200	Errors (1) AND/OR Time (-1.0 z)	1*, -1 z	0.81	0.31	0.25	0.85	0.22
Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Symbol	**Cahn 1995**[9]	45	NC	238	Total score	33	0.95	0.67	0.35	0.99	0.16
	Sunderaraman 2015[58]	107	NC	162	Row 1 Unique Designs	15	0.81	0.36	0.46	0.74	0.40

Executive Test	Author Year	CATD N	Comp Group	Comp N	Score (Subgroup)	Cut point	SE	SP	PPV+	NPV+	CATD Base Rate
Graphic Pattern Generation Test (GPGT)	**Sunderaraman 2015**[58]	107	NC	162	Row 1 Perseverations	4	0.76	0.37	0.44	0.70	0.40
Modified Wisconsin Card Sorting Test (WCST)	**Bondi 1993**[2]	87	NC	75	Categories	4	0.93	0.81	0.85	0.91	0.54
	Bondi 1993[2]	23	NC	75	Categories (mild CATD)	4	0.83	0.81	0.58	0.94	0.23
	Bondi 1993[2]	87	NC	75	Nonperseverative errors	16*	0.58	0.84	0.81	0.64	0.54
	Bondi 1993[2]	23	NC	75	Nonperseverative errors (mild CATD)	16*	0.48	0.84	0.48	0.84	0.23
	Bondi 1993[2]	87	NC	75	Perseverative errors	6*	0.76	0.93	0.93	0.77	0.54
	Bondi 1993[2]	23	NC	75	Perseverative errors (mild CATD)	6*	0.74	0.93	0.77	0.92	0.23

Abbreviations: CATD=Clinical Alzheimer's-type dementia; Comp=comparator; GPGT=Graphic Pattern Generation Test; MCI=mild cognitive impairment; NC=normal control; NPV=negative predictive value; PPV=positive predictive value; SE=sensitivity; SP=specificity; TMT=Trail Making Test; WAIR-R=Wechsler Adult Intelligence Scale-Revised; WCST=Wisconsin Card Sorting Test*indicates that values equal to or higher than the specified cutpoint indicate CATD

+indicates that some PPV and NPV values were back-calculated

Appendix Table C.6. Classification accuracy results for language tests in eligible studies with low-moderate risk of bias

Language Test	Author Year	CATD N	Comp Group	Comp N	Score (Subgroup)	Cut point	SE	SP	PPV+	NPV+	CATD Base Rate
Semantic (Category) Verbal Fluency (SVF)	**Welsh 1991, 1992**[65, 66]	49	NC	49	Animals (mild CATD)	9	0.35	1.00	1.00	0.61	0.50
	Welsh 1991, 1992[65, 66]	49	NC	49	Animals (moderate CATD)	9	0.49	1.00	1.00	0.66	0.50
	Welsh 1991, 1992[65, 66]	49	NC	49	Animals (severe CATD)	9	0.94	1.00	1.00	0.94	0.50
	Connor 2005[18]	50	NC	50	Animals	12	0.88	0.86	0.86	0.88	0.50
	Connor 2005[18]	10	NC	50	Animals (DRS 101-105)	12	0.90	0.86	0.56	0.98	0.17
	Connor 2005[18]	10	NC	50	Animals (DRS 106-110)	12	1.00	0.86	0.59	1.00	0.17
	Connor 2005[18]	10	NC	50	Animals (DRS 111-115)	12	1.00	0.86	0.59	1.00	0.17
	Connor 2005[18]	10	NC	50	Animals (DRS 116-120)	12	0.70	0.86	0.50	0.93	0.17
	Connor 2005[18]	10	NC	50	Animals (DRS 121-125)	12	0.40	0.86	0.36	0.88	0.17
	Monsch 1992[46]	89	NC	53	Animals	13	0.92	0.94	0.96	0.88	0.63
	Canning 2004[11]	37	NC	46	Animals (mild CATD)	13	0.73	1.00	1.00	0.82	0.45
	Canning 2004[11]	98	NC	46	Animals	14	0.87	0.96	0.98	0.78	0.68
	Monsch 1992[45]	21	NC	53	Animals (mild CATD)	16	0.95	0.79	0.64	0.98	0.28
	Monsch 1992[45]	89	NC	53	First names	15	0.94	0.87	0.92	0.90	0.63
	Monsch 1992[45]	21	NC	53	First names (mild CATD)	17	0.91	0.83	0.68	0.96	0.28
	Monsch 1992[45]	43	NC	17	First names (males)	12	0.84	0.94	0.97	0.70	0.72
	Monsch 1992[45]	46	NC	36	First names (females)	16	0.96	0.92	0.94	0.94	0.56
	Monsch 1992[45]	89	NC	53	Fruits	10	0.96	0.89	0.93	0.92	0.63
	Monsch 1992[45]	21	NC	53	Fruits (mild CATD)	10	0.91	0.89	0.76	0.96	0.28
	Monsch 1992[45]	89	NC	53	Vegetables	9	0.96	0.87	0.92	0.92	0.63
	Monsch 1992[45]	21	NC	53	Vegetables (mild CATD)	10	1.00	0.79	0.66	1.00	0.28
	Monsch 1992[45]	89	NC	53	Supermarket	15	0.92	0.96	0.98	0.88	0.63
	Monsch 1992[45]	21	NC	53	Supermarket (mild CATD)	15	0.76	1.00	0.89	0.91	0.28
	Monsch 1992[45]	43	NC	17	Supermarket (males)	14	0.93	0.94	0.98	0.84	0.72
	Monsch 1992[45]	46	NC	36	Supermarket (females)	16	0.94	0.97	0.98	0.92	0.56

Language Test	Author Year	CATD N	Comp Group	Comp N	Score (Subgroup)	Cut point	SE	SP	PPV+	NPV+	CATD Base Rate
	Kalbe 2004[31]	88	NC	97	Supermarket	?	0.92	0.81	0.81	0.92	0.48
	Cerhan 2002[12]	40	NC	221	Total (animals, fruits, vegetables)	28	0.93	0.89	0.60	0.98	0.15
	Monsch 1992[45]	89	NC	53	Total (animals, fruits, vegetables)	37	1.00	0.93	0.96	1.00	0.63
	Salmon 2002[54]	95	NC	95	Total (animals, fruits, vegetables)	37	0.96	0.88	0.89	0.96	0.50
	Monsch 1992[45]	21	NC	53	Total (animals, fruits, vegetables; mild AD)	37	1.00	0.92	0.82	1.00	0.28
	Monsch 1992[45]	43	NC	17	Total (animals, fruits, vegetables; males)	24	0.84	1.00	1.00	0.71	0.72
	Monsch 1992[45]	36	NC	46	Total (animals, fruits, vegetables; females)	37	1.00	1.00	1.00	1.00	0.44
	Cahn 1995[9]	45	NC	238	Total Category (unspecified)	31	0.90	0.83	0.50	0.98	0.16
	Clark 2014[16]	41	NC	44	Combined correct, perservations, intrusions	NR	0.90	0.89	0.88	0.91	0.48
	Clark 2014[16]	41	NC	44	Combined correct, perseverations, intrusions, clustering, switching, ICA component scores	NR	0.93	0.95	0.95	0.94	0.48
Phonemic (Letter) Verbal Fluency (PVF)	**Monsch 1992**[45]	89	NC	53	A words	6	0.72	0.93	0.94	0.66	0.63
	Monsch 1992[45]	21	NC	53	A words (mild CATD)	11	0.86	0.59	0.45	0.91	0.28
	Canning 2004[11]	98	NC	46	A words	12	0.76	0.74	0.86	0.59	0.68
	Monsch 1992[45]	89	NC	53	F words	8	0.79	0.87	0.91	0.71	0.63
	Monsch 1992[45]	21	NC	53	F words (mild CATD)	8	0.67	0.87	0.67	0.87	0.28
	Monsch 1992[45]	89	NC	53	S words	10	0.87	0.87	0.92	0.79	0.63
	Monsch 1992[45]	21	NC	53	S words (mild CATD)	10	0.67	0.87	0.67	0.87	0.28
	Cerhan 2002[12]	40	NC	221	Total (C, F, L)	25	0.73	0.78	0.37	0.94	0.15
	Monsch 1992[45]	89	NC	53	Total (F, A, S)	29	0.87	0.92	0.95	0.81	0.63
	Monsch 1992[45]	89	NC	53	Total (F, A, S)	30	0.89	0.85	0.91	0.82	0.63
	Monsch 1992[45]	21	NC	53	Total (F, A, S; mild CATD)	31	0.81	0.83	0.65	0.92	0.28
	Monsch 1992[45]	43	NC	17	Total (F, A, S; males)	27	0.81	0.88	0.95	0.65	0.72
	Cahn 1995[9]	45	NC	238	Total Letter (unspecified)	30	0.76	0.69	0.32	0.94	0.16

Language Test	Author Year	CATD N	Comp Group	Comp N	Score (Subgroup)	Cut point	SE	SP	PPV+	NPV+	CATD Base Rate
Combined Semantic and Phonemic Verbal Fluency	**Cahn 1997[8]**	38	NC	236	Intrusion error proportion	1*	0.39	0.87	0.33	0.90	0.14
	Cahn 1997[8]	38	NC	236	Preservative error proportion	2*	0.67	0.52	0.18	0.90	0.14
	Canning 2004[11]	98	NC	46	Difference (animal - letter F)	0	0.53	0.96	0.97	0.49	0.68
Boston Naming Test (BNT 15-item)	**Welsh 1991, 1992[65, 66]**	49	NC	49	Total score (Mild CATD)	13	0.53	0.92	0.87	0.66	0.50
	Welsh 1991, 1992[65, 66]	49	NC	49	Total score (Moderate CATD)	13	0.55	0.92	0.87	0.67	0.50
	Welsh 1991, 1992[65, 66]	49	NC	49	Total score (Severe CATD)	13	0.84	0.92	0.91	0.85	0.50
Boston Naming Test (BNT 30-item)	**Cahn 1995[9]**	45	NC	238	Total score	22	0.75	0.85	0.49	0.95	0.16
	Cahn 1997[8]	38	NC	236	Semantic naming errors	1*	0.50	0.72	0.22	0.90	0.14
	Cahn 1997[8]	38	NC	236	Lexical naming errors	1*	0.74	0.70	0.28	0.94	0.14
	De Jager 2003[19]	36	MCI	27	Total score	21	0.64	0.81	0.82	0.63	0.57

Abbreviations: BNT=Boston Naming Test; CATD=Clinical Alzheimer's-type dementia; Comp=comparator; DRS=dementia rating scale; ICA=independent component analysis; MCI=mild cognitive impairment; NC=normal control; NR=not reported; NPV=negative predictive value; PPV=positive predictive value; PVF=phonemic verbal fluency; SE=sensitivity; SP=specificity; SVF=semantic verbal fluency

*indicates that values equal to or higher than the specified cutpoint indicate CATD

+indicates that some PPV and NPV values were back-calculated

Appendix Table C.7. Classification accuracy results for combination cognitive tests in eligible studies with low-moderate risk of bias

Combination Cognitive Test	Author Year	CATD N	Comp Group	Comp N	Score (Subgroup)	Cut Point	SE	SP	PPV+	NPV+	CATD Base Rate
Supplementing the MMSE	**Brodaty 1997**[5]	28	NC	28	MMSE, CD (Shulman)	Fail both (23, 3*)	0.40	1.00	1.00	0.63	0.50
	Brodaty 1997[5]	28	NC	28	MMSE, CD (Sunderland)	Fail both (23, 8)	0.50	1.00	1.00	0.67	0.50
	Brodaty 1997[5]	28	NC	28	MMSE, CD (Wolf-Klein)	Fail both (23, 8)	0.36	1.00	1.00	0.61	0.50
	Brodaty 1997[5]	28	NC	28	MMSE, CD (Shulman)	Fail either (23, 3*)	0.96	0.96	0.96	0.96	0.50
	Brodaty 1997[5]	28	NC	28	MMSE, CD (Sunderland)	Fail either (23, 8)	0.86	0.96	0.96	0.87	0.50
	Brodaty 1997[5]	28	NC	28	MMSE, CD (Wolf-Klein)	Fail either (23, 8)	0.86	1.00	1.00	0.88	0.50
	Galasko 1990[23]	50	NC	74	MMSE, PVF (FAS)	NR	1.00	0.99	0.98	1.00	0.40
	Galasko 1990[23]	24	NC	74	MMSE, PVF (FAS)	NR	0.88	0.99	0.95	0.96	0.24
Other Test Combinations	**Cahn 1997**[8]	38	NC	236	Errors/intrusions (SVF, PVF, BNT-30, CERAD List)	>0.5 (logistic equation cutoff)	0.29	0.98	0.70	0.90	0.14
	Cahn 1995[9]	28	NC	233	TMT-B, CERAD List, BNT-30, WMS VR	>0.5 (logistic equation cutoff)	0.82	0.98	0.83	0.98	0.11
	Cahn 1995[9]	28	NC	233	TMT-B, CERAD List, BNT-30, WMS VR (+ age)	>0.5 (logistic equation cutoff)	0.79	0.97	0.76	0.97	0.11
	Salmon 2002[54]	93	NC	16	SVF, WMS VR	Fail both (39.5, 8.5)	0.96	0.93	0.99	0.80	0.85
	Salmon 2002[54]	93	NC	16	SVF, DRS total	Fail both (39.5, 132.5)	0.95	0.94	0.99	0.76	0.85
	Grober 2008[27]	34	NC	261	MIS, SVF animals	Fail either (4, 9)	0.91	0.81	0.38	0.99	0.12
	Storandt 1989[57]	66	NC	83	WMS LM, WAIS DSy, BNT 60-item	≥0 (canonical variate)	0.95	1.00	1.00	0.96	0.44
	Gomez 2006[25]	77	NC	76	WMS LM, WAIS DSy, BNT 60-item	NR	0.68	0.74	0.73	0.70	0.50
	Gomez 2006[25]	77	NC	76	WMS LM, SVF animals	NR	0.78	0.74	0.75	0.77	0.50
	Welsh 1992[66]	49	NC	49	CERAD List DR, BNT-15	NR	0.90	0.92	0.92	0.90	0.50
	Petersen 1994[50]	106	NC	106	WAIS-R Moans PIQ and FCSRT FR trials total	NR	0.93	0.93	0.93	0.93	0.50

Abbreviations: BNT=Boston Naming Test; CERAD= Consortium to Establish a Registry for Alzheimer's Disease; CATD=Clinical Alzheimer's-type dementia; CD=clock drawing; Comp=comparator; DR=delayed recall; DRS=dementia rating scale; DSy=Digit Symbol; FCSRT=Free and Cued Selective Reminding Test; FR=free recall; LM=logical memory; MCI=mild cognitive impairment; MIS=Memory Impairment Screen; MMSE=Mini Mental State Examination; NC=normal control; NR=not reported; NPV=negative predictive value; PIQ=performance intelligence quotient; PPV=positive predictive value; PVF=phonemic verbal fluency; SE=sensitivity; SP=specificity; SVF=semantic verbal

fluency; WAIS=Wechsler Adult Intelligence Scale; WMS=Wechsler Memory Scale; VR=visual reproduction; VRT=visual reproduction test
*indicates that values equal to or higher than the specified cut point indicate CATD
+indicates that some PPV and NPV values were back-calculated

Appendix Table C.8. Cognitive studies: Participant characteristics by diagnostic group in eligible cognitive studies with low-medium risk of bias

Study	N	CATD		NC		MCI		Cognitive Tests
Ashendorf 2008[1]	257	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	79.7 14.6 58% 77% (all subjects) NINCDS-ADRDA 24.2 ≥1.0	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	72.5 14.6 41% 77% (all subjects) Petersen criteria 28.1 NR	TMT B
Bondi 1993[2]	162	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	72.2 13.0 47% NR NINCDS-ADRDA 20.7 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	71.1 13.7 36% NR Self-Report 28.9 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	WCST
Brodaty 1997[5]	56	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	73.1 8.7 32% NR DSM-III-R, NINCDS-ADRDA 19.5 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	69.5 11.3 25% NR Unclear 28.7 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	CD MMSE & CD
Brown 2009[6]	376	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	69 NR NR NR NINCDS-ADRDA 22.5 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NR (age-matched) NR NR NR Medical history NR NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	TYM
Buschke 1999[7]	472	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	81.1 11.3 33% 81% (all subjects) DSM-III-R, NINCDS-ADRDA NR NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	79.3 12.2 36% 81% (all subjects) Diagnostic workup NR NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	MIS
Cahn 1995, 1996, 1997[8-10]	283	Age (yrs) Education (yrs)	83.6 13.8	Age (yrs) Education (yrs)	78.4 13.8	Age (yrs) Education (yrs)	NA NA	CD CERAD List

Study	N	CATD		NC		MCI		Cognitive Tests
		Gender (% male) Race (% white) Dx Criteria MMSE CDR	60% NR NINCDS-ADRDA NR NR	Gender (% male) Race (% white) Dx Criteria MMSE CDR	41% NR Diagnostic Workup NR NR	Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA	WMS VR WAIS DSy TMT B BNT PVF, SVF Combinations
Canning 2004[11]	144	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	73 13.6 NR NR NINCDS-ADRDA 23 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	70.1 15 NR NR normal cognitive testing, MRI 28.7 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	PVF, SVF
Cerhan 2002[12]	261	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	77.3 12.4 43% NR NINCDS-ADRDA NR NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	76.1 13.7 41% NR Diagnostic Workup NR NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	PVF, SVF
Chandler 2005[13]	250	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	74.4 13.6 39% 100% NINCDS-ADRDA 21.1 1	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	74.2 15.3 40% 100% 28.6 0	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	72.8 14.8 48% 100% Petersen criteria 27.5 NR	MMSE CERAD TS CERAD List
Chapman 2010[14]	133	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	75.8 14.3 56% NR DSM-IV-TR, NINCDS-ADRDA 24.3 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	70.3 15.9 40% NR Physician assessment 28.64 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	MMSE
Clark 2010[15]	117	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria	76.2 12.8 37% 91% (all subjects) NINCDS-ADRDA	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria	NA NA NA NA NA	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria	74.8 13.9 34% 91% (all subjects) Diagnostic Workup	RBANS List RBANS Story

Study	N	CATD		NC		MCI		Cognitive Tests
		MMSE CDR	21.79 4.4 (sum of boxes)	MMSE CDR	NA NA	MMSE CDR	27 1.4 (sum of boxes)	
Clark 2014[16]	85	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	72.5 14 63% NR NINCDS-ADRDA 24.3 4.0 (SOB)	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	70.5 14.4 32% NR Diagnostic workup 29.3 0.2 (SOB)	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	SVF
Connor 2005[18]	100	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	73.3 12.6 NR NR NINCDS-ADRDA 21.3 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	73.7 13.1 NR NR Diagnostic Workup 28.92 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	CD SVF
De Jager 2003[19]	84	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	77 12 (all subjects) 55% NR NINCDS-ADRDA 21 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	76 12 (all subjects) 41% NR Petersen criteria 28 NR	CLOX HVLT BNT TPT
Elamin 2016[20]	59	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	62.6 46.7%<16, 26.7% 16-18, 16.7%>18 48.4% NR Full diagnostic workup NR NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	66.6 53.6%<16, 42.9% 16-18, 3.6%>18 57.1% NR NR NR NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	ACE-III
Esteban-Santillas 1998[21]	80	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	72 14 ~50% NR NINCDS-ADRDA NR 1	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	72 14 ~50% NR Screening test and staging NR 0	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	CD
	148	Age (yrs)	71.3	Age (yrs)	69.7	Age (yrs)	NA	

Study	N	CATD		NC		MCI		Cognitive Tests
Galasko 1990[23]		Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	14.2 47% NR NINCDS-ADRDA 20.47 NR	Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	14.5 37% NR Diagnostic workup 29 NR	Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA	MMSE MMSE & PVF
Gavett 2009[24]	153	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	80.6 14.7 58% 89% NINCDS-ADRDA 23.1 1.21	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	71.5 16.5 67% 83% Diagnostic Workup 29.6 0.0	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	76.1 14.7 45% 83% Diagnostic Workup 28 0.3	NAB List
Gomez 2006[25]	153	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	76.8 14.3 47% 93% (all subjects) NINCDS-ADRDA, DSM III-R NR 0.5	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	77 14.9 42% 93% (all subjects) CDR NR 0	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	Combination (WMS LM, WAIS digit symbol, BNT) Combination (WMS LM, SVF)
Grober 2008}[26]	318	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	65+ NR NR African American and Caucasian patients DSM-IV, neurologist dx 18+ Most 0.5	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	65+ NR NR African American and Caucasian patients Neuropsychological evaluation NR NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	FCSRT free recall, FCSRT total recall
Grober 2008[27]	295	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE	NR for CATD NR for CATD NR for CATD African American and Caucasian patients DSM-IV and NINCDS-ADRDA 18+	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE	78.2 12.9 18% African American and Caucasian patients Diagnostic battery, informant responses 27.4	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE	NA NA NA NA NA NA	Combination (MIS or SVF)

Study	N	CATD		NC		MCI		Cognitive Tests
		CDR	NR for CATD	CDR	0	CDR	NA	
Hollocks 2018[29]	102	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	73.4 NR 49% NR DSM-IV and ICD-10 22.0 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	73.3 NR 49% NR Medical history 28.3 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	BMET
Johnson 2003[30]	242	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	74.3 (both cohorts) 12.9 (both cohorts) 45% (cohort 1) NR DSM-IV (cohort 1); DSM-III-R and NINCDS-ADRDA (cohort 2) NR 0.5 (both cohorts)	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	76.7 (both cohorts) 14.1 (both cohorts) 28% (cohort 1) NR Neuro exam (both cohorts) NR 0.0 (both cohorts)	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	WMS LM
Kalbe 2004[31]	185	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	73.3 9.8 40% NR NINCDS-ADRDA 24.1 1.0-2.0	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	70.2 11.4 28% NR Diagnostic Workup 28.5 0	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	MMSE DemTect List SVF
Knopman 1989[32]	83	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	74 14 36% NR NINCDS-ADRDA 23.4 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	73.5 12 45.5% NR Self-Report 28.7 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	DWR List
Kuslansky 2002[33]	240	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	77.2 11.6 43% 61% DSM-III-R, NINCDS-ADRDA NR 1.2	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	78.9 12.6 35% 73% Diagnostic workup NR 0.2	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	MIS

Study	N	CATD		NC		MCI		Cognitive Tests
Kuslansky 2004[34]	380	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	81.7 11.8 33% 65% NINCDS-ADRDA 22.4 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	78.6 12.9 40% 65% Self-report 26.1 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	MMSE HVLT List
Lange 2006[35]	68	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	73 14.5 55.9% 91.2% NINCDS-ADRDA 18-23 (or >95 DRS) NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	72.9 14.2 55.9% 91.2% Diagnostic workup NR NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	WMS-III GMI, WMS-III IMI, WMS-III DMI, WAIS-III GAI
Lee 1996[36]	60	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	72.4 NR 33% NR NINCDS-ADRDA 20.9 0.98	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	67.7 NR 36% NR Self-Report 27.9 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	CD
Loewenstein 2001[38]	412	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	77.7 12.1 35% NR NINCDS-ADRDA >18 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	73.8 14.1 38% NR Diagnostic Workup ≥24 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	FOME
Logsdon 1989[37]	98	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	70 14 53% NR NINCDS-ADRDA, DSM III 23 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	68 14 43% NR Diagnostic workup 30 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	WAIS-R Fuld Profile
Maruff 2013[40]	710	Age (yrs) Education (yrs) Gender (% male) Race (% white)	79.3 Median 12 49% NR	Age (yrs) Education (yrs) Gender (% male) Race (% white)	69.5 Median 12 42% NR	Age (yrs) Education (yrs) Gender (% male) Race (% white)	NA NA NA NA	CBB

Study	N	CATD		NC		MCI		Cognitive Tests
		Dx Criteria MMSE CDR	NINCDS-ADRDA 19.8 5.9 (sum of boxes)	Dx Criteria MMSE CDR	Neuropsych testing 28.7 0	Dx Criteria MMSE CDR	NA NA NA	
Mendez 1992[42]	72	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	70.7 12 39% NR NINCDS-ADRDA 13-23 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	69.3 12.1 38% NR Medical history, cognitive screening ≥28 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	CD
Mendiondo 2003[43]	1,534	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	72.8 (CERAD) 62.1 (UK-ADRC) 13.4 (CERAD) 12.9 (UK-ADRC) 41% (CERAD) 28.4% (UK-ADRC) 87% (CERAD) 98.4% (UK-ADRC) NINCDS-ADRDA (CERAD) NR (UK-ADRC) 22.6 (CERAD) NR (UK-ADRC) NR (CERAD) 0.5 or 1.0 (UK-ADRC)	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	68.6 (CERAD) 73.1 (UK-ADRC) 13.8 (CERAD) 15.8 (UK-ADRC) 34% (CERAD) 36.6% (UK-ADRC) 94% (CERAD) 98.9% (UK-ADRC) No dementia dx, screen, no other neurological conditions (CERAD) Diagnostic workup (UK-ADRC) 28.9 (CERAD) NR (UK-ADRC) NR (CERAD) NR (UK-ADRC)	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	BAS
Millar 2017[44]	583	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	75.0 15.1 58% NR NINCDS-ADRDA 26.2 0.5	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	68.9 15.6 38% NR CDR 29 0	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	PDP memory task, FCSRT, WMS LM II
Monsch 1992[45]	142	Age (yrs) Education (yrs) Gender (% male)	72.1 13.5 48%	Age (yrs) Education (yrs) Gender (% male)	71.2 13.6 32%	Age (yrs) Education (yrs) Gender (% male)	NA NA NA	PVF, SVF

Study	N	CATD		NC		MCI		Cognitive Tests
		Race (% white) Dx Criteria MMSE CDR	98% DSM-III and NINCDS-ADRDA 18 NR	Race (% white) Dx Criteria MMSE CDR	98% Medical history 28.8 NR	Race (% white) Dx Criteria MMSE CDR	NA NA NA NA	
Monsch 1995[46]	641	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	74.2 (both cohorts) 13.2 (both cohorts) 50% (both cohorts) majority white (cohort 1) DSM-III and NINCDS-ADRDA (both cohorts) NR NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	75.9 (both cohorts) 14.2 (both cohorts) 41% (both cohorts) Majority white (cohort 1) Diagnostic workup (both cohorts) NR NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	DRS
Morgan 2010[48]	238	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	77.8 3.5* (3=12 years; 4=13-15 years) 37% 87% (all subjects) Cognitive scores 22.9 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	76.5 3.8* (3=12 years; 4=13-15 years) 37% 87% (all subjects) Self-Report NR NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	76.5 3.4* (3=12 years; 4=13-15 years) 37% 87% (all subjects) Petersen criteria 26.2 NR	RBANS
Parsey 2011[49]	66	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	74.1 15.7 61% NR NINCDS-ADRDA NR 1.0	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	70.5 16.2 39% NR Petersen criteria NR 0.5	CLOX
Petersen 1994[50]	212	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	80.7 11.8 NR NR NINCDS-ADRDA, DSM III-R 20.9 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	80.2 12.6 NR NR Diagnostic workup 28.5 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	Brief Battery (WIAS-R PIQ and FCSRT trials total free recall)
Quarmley 2017[51]	496	Age (yrs) Education (yrs)	NA (subsample data reported) NA	Age (yrs) Education (yrs)	NA (subsample data reported) NA	Age (yrs) Education (yrs)	NA (subsample data reported) NA	MoCA

Study	N	CATD		NC		MCI		Cognitive Tests
		Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA DSM-IV NA NA	Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA Diagnostic workup NA NA	Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA Petersen criteria NA NA	
Roalf 2017[53]	587	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	75.9 13.4 35% 71% DSM-IV-TR 20 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	70.3 17 33% 79% Diagnostic workup 29 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	73 14.7 48 78% Petersen criteria 26 NR	MoCA, MMSE
Salmon 2002[54]	196	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	71.6 14.2 49% NR DSM-III/DSM-III-R, NINCDS-ADRDA, pathological or clinical verification 25.6 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	AD Match (2 years) AD Match (3years) AD Match NR Diagnostic workup NR NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	DRS WMS LM WMS VR TMT B SVF Combinations
Solomon 1998[70]	120	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	77.6 13.3 33% NR NINCDS-ADRDA 21 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	77.5 14.4 35% NR Medical history, functionally independent 28.7 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	7MS
Springate 2014[56]	147	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	73.9 12.5 43% 94% NINCDS-ADRDA 23.1 0.9	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	72.9 13.3 43% 98% Diagnostic Workup 26.8 0.5	DRS
Storandt 1989[57]	149	Age (yrs) Education (yrs) Gender (% male)	72.2 12.8 (all subjects) 44%	Age (yrs) Education (yrs) Gender (% male)	71.6 12.8 (all subjects) 39%	Age (yrs) Education (yrs) Gender (% male)	NA NA NA	Combination (WMS LM,

Study	N	CATD		NC		MCI		Cognitive Tests
		Race (% white) Dx Criteria MMSE CDR	100% CDR and physician diagnosis NR 1.0	Race (% white) Dx Criteria MMSE CDR	100% CDR NR 0	Race (% white) Dx Criteria MMSE CDR	NA NA NA NA	WAIS DSy, BNT)
Sunderarama n 2015[58]	269	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	77.6 15.4 43% NR NINCDS-ADRDA ≥17 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	75.7 16.0 34% NR Interview, cognitive screen ≥27 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	GPGT
Thompson 2011[59]	183	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	73.5 11.7 58% NR NINCDS-ADRDA 22.3 4.9 (sum of boxes)	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	73.1 12.1 53% NR Cognitive testing, neuro exam 29.1 0 (sum of boxes)	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	Cogstate ISLT
Tremont 2011[60]	150	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	74.1 12.5 42% 94% NINCDS-ADRDA NR 0.5-1.0	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	72.9 13.3 42% 98% Diagnostic Workup NR 0.5	MCAS
Troster 1993[61]	127	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	72.9 13.2 47% NR NINCDS-ADRDA NR NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	74.4 13.5 41% NR Medical history NR NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	WMS LM & VR
Trzepacz 2015[62]	399	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE	77.6 15.8 67% NR NINCDS-ADRDA 20.3	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE	NA NA NA NA NA NA	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE	74.2 16.2 61% NR Petersen criteria 27.8	MoCA

Study	N	CATD		NC		MCI		Cognitive Tests
		CDR	0.5-1.0	CDR	NA	CDR	0.5	
Tuokko 1992[63]	120	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	70.6 10.7 33% NR DSM-III-R and NINCDS-ADRDA 15.5 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	71.3 13.1 40% NR Interview, medical questionnaire NR NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	CD
Uhlmann 1991[64]	209	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	76 (all subjects) 19% middle, 30% HS, 38% college, 13% graduate (all subjects) 42% (all subjects) 97% DSM-III, NINCDS/ADRDA 19 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	76 (all subjects) 19% middle, 30% HS, 38% college, 13% graduate (all subjects) 42% (all subjects) 95% Unclear 27 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	MMSE
Welsh 1991, 1992[65, 66]	196	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	71.1 13.8 51% NR NINCDS-ADRDA 20.0 1.3	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	71.1 14 51% NR Diagnostic Workup, free of cognitive impairment 28.9 0	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	CERAD List BNT SVF CERAD List & BNT
Wolf-Klein 1989[67]	251	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	79 NR 30% (all subjects) NR NINCDS-ADRDA 12.8 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	77 NR 30% (all subjects) NR Diagnostic Workup 27.7 NR	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria MMSE CDR	NA NA NA NA NA NA NA	CD
Zainal 2016[68]	269	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria	72.2 6.0 63% 77% Chinese NINCDS-ADRDA	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria	61.8 11.7 31% 90% Chinese Staging	Age (yrs) Education (yrs) Gender (% male) Race (% white) Dx Criteria	66.4 10.9 50% 89% Chinese Petersen criteria	ADAS-Cog ADAS-Cog List

Study	N	CATD		NC		MCI		Cognitive Tests
		MMSE CDR	22.3 0.5-1.0	MMSE CDR	29.1 0	MMSE CDR	27.4 0.5	

Abbreviations: ACE=Addenbrooke's Cognitive Examination; ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive subscale; BAS=Brief Alzheimer's Screen; BMET=Brief Memory and Executive Test; BNT=Boston Naming Test; CATD=clinical Alzheimer-type dementia; CBB=Cogstate Brief Battery; CD=Clock drawing; CDR=Clinical Dementia Rating; CERAD=Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery; DMI=Delayed Memory Index; DRS=Dementia Rating Scale; DSM=Diagnostic and Statistical Manual of Mental Disorders; DSy=Digit Symbol; FCSRT=Free and Cued Selective Reminding Test; FOME=Fuld Object Memory Evaluation; GAI=General Ability Index; GMI=General Memory Index; GPGT=Graphic Pattern Generation Test; HS=high school; HVLT=Hopkins Verbal Learning Test; IMI=Immediate Memory Index; ISLT=International Shopping List Test; LM=Logical Memory; MCAS=Minnesota Cognitive Acuity Screen; MCI=Mild Cognitive Impairment; MIS=Memory Impairment Screen; MMSE=Mini-Mental State Examination; MoCA=Montreal Cognitive Assessment; NA=not applicable; NAB=Neuropsychological Assessment Battery; NC=normal cognition; NINCDS-ADRDA=National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders; NR=not reported; PDP=Process Dissociation Procedure; PIQ=Performance Intelligent Quotient; PVF=phonemic verbal fluency; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status; SVF=semantic verbal fluency; TMT B=Trail Making Test Part B; TPT=The Placing Test; TYM=Test Your Memory; VR=visual reproduction; WAIS=Wechsler Adult Intelligence Scale; WCST=Wisconsin Card Sorting Test; WMS=Wechsler Memory Scale

Appendix Table C.9. Brief cognitive tests and scores represented in extracted studies with low-moderate risk of bias

Test, estimated administration time	Score	Range*	Better performance
7 Minute Screen (7MS), 5-10 min	Total score	0-no ceiling	Higher
Addenbrooke's Cognitive Exam (ACE), 15-20 min	Total score	0-100	Higher
Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog), 30 min	11-item total score	0-70	Lower
	12-item total score	0-80	Lower
	12-item list learning score	0-32	Lower
Boston Naming Test (BNT)	15-item total score, 5-10 min	0-15	Higher
	30-item total score, 15 min	0-30	Higher
	30-item semantic errors	0-30	Lower
	30-item lexical errors	0-30	Lower
Brief Alzheimer's Screen (BAS), < 5 min	Total score	0-no ceiling	Higher
Brief Memory and Executive Test (BMET), 10 min	Total score	0-16	Higher
Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery, 30 min	CERAD total score, 20 min	0-100	Higher
	List learning delayed recall	0-10	Higher
	List learning % retention (savings)	0-100	Higher
	List learning recognition scores	Varies	Higher
	List learning intrusion scores	Varies	Lower
Clock Drawing, multiple versions, 5 min	Rouleau quantitative scale	10	Higher
	Sunderland	10	Higher
	Mendez	20	Higher
	Shulman	5	Higher
	Tuokko	--	Lower
	Watson	0-7	Lower

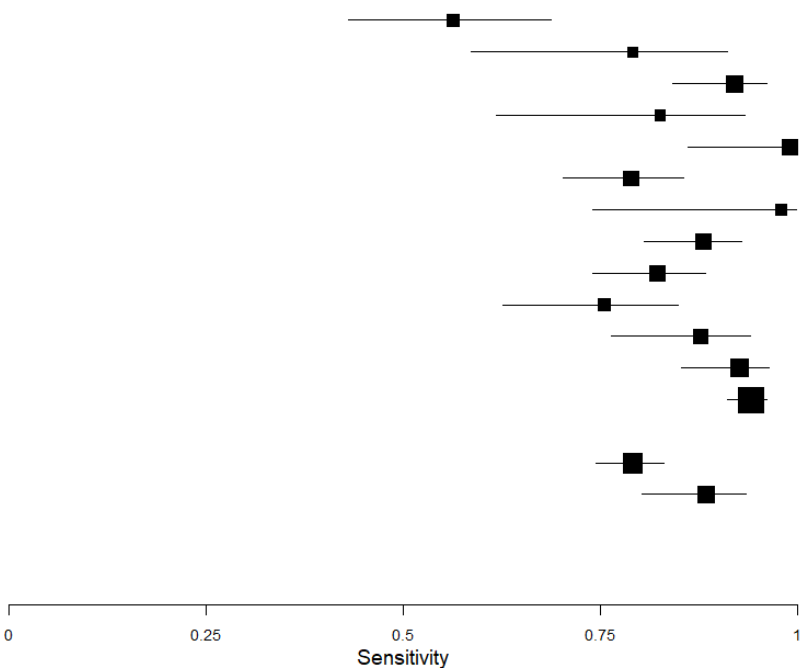
Test, estimated administration time	Score	Range*	Better performance
	Wolf-Klein	10	Higher
	CLOX 1 (draw)	15	Higher
	CLOX 2 (copy)	15	Higher
Cogstate Brief Battery (CBB), 15 min	Learning & Working Memory composite	M 100 ±10	Higher
	Attention & Psychomotor composite	M 100 ±10	Higher
Cogstate International Shopping List Test (ISLT), 20-25 min	Trials total	0-36	Higher
	Delayed recall	0-12	Higher
Dementia Rating Scale (DRS), multiple versions, 30 min	Total score	0-144	Higher
	Attention	0-37	Higher
	Initiation/Perseveration	0-37	Higher
	Construction	0-6	Higher
	Conceptualization	0-39	Higher
	Memory	0-25	Higher
Delayed Word Recall (DWR), 5-10 min	Total score	0-10	Higher
DemTect, 8-10 min	Delayed recall	0-18	Higher
Free and Cued Selective Reminding (FCSR), 15 min	Free recall	0-48	Higher
	Total recall	0-48	Higher
Fuld Object Memory Evaluation (OME), 15 min	3 trials total	0-30	Higher
Graphic Pattern Generation (GPG)	Row 1 perseverations	0-9	Lower
	Row 1 unique designs	0-10	Higher
Hopkins Verbal Learning Test (HVLT), multiple versions, 30+ min	Trials total, 10-15 min	0-36	Higher
Memory Impairment Screen (MIS), < 5 min	Total score	0-8	Higher
Mini-Mental State Exam (MMSE), 5-10 min	Total score	0-30	Higher
Minnesota Cognitive Acuity Screen (MCAS), 15 min	Total score	0-no ceiling	Higher
Montreal Cognitive Assessment (MoCA), 10 min	Total score	0-30	Higher
Neuropsychological Assessment Battery (NAB) List Learning subtest, 20-25 min	List A immediate recall	M 50 ±10	Higher
	List B immediate recall	M 50 ±10	Higher
	List A short delayed recall	M 50 ±10	Higher
	List A long delayed recall	M 50 ±10	Higher
Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), 30 min	Verbal index	M 100 ±15	Higher
	Visual index	M 100 ±15	Higher
	% Retention scores (savings)	0-100	Higher
Test Your Memory (TYM), < 5 min (scoring time)	Total score	0-50	Higher

Test, estimated administration time	Score	Range*	Better performance
Trail Making Test (TMT), part B, 5 min	TMT B time (seconds)	0-300	Lower
	TMT B errors	0-5	Lower
Wechsler Adult Intelligence Scale (WAIS), multiple versions	Fuld profile, 30 min	Yes/No	--
	Digit Symbol total, < 5 min	Varies	Higher
Wechsler Memory Scale (WMS), multiple versions, 30-40 min	General Memory index	M 100 ±15	Higher
	Immediate Memory index	M 100 ±15	Higher
	Delayed Memory index	M 100 ±15	Higher
	Logical Memory I & II	Varies	Higher
	Visual Reproduction I & II	Varies	Higher
	% Retention scores (savings)	0-100	Higher
	Intrusion error scores	0-no ceiling	Lower
Wisconsin Card Sorting Test (WCST), 20-30 min	Categories achieved	0-6	Higher
	Perseverative errors	count or %	Lower
	Non-perseverative errors	count or %	Lower
The Placing Test, 6 min	Total score	0-20	Higher
	Objects	0-10	Higher
	Faces	0-10	Higher
Verbal fluency, < 5 min	Semantic (category)	0-no ceiling	Higher
	Phonemic (letter)	0-no ceiling	Higher

* Scores presented as M ±SD indicate a normed score with a known distribution (Standard score, T score, etc.)

Figure C.1. Sensitivity results of MMSE in eligible studies with low-moderate risk of bias

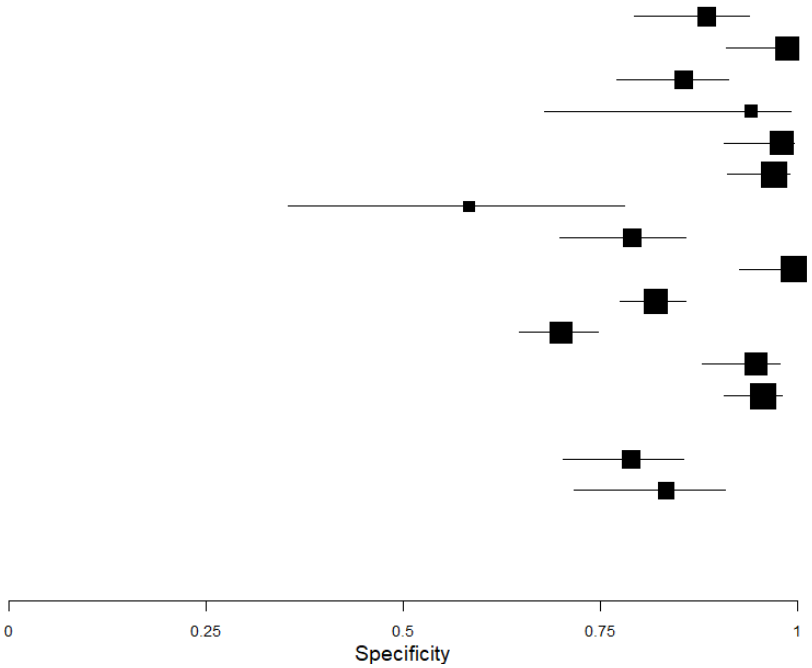
Studies	Estimate (95% C.I.)	TP/(TP + FN)
CATD vs. NC		
NR; Chapman 2010	0.564 (0.431, 0.688)	31/55
NR [Mild CATD]; Galasko 1990	0.792 (0.587, 0.911)	19/24
21; Kalbe 2004	0.920 (0.842, 0.962)	81/88
21 [Middle School]; Uhlmann 1991	0.826 (0.618, 0.933)	19/23
23 [Moderate CATD]; Galasko 1990	0.990 (0.862, 0.999)	50/50
23 [High school educated]; Uhlmann 1991	0.789 (0.702, 0.856)	86/109
24 [Middle School]; Uhlmann 1991	0.979 (0.741, 0.999)	23/23
24 [High school educated]; Uhlmann 1991	0.881 (0.805, 0.929)	96/109
24 [College educated]; Uhlmann 1991	0.823 (0.740, 0.883)	90/109
24; Kuslansky 2004	0.754 (0.627, 0.849)	43/57
25; Kuslansky 2004	0.877 (0.764, 0.940)	50/57
26; Chandler 2005	0.926 (0.853, 0.964)	88/95
27, Roalf 2017	0.941 (0.911, 0.962)	320/340
CATD vs. MCI		
18; Roalf 2017	0.791 (0.745, 0.831)	269/340
25; Chandler 2005	0.884 (0.803, 0.935)	84/95



Abbrevations: CATD=Clinical Alzheimer's type dementia; MCI=mild cognitive impairment; MMSE=Mini Mental State Examination; NC=normal control; OS=optimal score

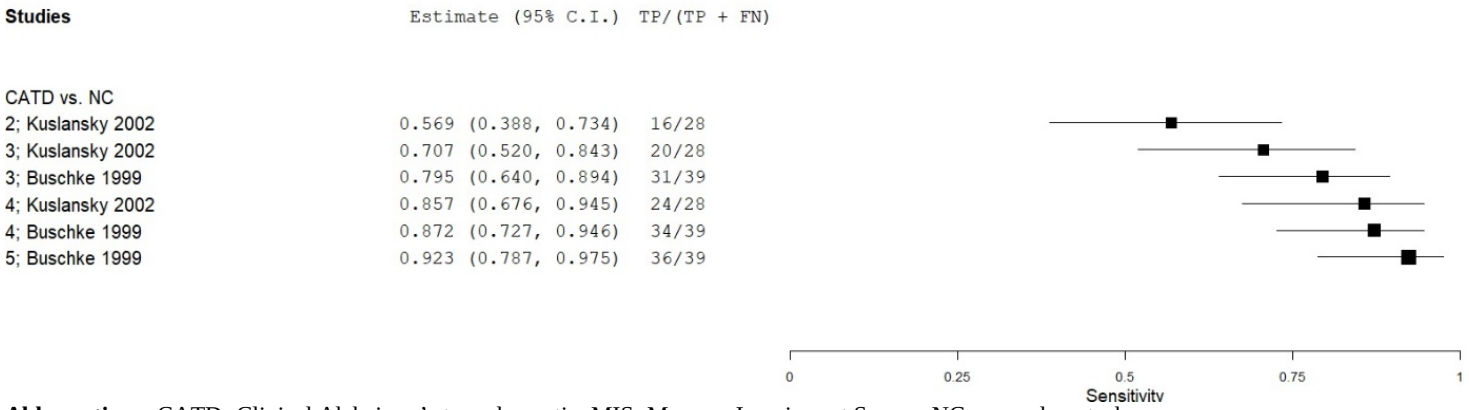
Figure C.2. Specificity results of MMSE in eligible studies with low-moderate risk of bias

Studies	Estimate (95% C.I.)	TN/(FP + TN)
CATD vs. NC		
NR; Chapman 2010	0.885 (0.793, 0.939)	69/78
NR [Mild CATD]; Galasko 1990	0.986 (0.910, 0.998)	73/74
21; Kalbe 2004	0.856 (0.771, 0.913)	83/97
21 [Middle School]; Uhlmann 1991	0.941 (0.680, 0.992)	16/17
23 [Moderate CATD]; Galasko 1990	0.980 (0.907, 0.996)	73/74
23 [High school educated]; Uhlmann 1991	0.970 (0.911, 0.990)	97/100
24 [Middle School]; Uhlmann 1991	0.583 (0.354, 0.781)	10/17
24 [High school educated]; Uhlmann 1991	0.790 (0.699, 0.859)	79/100
24 [College educated]; Uhlmann 1991	0.995 (0.926, 1.000)	100/100
24; Kuslansky 2004	0.820 (0.775, 0.859)	265/323
25; Kuslansky 2004	0.700 (0.647, 0.747)	226/323
26; Chandler 2005	0.947 (0.880, 0.978)	90/95
27, Roalf 2017	0.957 (0.907, 0.980)	132/138
CATD vs. MCI		
18; Roalf 2017	0.789 (0.702, 0.856)	86/109
25; Chandler 2005	0.833 (0.717, 0.908)	50/60



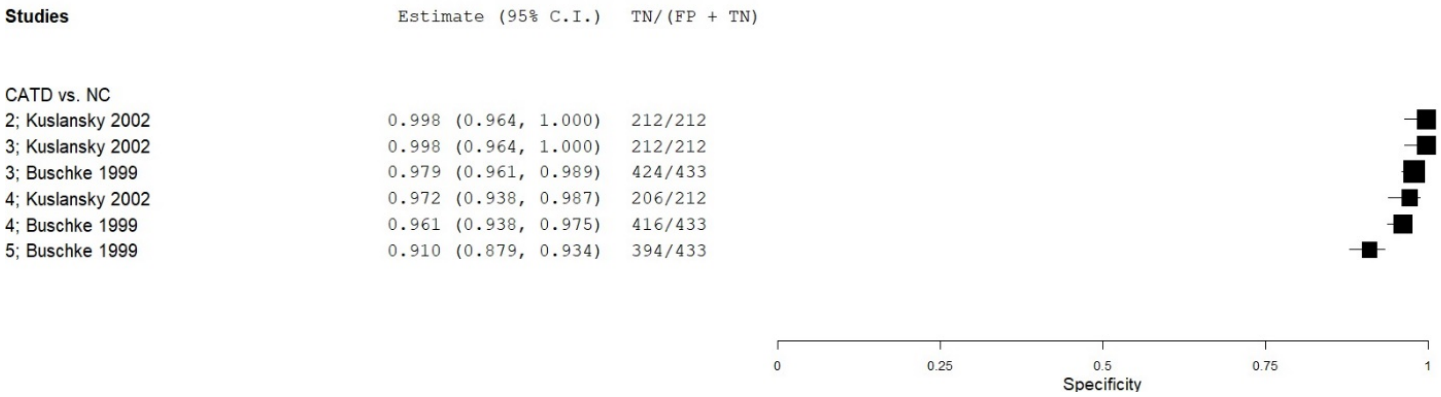
Abbrevations: CATD=Clinical Alzheimer's type dementia; MCI=mild cognitive impairment; MMSE=Mini Mental State Examination; NC=normal control; OS=optimal score

Figure C.3. Sensitivity results of MIS in eligible studies with low-moderate risk of bias



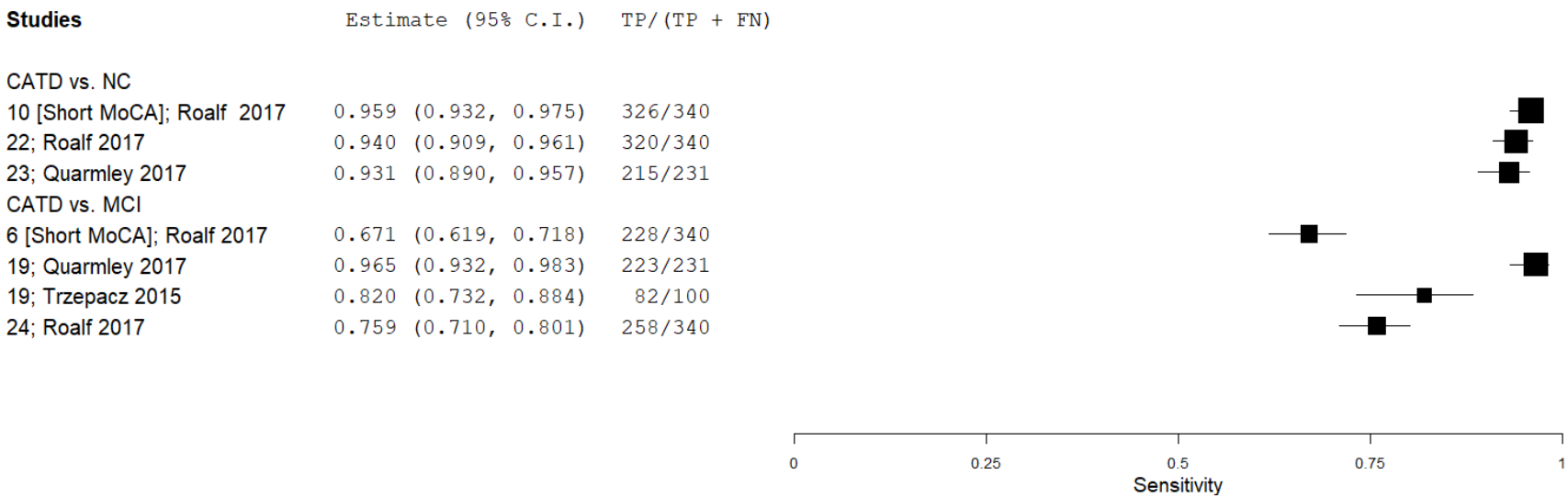
Abbrevations: CATD=Clinical Alzheimer's type dementia; MIS=Memory Impairment Screen; NC=normal control

Figure C.4. Specificity results of MIS in eligible studies with low-moderate risk of bias



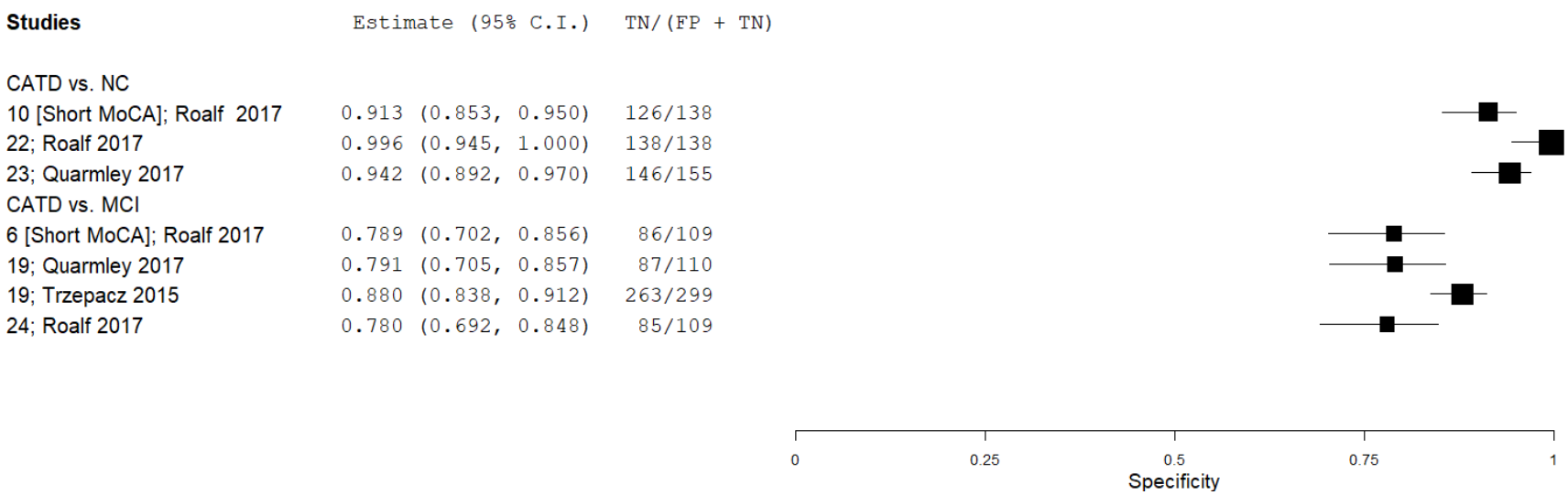
Abbrevations: CATD=Clinical Alzheimer's type dementia; MIS=Memory Impairment Screen; NC=normal control

Figure C.5. Sensitivity results of MoCA in eligible studies with low-moderate risk of bias



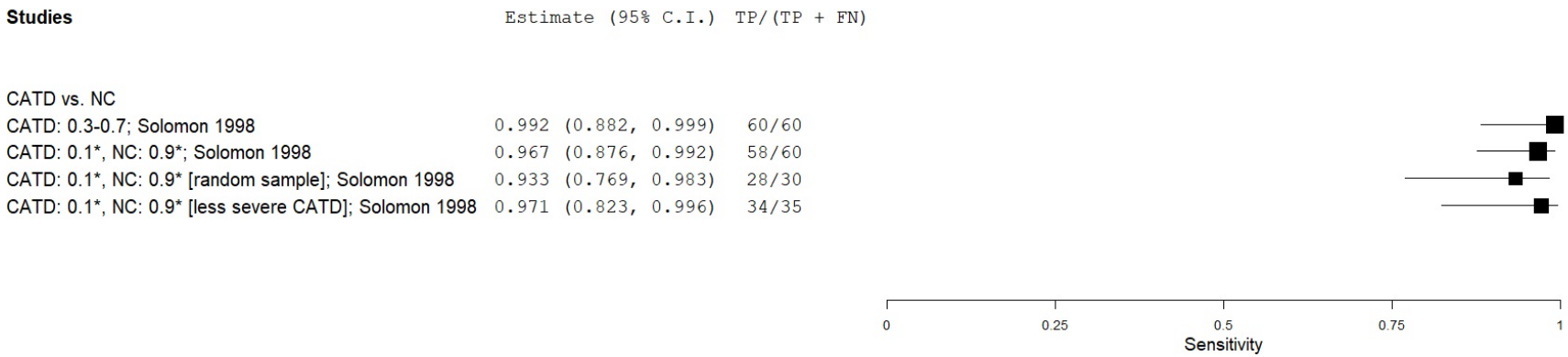
Abbrevations: CATD=Clinical Alzheimer's type dementia; MCI=mild cognitive impairment; MoCA=Montreal Cognitive Assessment; NC=normal control

Figure C.6. Specificity results of MoCA in eligible studies with low-moderate risk of bias



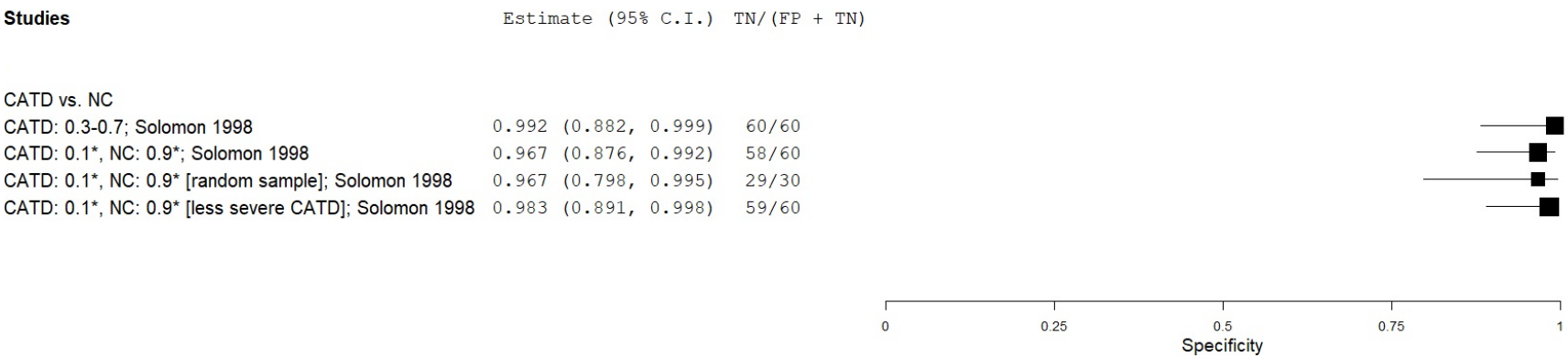
Abbrevations: CATD=Clinical Alzheimer's type dementia; MCI=mild cognitive impairment; MoCA=Montreal Cognitive Assessment; NC=normal control

Figure C.7. Sensitivity results of 7MS in eligible studies with low-moderate risk of bias



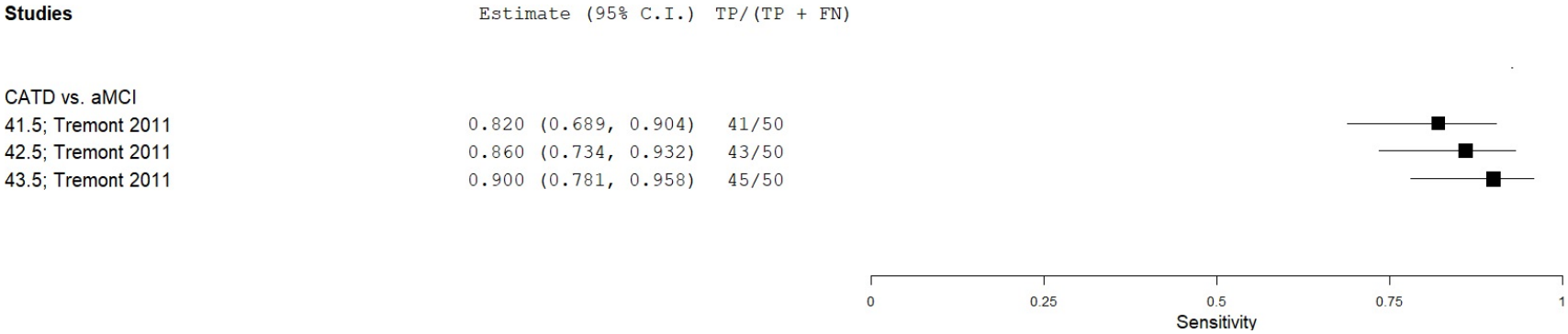
Abbrevations: CATD=Clinical Alzheimer's type dementia; NC=normal control; 7MS=7 Minute Screen

Figure C.8. Specificity results of 7MS in eligible studies with low-moderate risk of bias



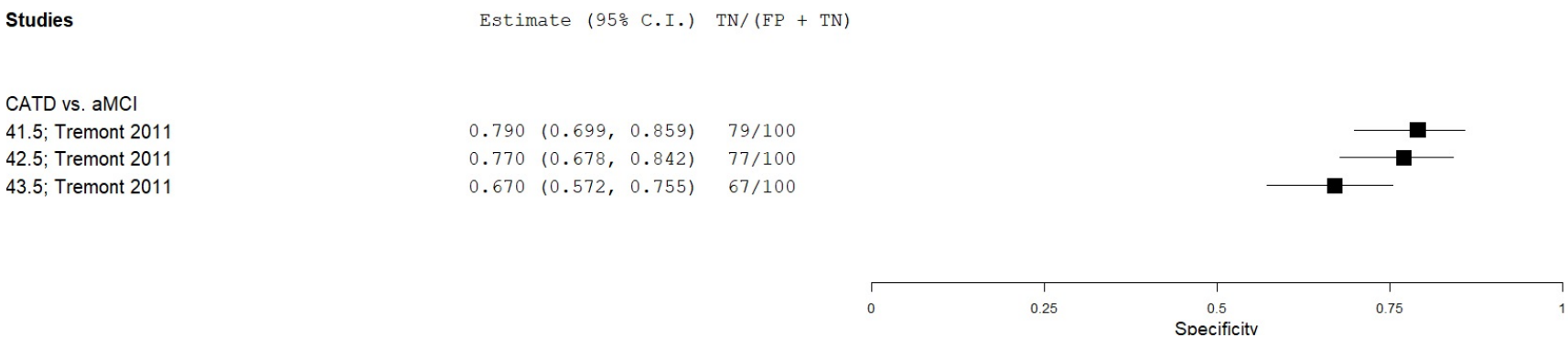
Abbrevations: CATD=Clinical Alzheimer's type dementia; NC=normal control; 7MS=7 Minute Screen

Figure C.9. Sensitivity results of MCAS in eligible studies with low-moderate risk of bias



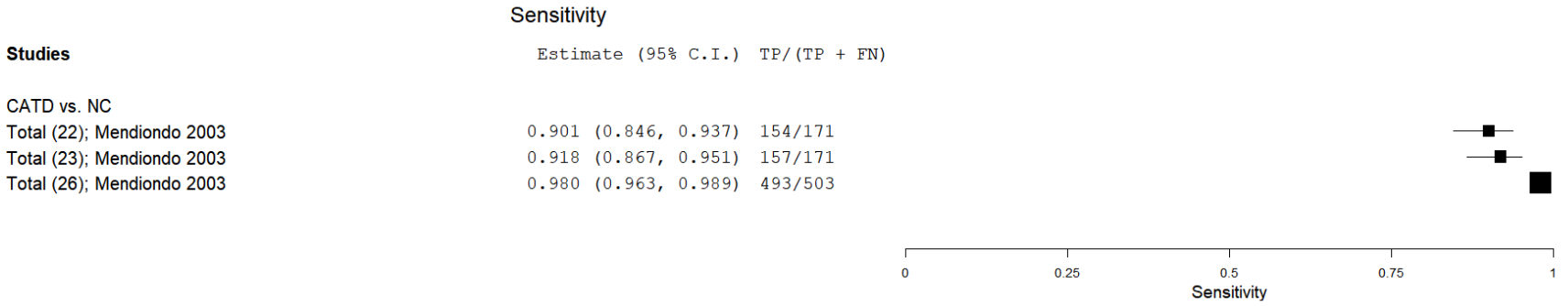
Abbrevations: aMCI=amnestic mild cognitive impairment; CATD=Clinical Alzheimer's type dementia; MCAS=Minnesota Cognitive Acuity Screen; NC=normal control

Figure C.10. Specificity results of MCAS in eligible studies with low-moderate risk of bias



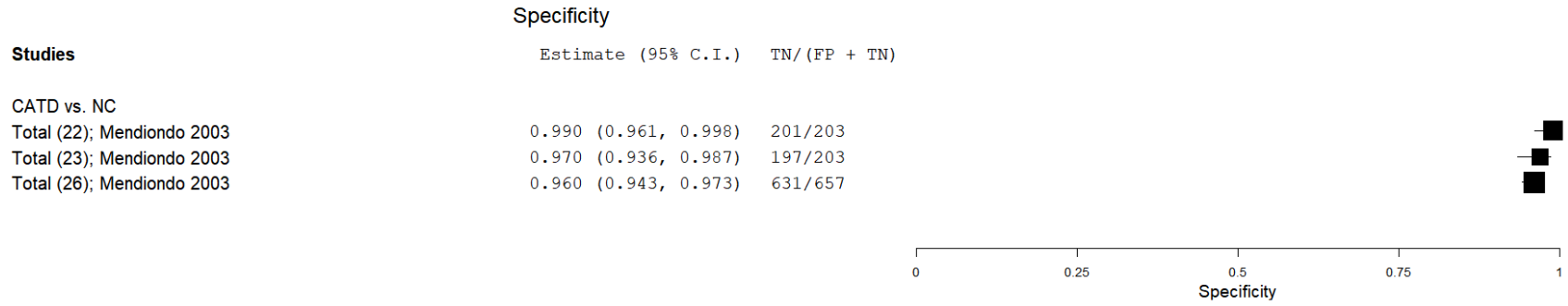
Abbrevations: aMCI=amnestic mild cognitive impairment; CATD=Clinical Alzheimer's type dementia; MCAS=Minnesota Cognitive Acuity Screen; NC=normal control

Figure C.11. Sensitivity results of BAS in eligible studies with low-moderate risk of bias



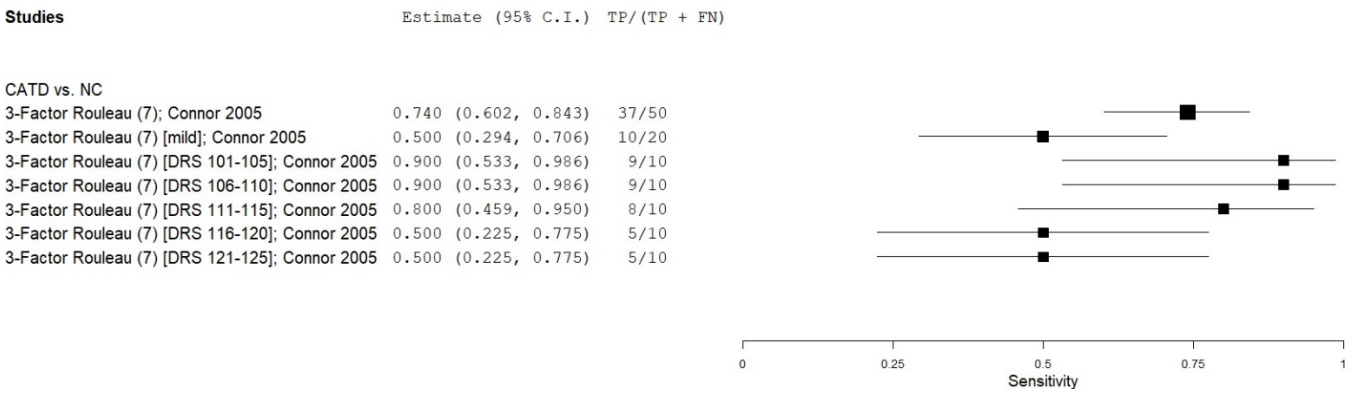
Abbrevations: BAS=Brief Alzheimer Screen; CATD=Clinical Alzheimer's type dementia; NC=normal control

Figure C.12. Specificity results of BAS in eligible studies with low-moderate risk of bias



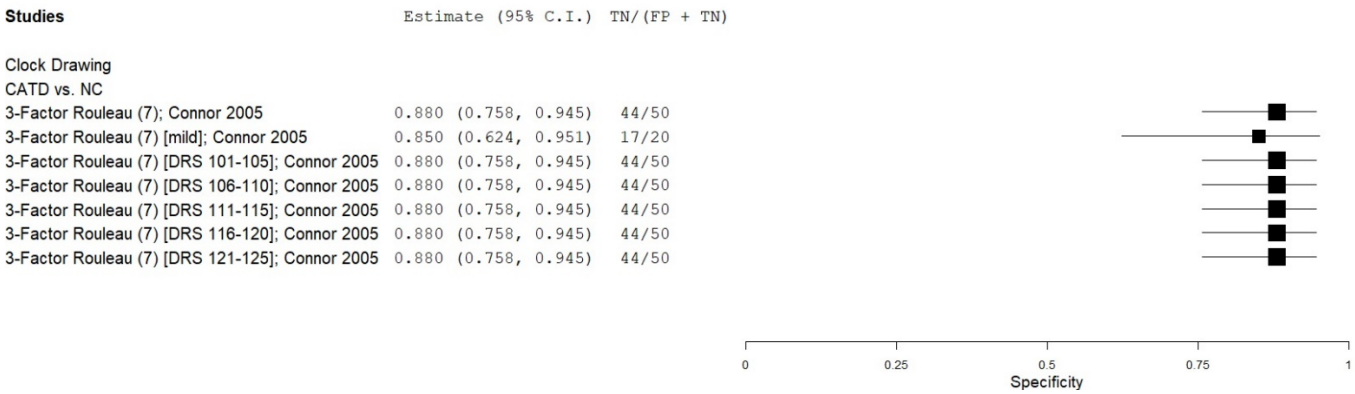
Abbrevations: BAS=Brief Alzheimer Screen; CATD=Clinical Alzheimer's type dementia; NC=normal control

Figure C.13 Sensitivity results of clock drawing tests (Rouleau scoring) in eligible studies with low-moderate risk of bias



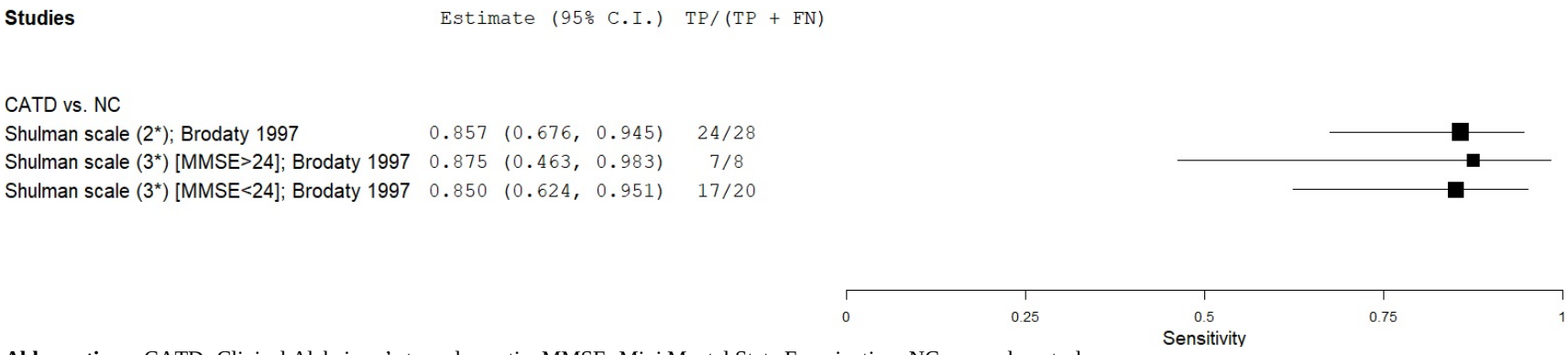
Abbrevations: CATD=Clinical Alzheimer's type dementia; DRS=Dementia Rating Scale; NC=normal control

Figure C.14. Specificity results of clock drawing tests (Rouleau scoring) in eligible studies with low-moderate risk of bias



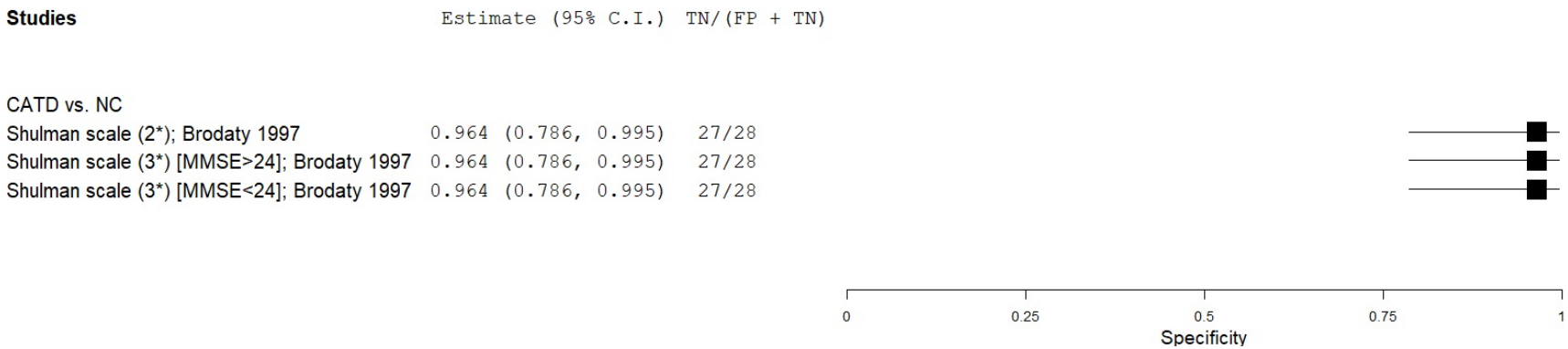
Abbrevations: CATD=Clinical Alzheimer's type dementia; DRS=Dementia Rating Scale; NC=normal control

Figure C.15. Sensitivity results of clock drawing tests (Shulman scale) in eligible studies with low-moderate risk of bias



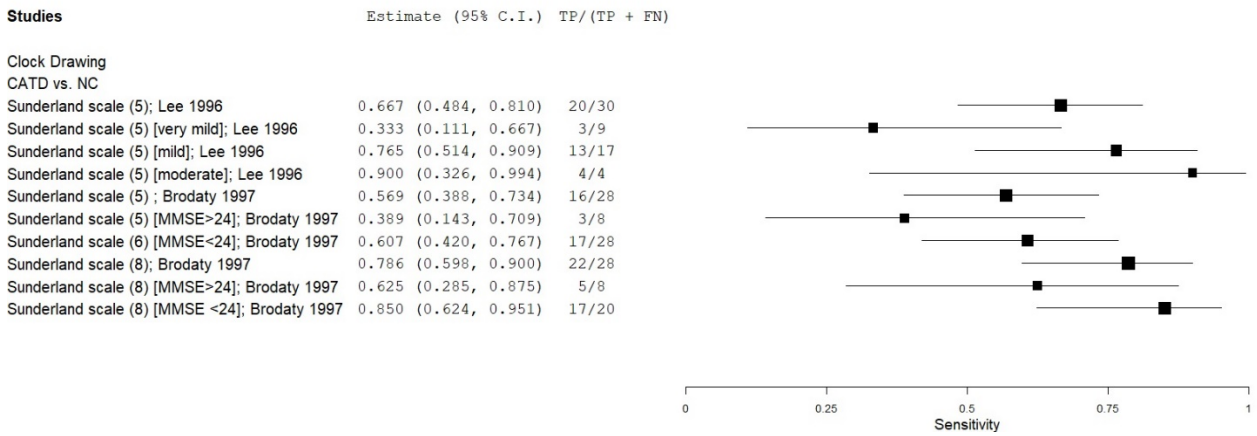
Abbrevations: CATD=Clinical Alzheimer's type dementia; MMSE=Mini Mental State Examination; NC=normal control

Figure C.16. Specificity results of clock drawing tests (Shulman scale) in eligible and low-moderate risk of bias studies



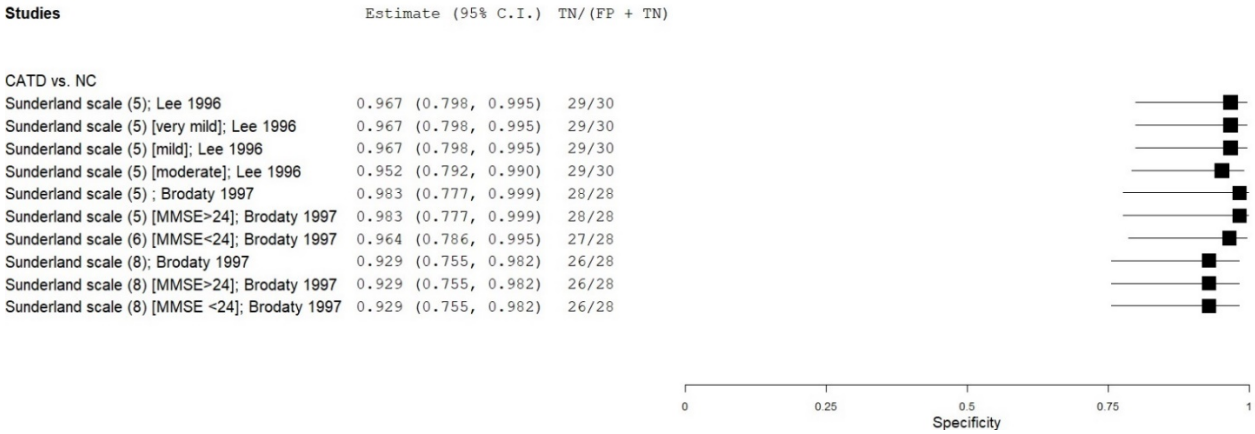
Abbrevations: CATD=Clinical Alzheimer's type dementia; MMSE=Mini Mental State Examination; NC=normal control

Figure C.17. Sensitivity results of clock drawing tests (Sunderland scale) in eligible studies with low-moderate risk of bias



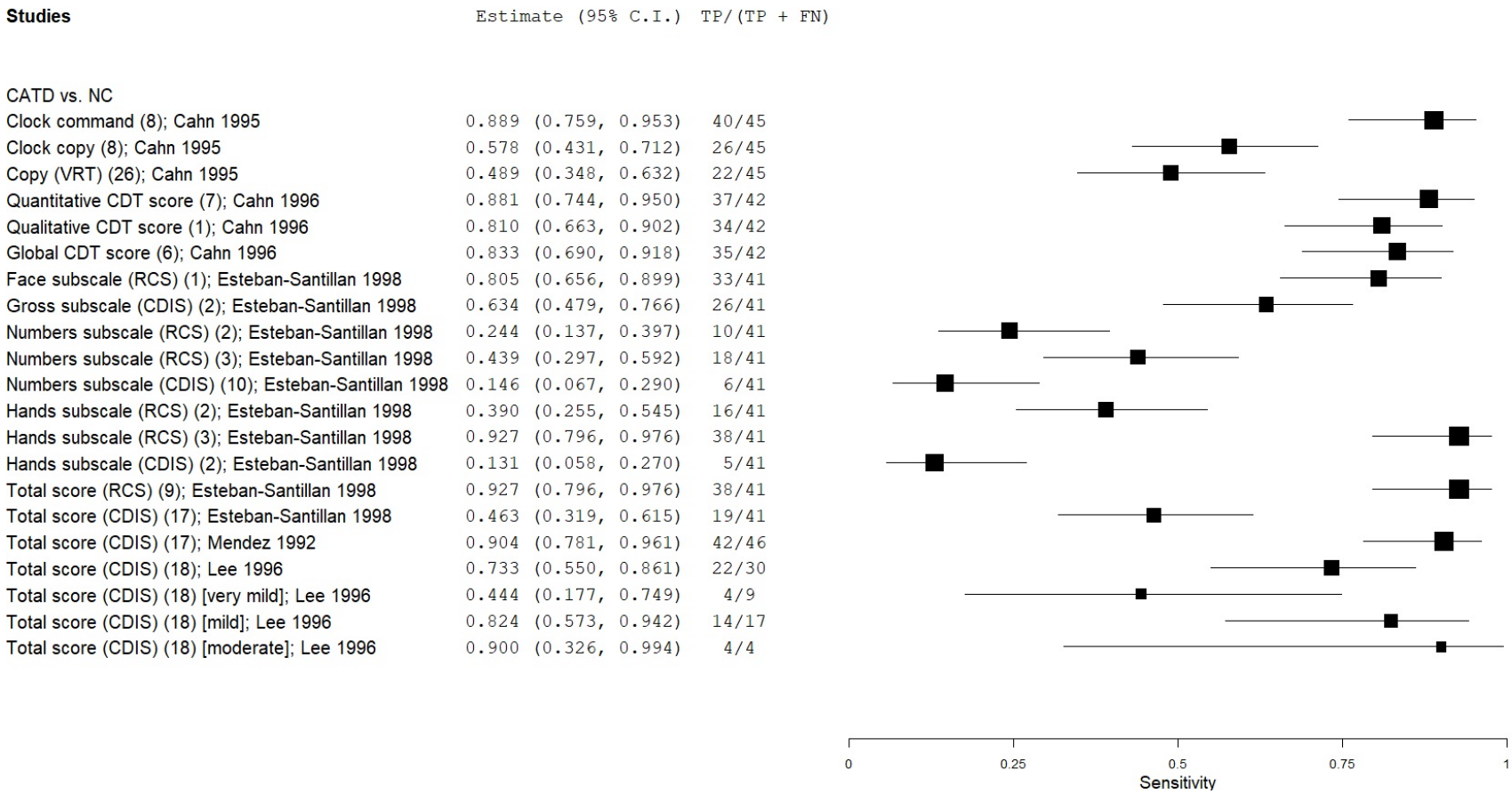
Abbrevations: CATD=Clinical Alzheimer's type dementia; MMSE=Mini Mental State Examination; NC=normal control

Figure C.18. Specificity results of clock drawing tests (Sunderland scale) in eligible studies with low-moderate risk of bias



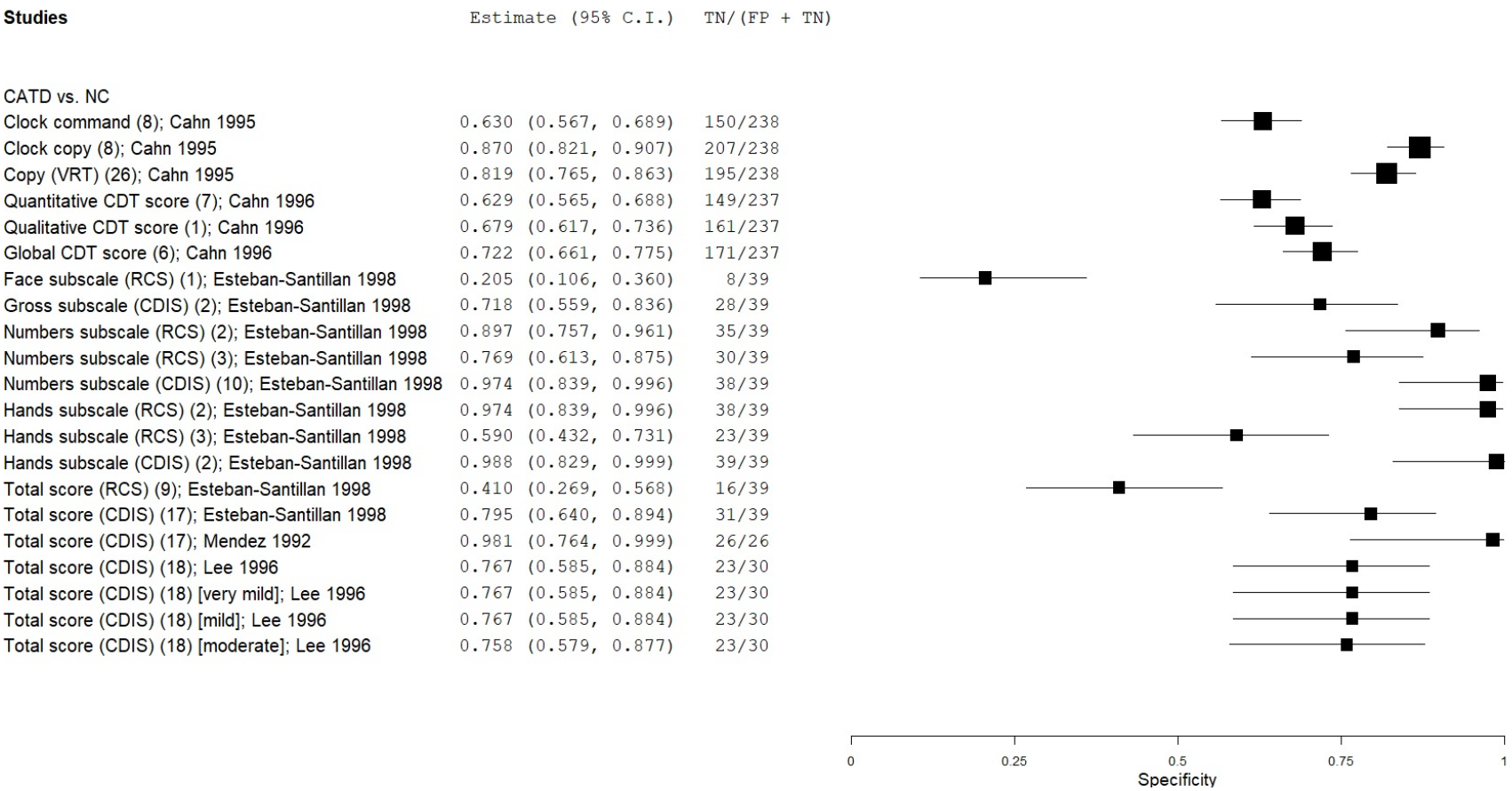
Abbrevations: CATD=Clinical Alzheimer's type dementia; MMSE=Mini Mental State Examination; NC=normal control

Figure C.19. Sensitivity results of other clock drawing tests in eligible studies with low-moderate risk of bias



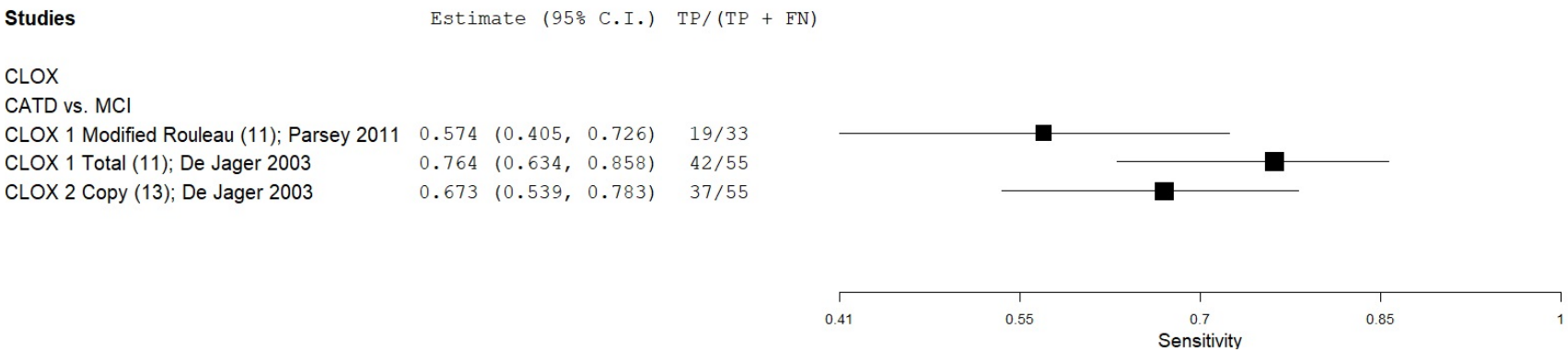
Abbrevations: CATD=Clinical Alzheimer's type dementia; CDIS=Clock Drawing Interpretation Scale; MMSE=Mini Mental State Examination; NC=normal control; RCS=Rapid Cognitive Screen; VRT=Visual Retention Test

Figure C.20. Specificity results of other clock drawing tests in eligible studies with low-moderate risk of bias



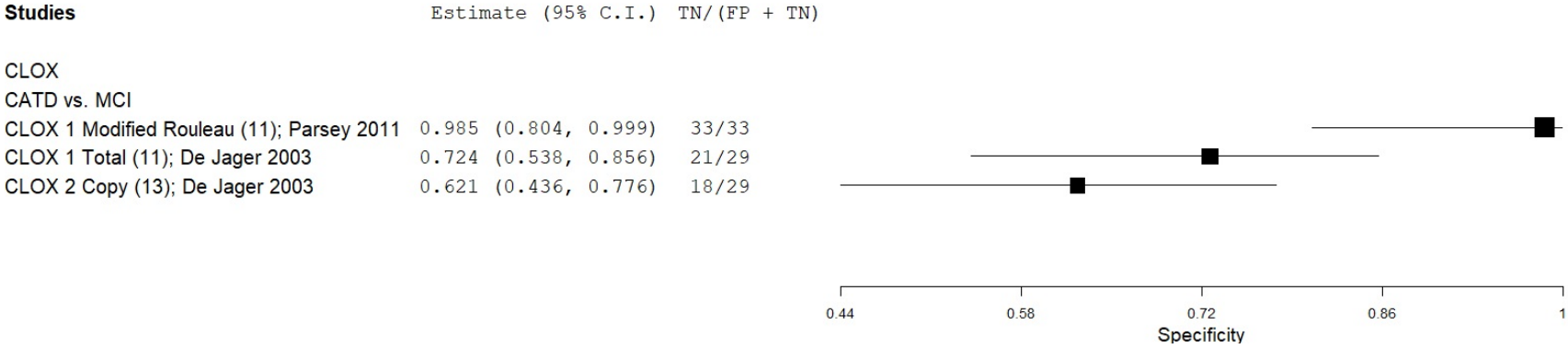
Abbrevations: CATD=Clinical Alzheimer's type dementia; CDIS=Clock Drawing Interpretation Scale; MMSE=Mini Mental State Examination; NC=normal control; RCS=Rapid Cognitive Screen; VRT=Visual Retention Test

Figure C.21. Sensitivity results of CLOX in eligible studies with low-moderate risk of bias



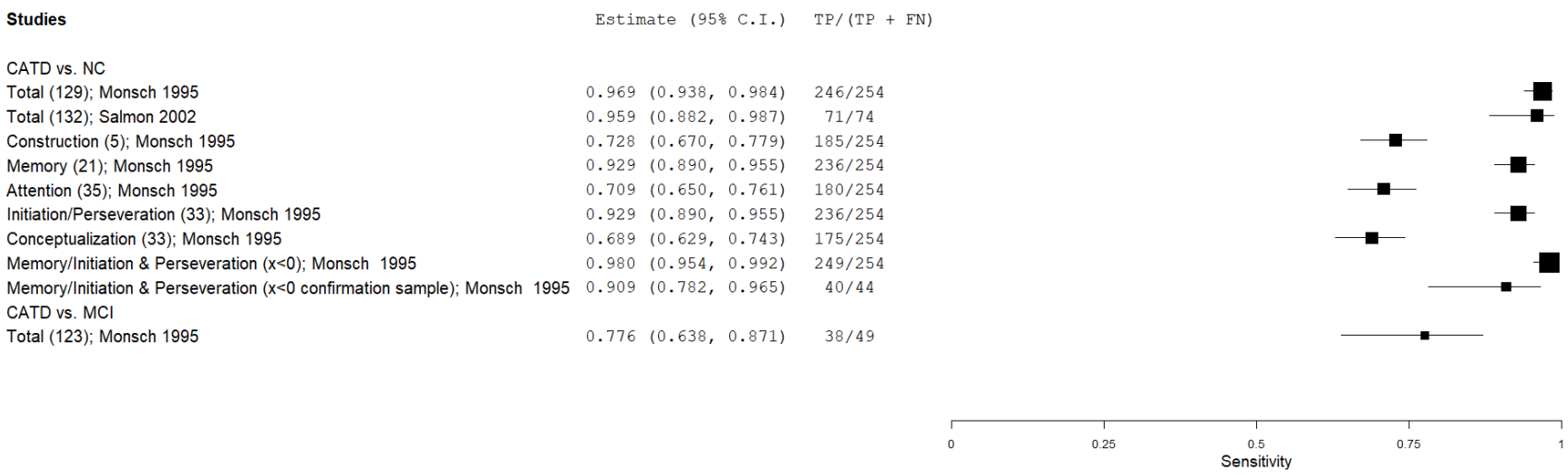
Abbrevations: CATD=Clinical Alzheimer's type dementia; MCI=mild cognitive impairment

Figure C.22. Specificity results of CLOX in eligible studies with low-moderate risk of bias



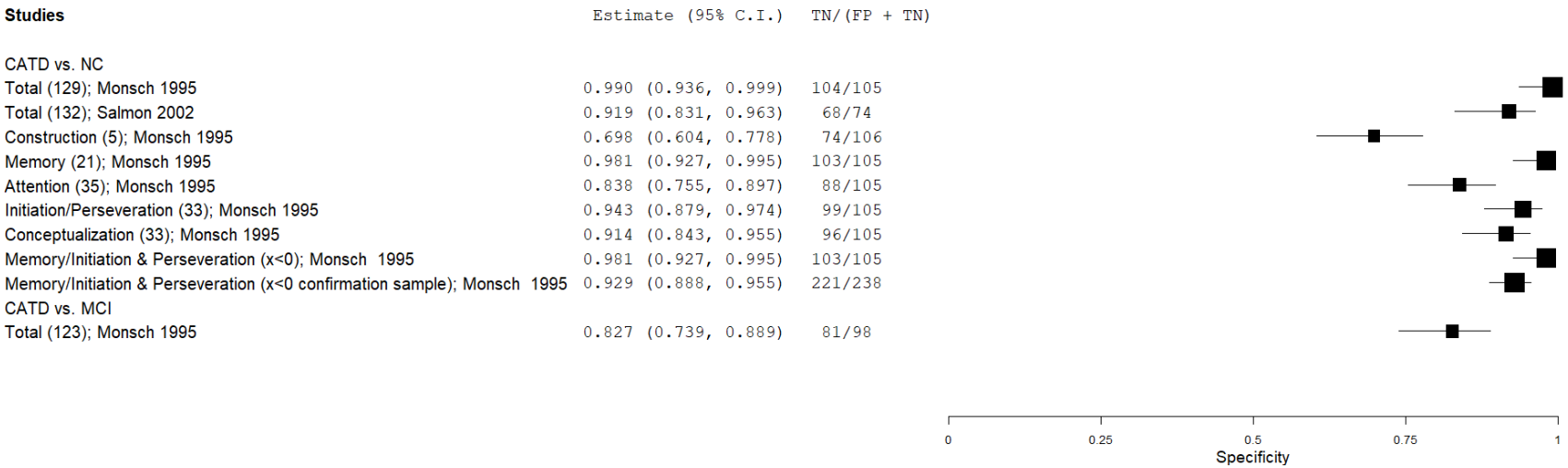
Abbrevations: CATD=Clinical Alzheimer's type dementia; MCI=mild cognitive impairment

Figure C.23. Sensitivity results of DRS in eligible studies with low-moderate risk of bias



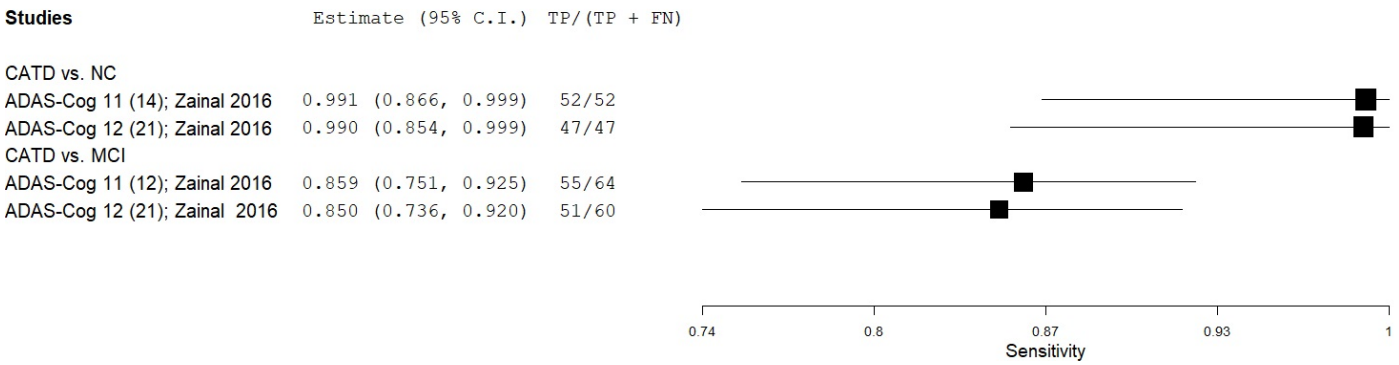
Abbrevations: CATD=Clinical Alzheimer's type dementia; DRS=Dementia Rating Scale; MCI=mild cognitive impairment; NC=normal control

Figure C.24. Specificity results of DRS in eligible studies with low-moderate risk of bias



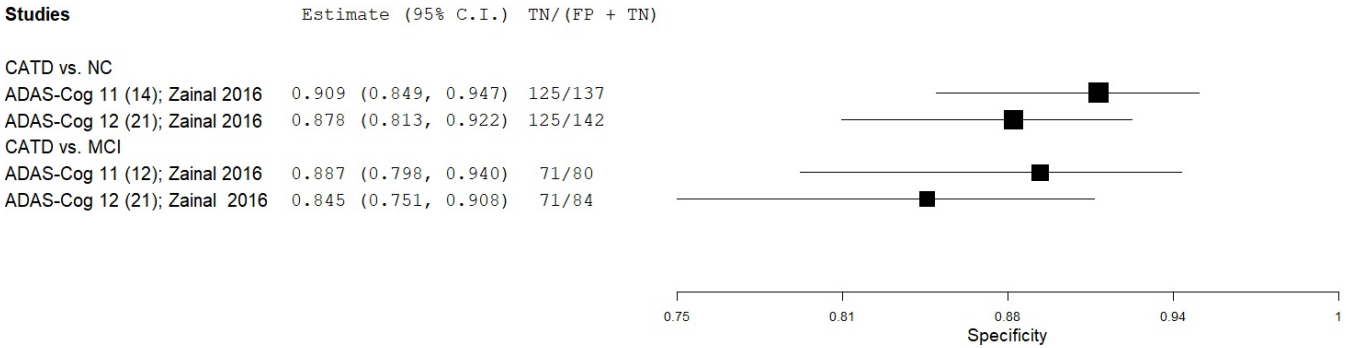
Abbrevations: CATD=Clinical Alzheimer's type dementia; DRS=Dementia Rating Scale; MCI=mild cognitive impairment; NC=normal control

Figure C.25. Sensitivity results of ADAS-Cog in eligible studies with low-moderate risk of bias



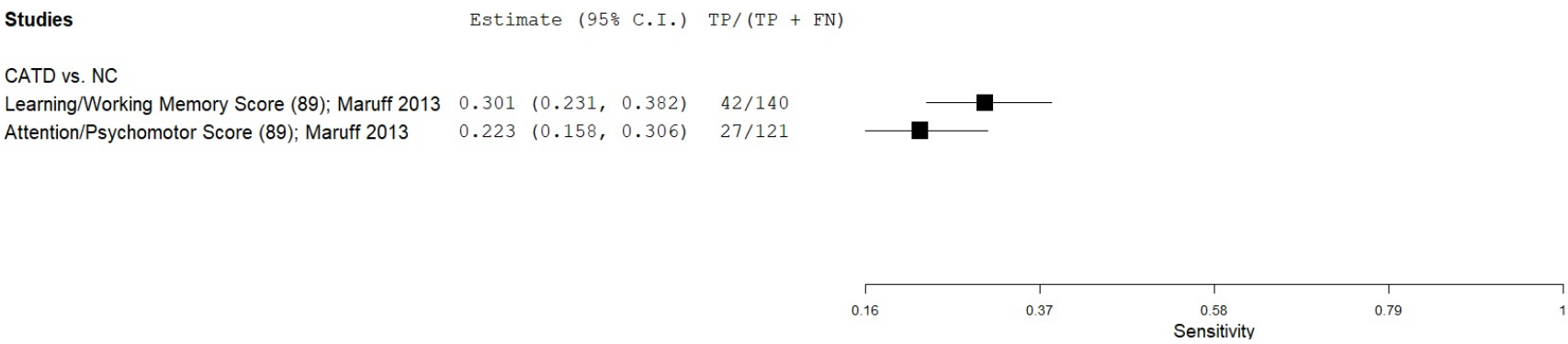
Abbrevations: ADAS-Cog= Alzheimer's Disease Assessment Scale-Cognitive; CATD=Clinical Alzheimer's type dementia; MCI=mild cognitive impairment; NC=normal control

Figure C.26. Specificity results of ADAS-Cog in eligible studies with low-moderate risk of bias



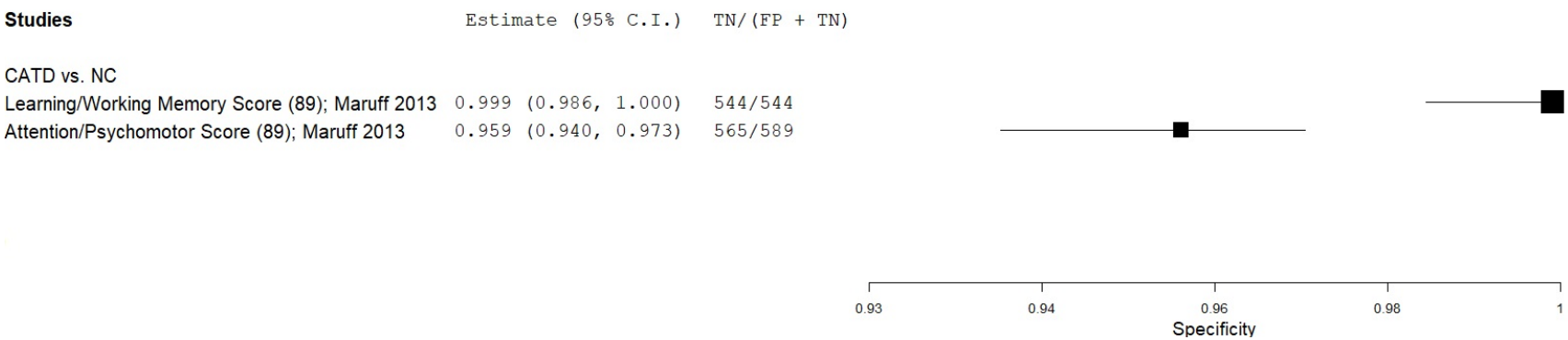
Abbrevations: ADAS-Cog= Alzheimer's Disease Assessment Scale-Cognitive; CATD=Clinical Alzheimer's type dementia; MCI=mild cognitive impairment; NC=normal control

Figure C.27. Sensitivity results of CSBB in eligible studies with low-moderate risk of bias



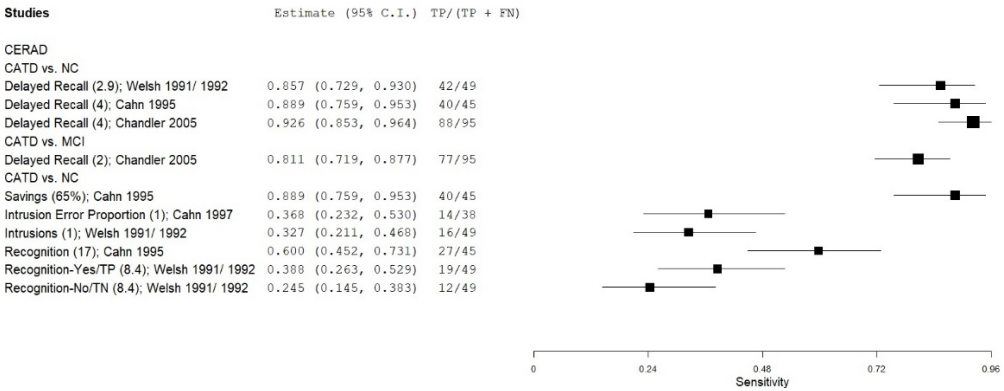
Abbrevations: CATD=Clinical Alzheimer's type dementia; CSBB=Cogstate Brief Battery; NC=normal control

Figure C.28. Specificity results of CSBB in eligible studies with low-moderate risk of bias



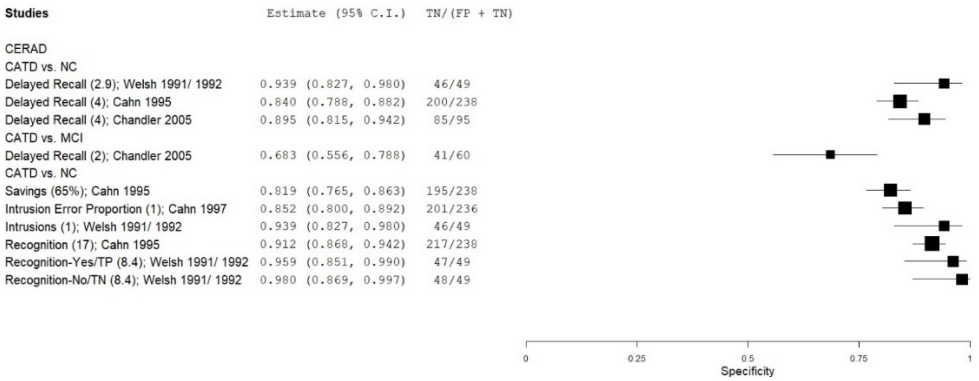
Abbrevations: CATD=Clinical Alzheimer's type dementia; CSBB=Cogstate Brief Battery; NC=normal control

Figure C.29. Sensitivity results of CERAD in eligible studies with low-moderate risk of bias



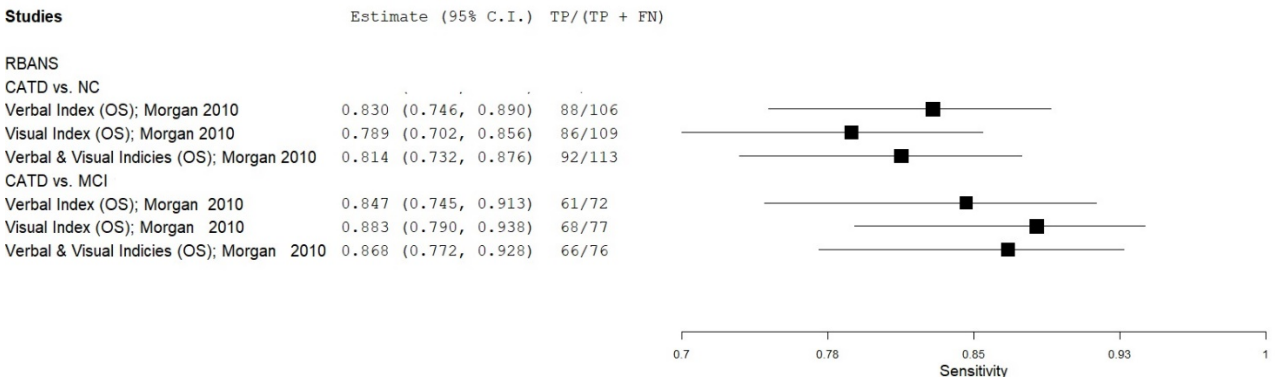
Abbrevations: CATD=Clinical Alzheimer's type dementia; CERAD= Consortium to Establish a Registry for Alzheimer's Disease; MCI=Mild cognitive impairment; NC=normal control

Figure C.30. Specificity results of CERAD in eligible studies with low-moderate risk of bias



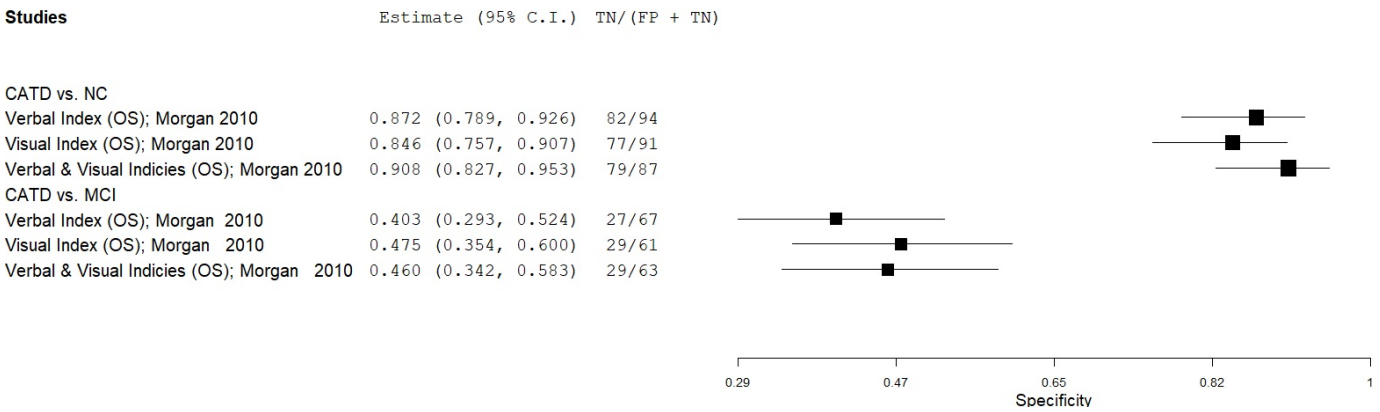
Abbrevations: CATD=Clinical Alzheimer's type dementia; CERAD= Consortium to Establish a Registry for Alzheimer's Disease; MCI=Mild cognitive impairment; NC=normal control

Figure C.31. Sensitivity results of RBANS in eligible studies with low-moderate risk of bias



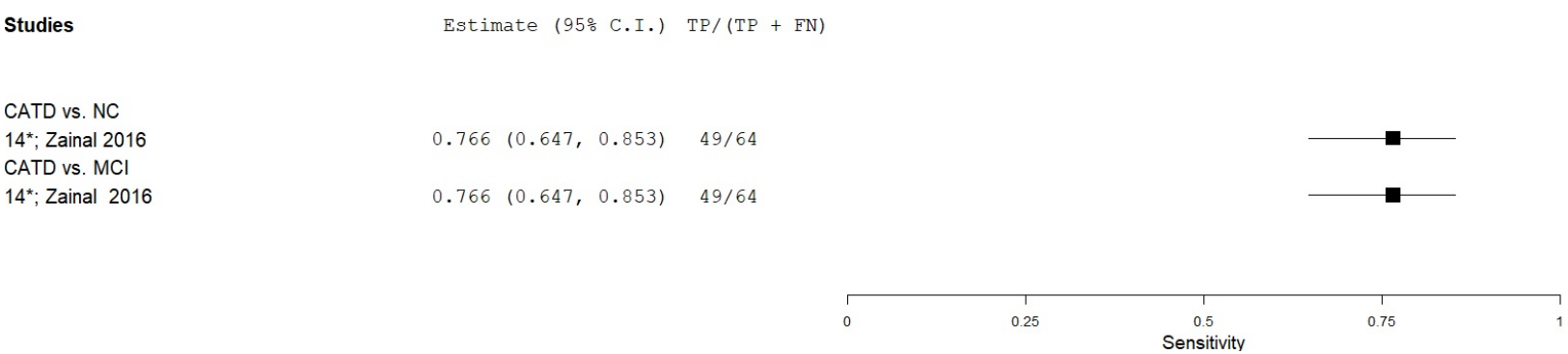
Abbrevations: CATD=Clinical Alzheimer's type dementia; MCI=Mild cognitive impairment; NC=normal control; OS=optimal score; RBANS= Repeatable Battery for the Assessment of Neuropsychological Status

Figure C.32. Specificity results of RBANS in eligible studies with low-moderate risk of bias



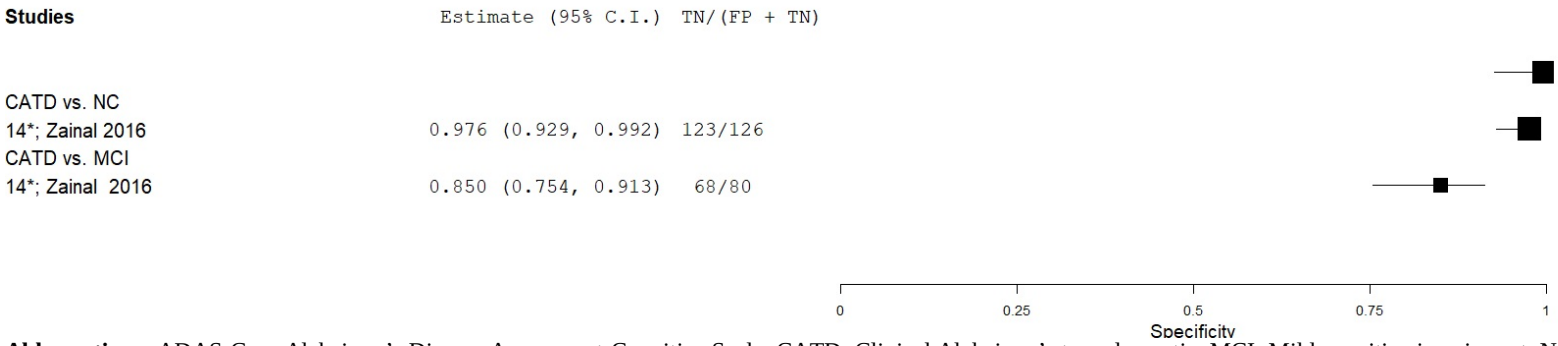
Abbrevations: CATD=Clinical Alzheimer's type dementia; MCI=Mild cognitive impairment; NC=normal control; OS=optimal score; RBANS= Repeatable Battery for the Assessment of Neuropsychological Status

Figure C.33. Sensitivity results of ADAS-Cog Combined Scores in eligible studies with low-moderate risk of bias



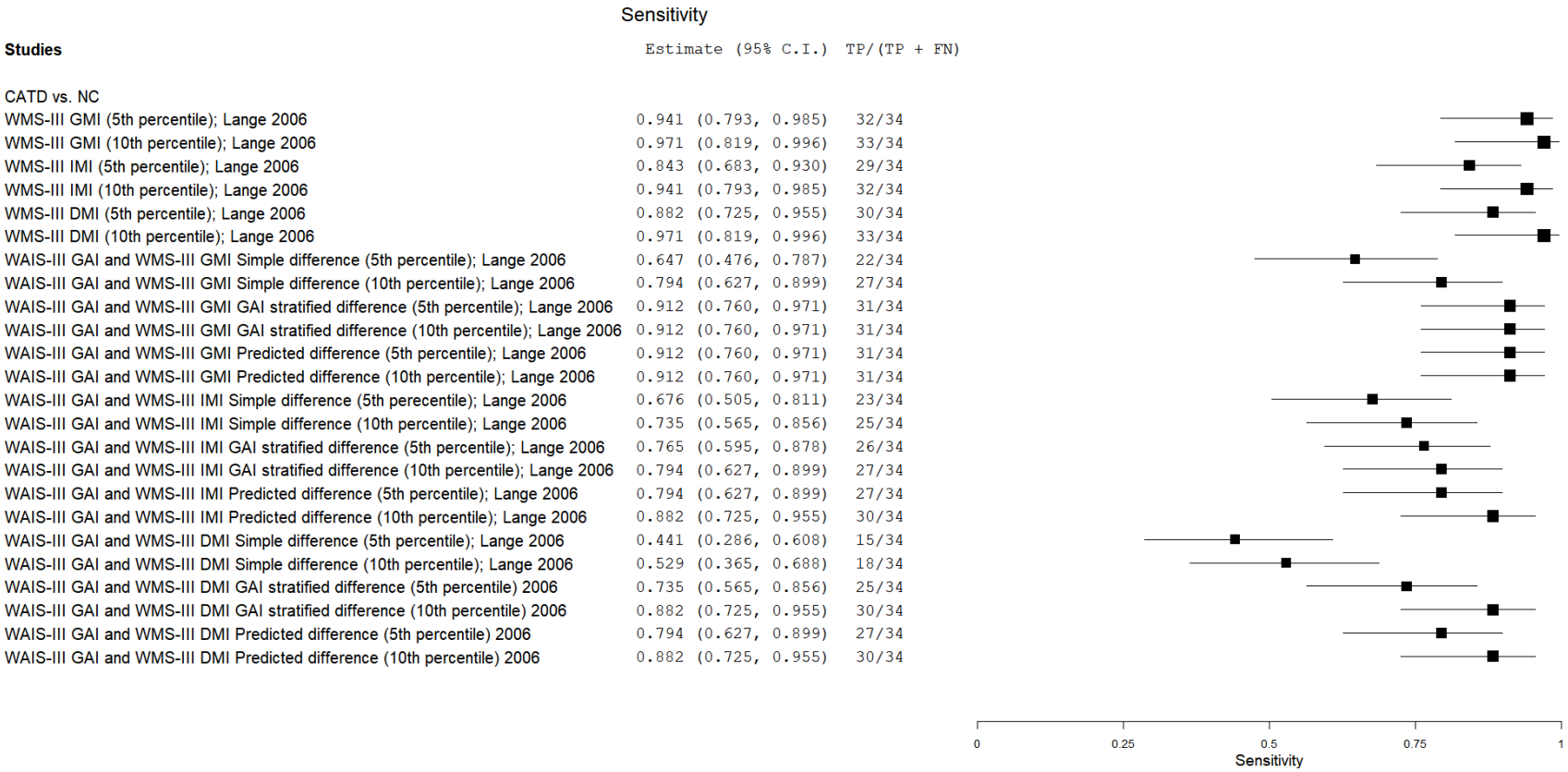
Abbrevations: ADAS-Cog=Alzheimer's Disease Assessment-Cognitive Scale; CATD=Clinical Alzheimer's type dementia; MCI=Mild cognitive impairment; NC=normal control

Figure C.34. Specificity results of ADAS-Cog Combined Scores in eligible studies with low-moderate risk of bias



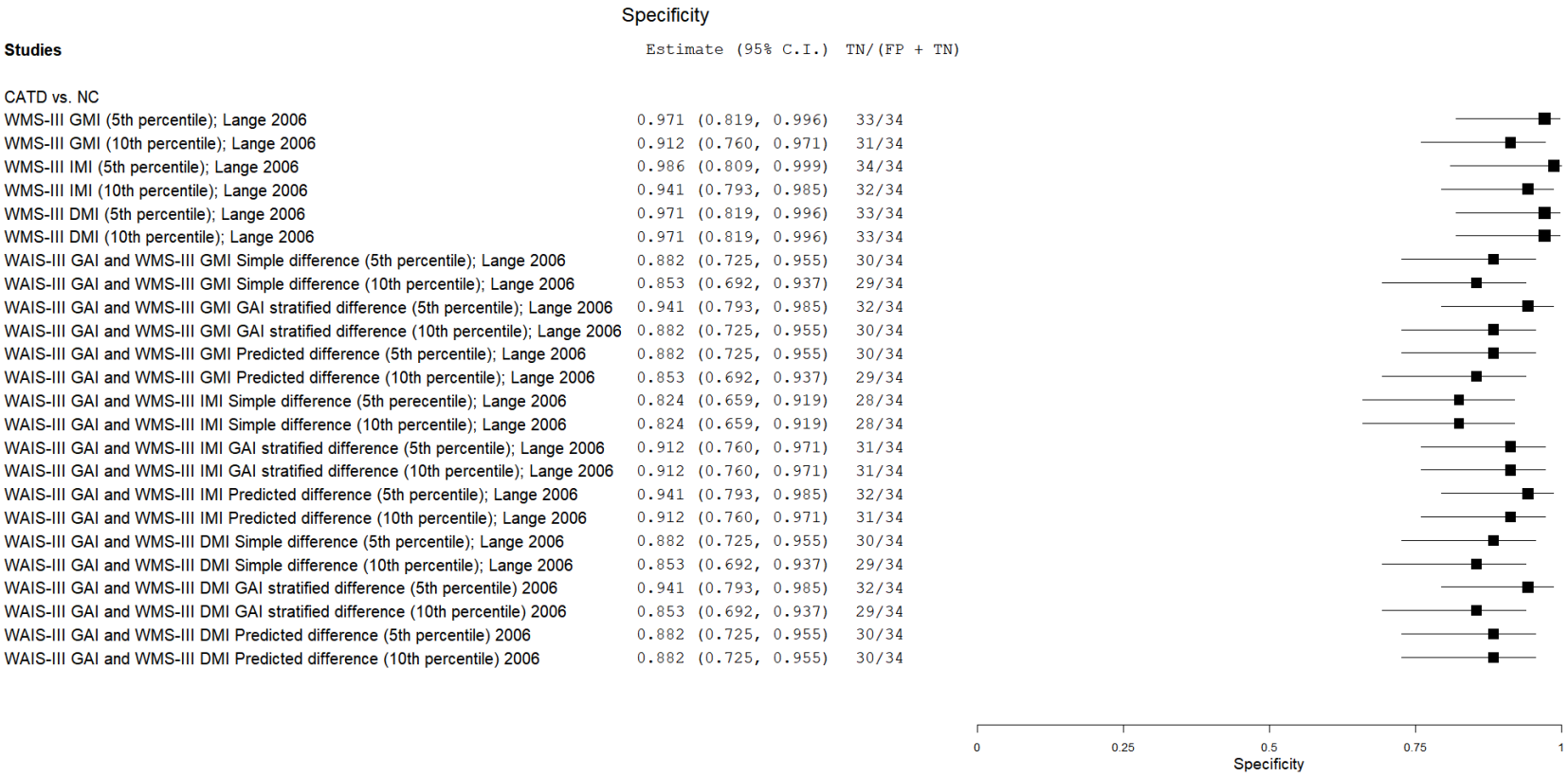
Abbrevations: ADAS-Cog=Alzheimer's Disease Assessment-Cognitive Scale; CATD=Clinical Alzheimer's type dementia; MCI=Mild cognitive impairment; NC=normal control

Figure C.35. Sensitivity results of WMS Indices in eligible studies with low-moderate risk of bias



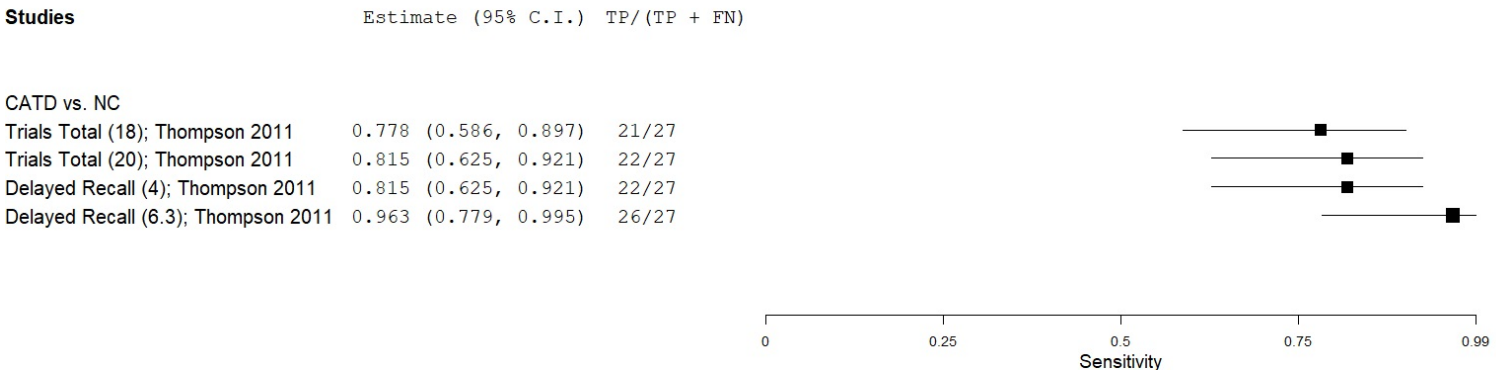
Abbrevations: CATD=Clinical Alzheimer's type dementia; DMI=Delayed Memory Index; GAI=General Ability Index; GMI=General Memory Index; IMI=Immediate Memory Index; NC=normal control; WAIS=Wechsler Adult Intelligence Scale; WMS=Wechsler Memory Scale

Figure C.36. Specificity results of WMS Indices in eligible studies with low-moderate risk of bias



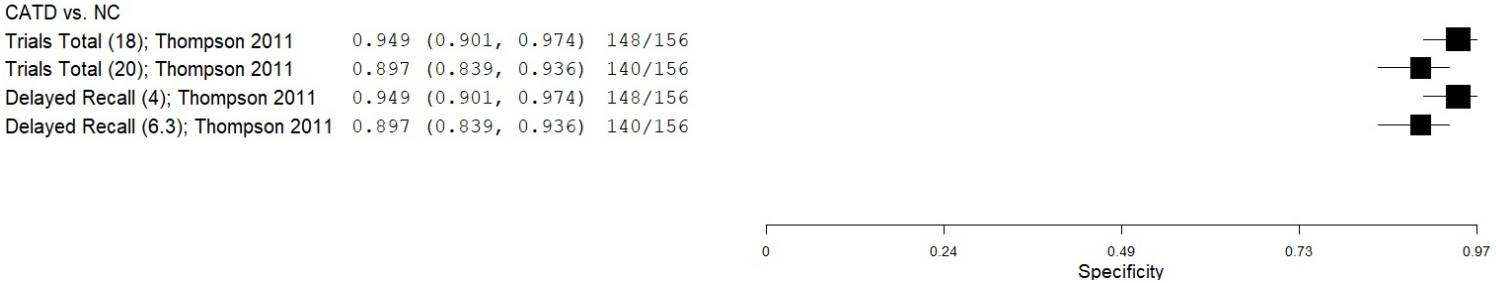
Abbrevations: CATD=Clinical Alzheimer's type dementia; DMI=Delayed Memory Index; GAI=General Ability Index; GMI=General Memory Index; IMI=Immediate Memory Index; NC=normal control; WAIS=Wechsler Adult Intelligence Scale; WMS=Wechsler Memory Scale

Figure C.37. Sensitivity results of CogState ISLT in eligible studies with low-moderate risk of bias



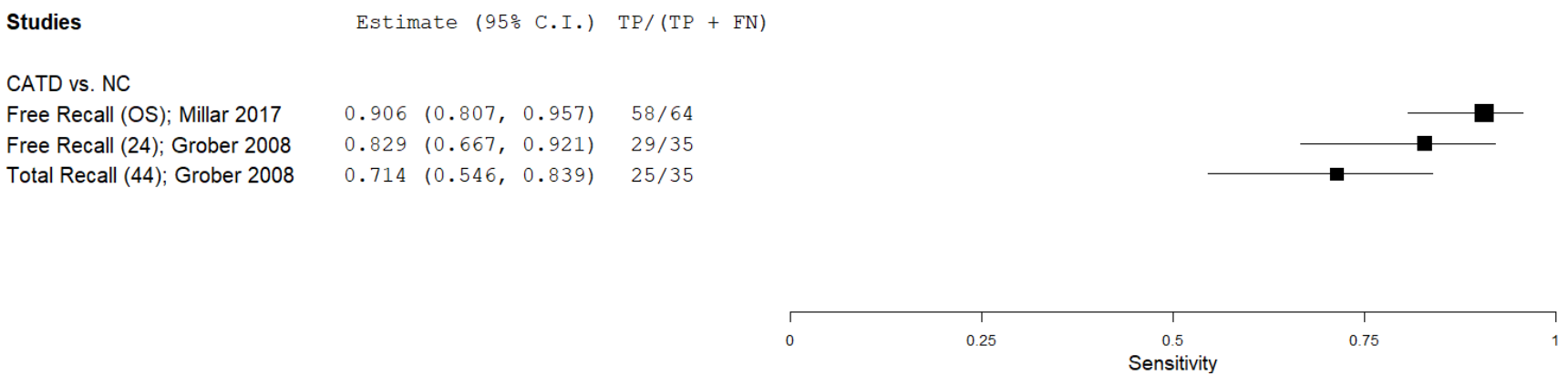
Abbrevations: CATD=Clinical Alzheimer's type dementia; CogState ISLT= Cogstate International Shopping List Test; NC=normal control

Figure C.38. Specificity results of CogState ISLT in eligible studies with low-moderate risk of bias



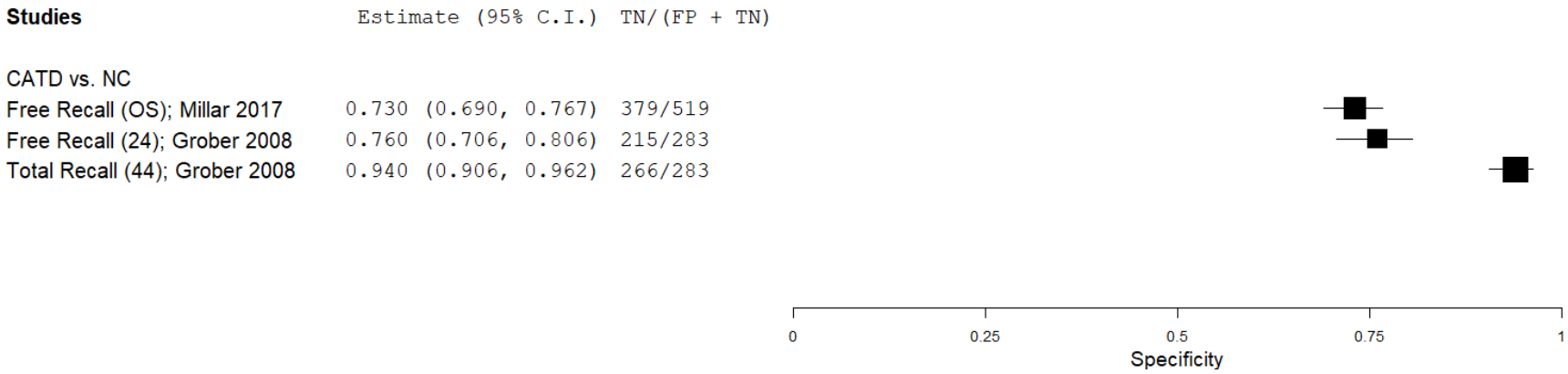
Abbrevations: CATD=Clinical Alzheimer's type dementia; CogState ISLT= Cogstate International Shopping List Test; NC=normal control

Figure C.39. Sensitivity results of FCSRT in eligible studies with low-moderate risk of bias



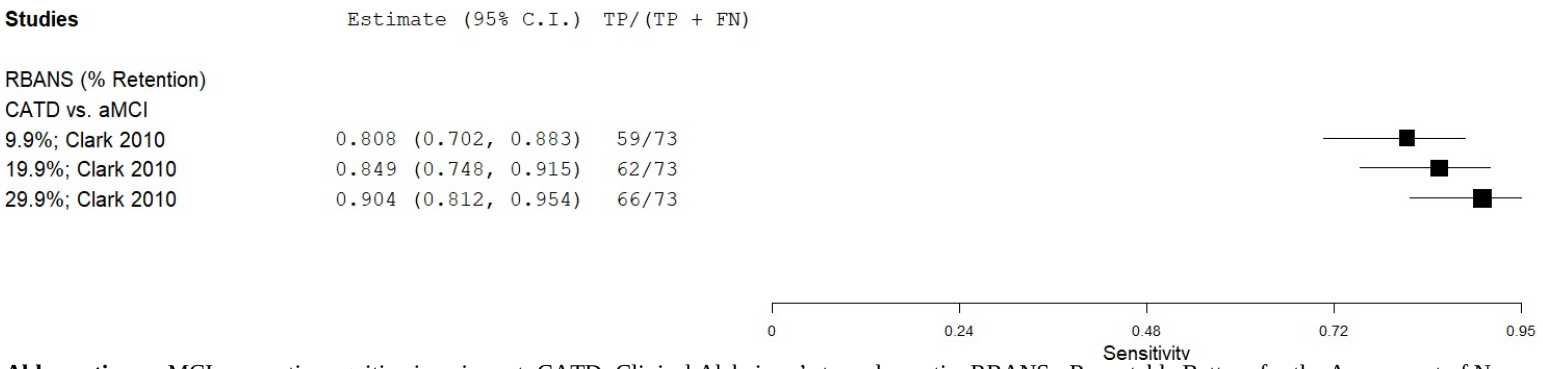
Abbrevations: CATD=Clinical Alzheimer's type dementia; FCSRT=Free and Cued Selective Reminding Test; NC=normal control; OS=optimal score

Figure C.40. Specificity results of FCSRT in eligible studies with low-moderate risk of bias



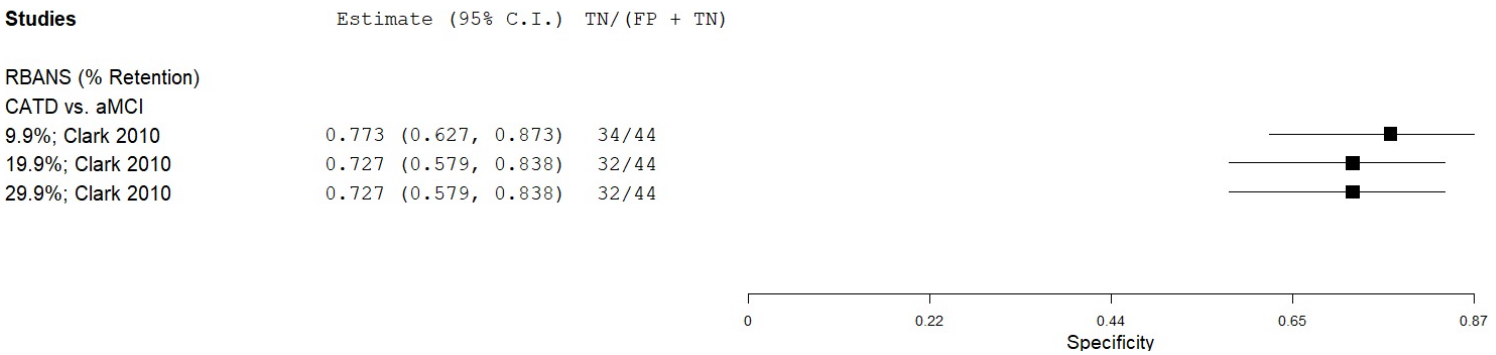
Abbrevations: CATD=Clinical Alzheimer's type dementia; FCSRT=Free and Cued Selective Reminding Test; NC=normal control; OS=optimal score

Figure C.41. Sensitivity results of RBANS (% retention) in eligible studies with low-moderate risk of bias



Abbrevations: aMCI=amnestic cognitive impairment; CATD=Clinical Alzheimer's type dementia; RBANS= Repeatable Battery for the Assessment of Neuropsychological Status

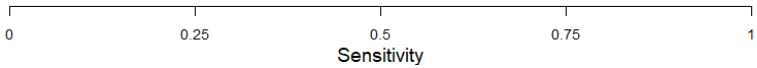
Figure C.42. Specificity results of RBANS (% retention) in eligible studies with low-moderate risk of bias



Abbrevations: aMCI=amnestic cognitive impairment; CATD=Clinical Alzheimer's type dementia; RBANS= Repeatable Battery for the Assessment of Neuropsychological Status

Figure C.43. Sensitivity results of WMS logical memory in eligible studies with low-moderate risk of bias

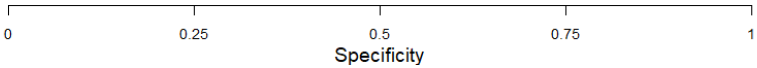
Studies	Estimate (95% C.I.)	TP/(TP + FN)
CATD vs. NC		
Veridical Reproduction (OS) [mild CATD]; Johnson 2003	0.839 (0.666, 0.931)	26/31
Veridical Reproduction (OS); Johnson 2003	0.765 (0.671, 0.839)	75/98
Veridicial + Gist Recall (OS); Johnson 2003	0.774 (0.596, 0.888)	24/31
Distortion of Text (OS) [mild CATD]; Johnson 2003	0.839 (0.666, 0.931)	26/31
Distortion of Text (OS); Johnson 2003	0.747 (0.653, 0.823)	74/99
Delayed Recall (OS); Millar 2017	0.703 (0.581, 0.802)	45/64
Delayed Recall (9); Salmon 2002	0.852 (0.665, 0.943)	23/27



Abbrevations: CATD=Clinical Alzheimer's type dementia; NC=normal control; OS=optimal score; WMS=Weschler Memory Scale

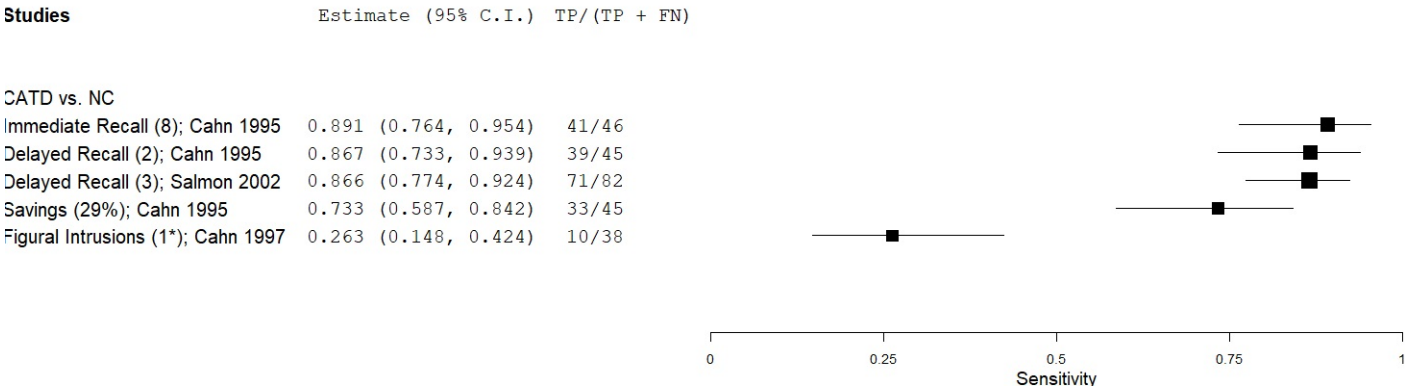
Figure C.44. Specificity results of WMS logical memory in eligible studies with low-moderate risk of bias

Studies	Estimate (95% C.I.)	TN/(FP + TN)
CATD vs. NC		
Veridical Reproduction (OS) [mild CATD]; Johnson 2003	0.872 (0.744, 0.942)	41/47
Veridical Reproduction (OS); Johnson 2003	0.805 (0.705, 0.877)	66/82
Veridicial + Gist Recall (OS); Johnson 2003	0.894 (0.769, 0.955)	42/47
Distortion of Text (OS) [mild CATD]; Johnson 2003	0.809 (0.671, 0.897)	38/47
Distortion of Text (OS); Johnson 2003	0.805 (0.705, 0.877)	66/82
Delayed Recall (OS); Millar 2017	0.830 (0.796, 0.860)	431/519
Delayed Recall (9); Salmon 2002	0.889 (0.707, 0.964)	24/27



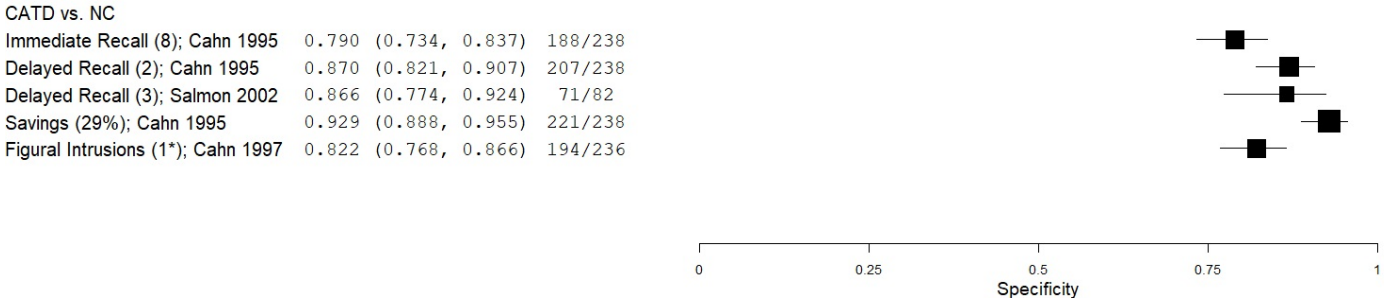
Abbrevations: CATD=Clinical Alzheimer's type dementia; NC=normal control; OS=optimal score; WMS=Weschler Memory Scale

Figure C.45. Sensitivity results of figure recall in eligible studies with low-moderate risk of bias



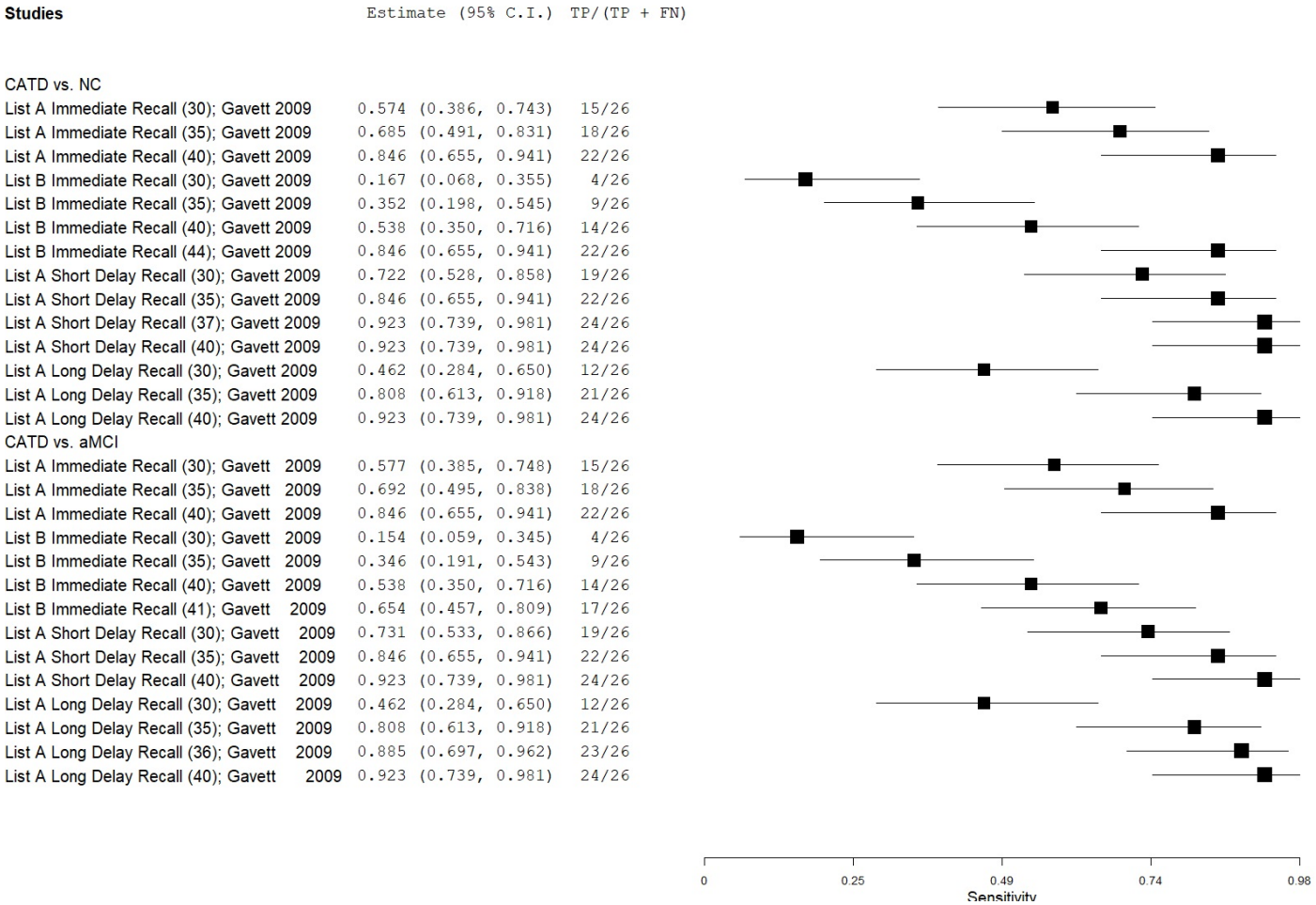
Abbrevations: CATD=Clinical Alzheimer's type dementia; NC=normal control; OS=optimal score

Figure C.46. Specificity results of figure recall in eligible studies with low-moderate risk of bias



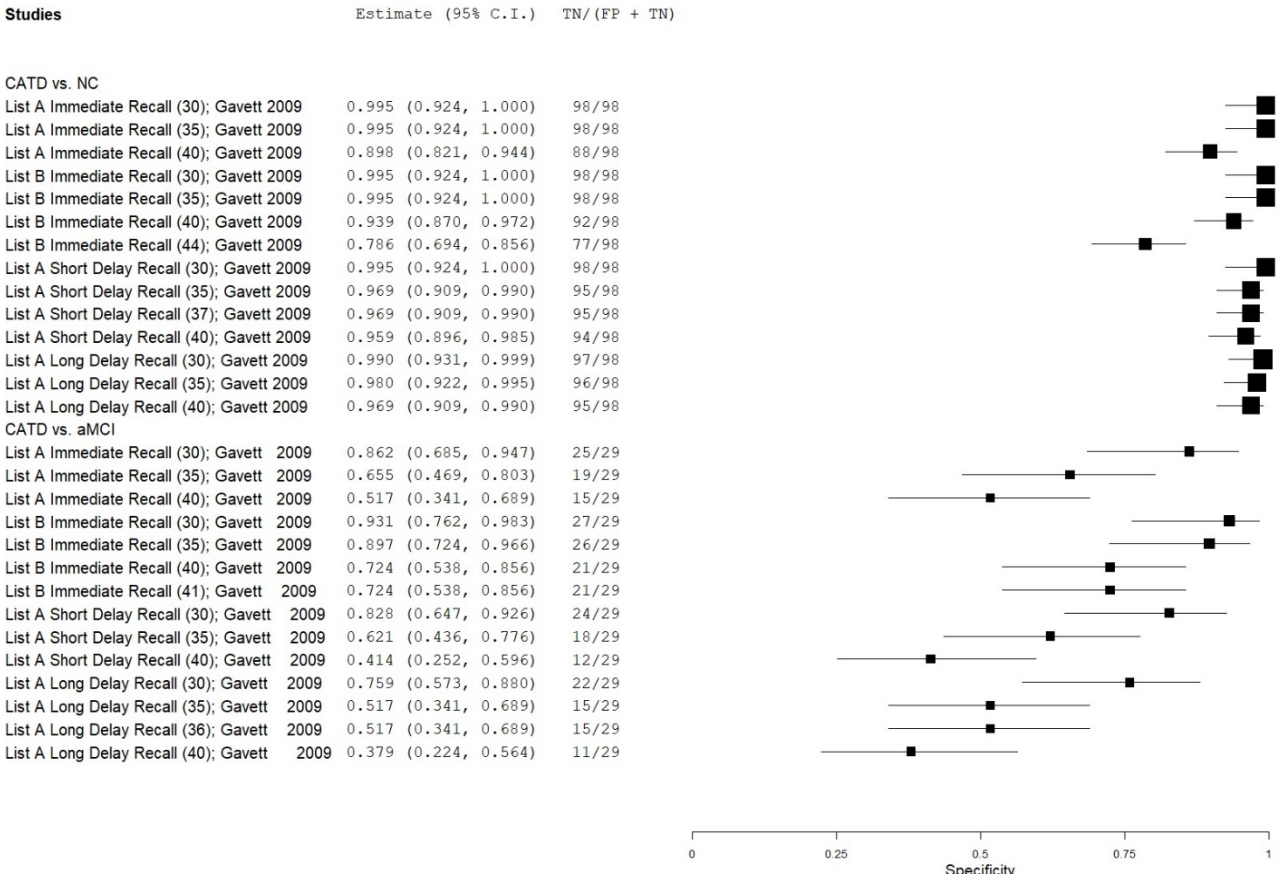
Abbrevations: CATD=Clinical Alzheimer's type dementia; NC=normal control; OS=optimal score

Figure C.47. Sensitivity results of NAB list learning in eligible studies with low-moderate risk of bias



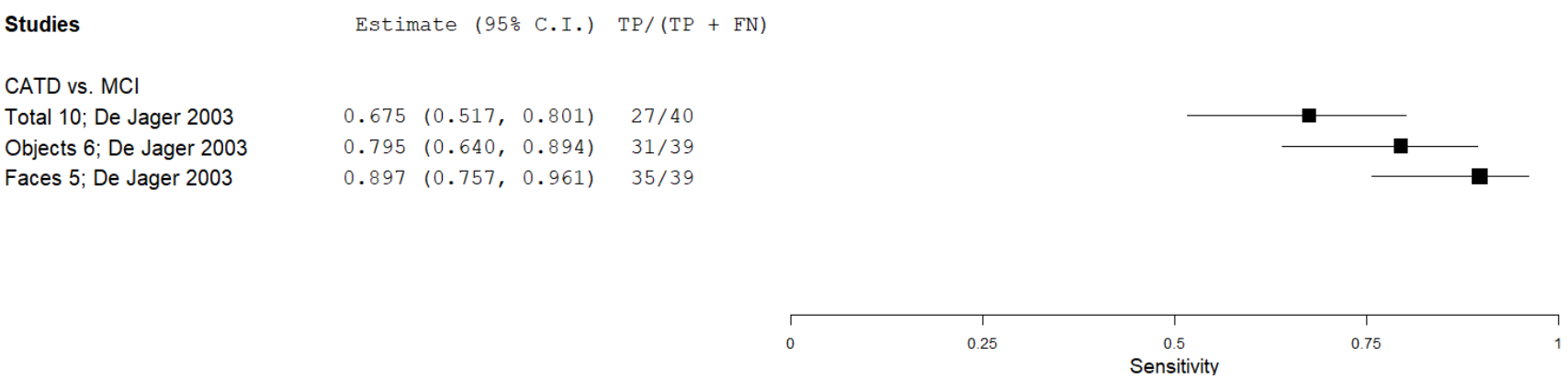
Abbrevations: aMCI=amnestic mild cognitive impairment; CATD=Clinical Alzheimer's type dementia; NAB=Neuropsychological Assessment Battery; NC=normal control

Figure C.48. Specificity results of NAB list learning in eligible studies with low-moderate risk of bias



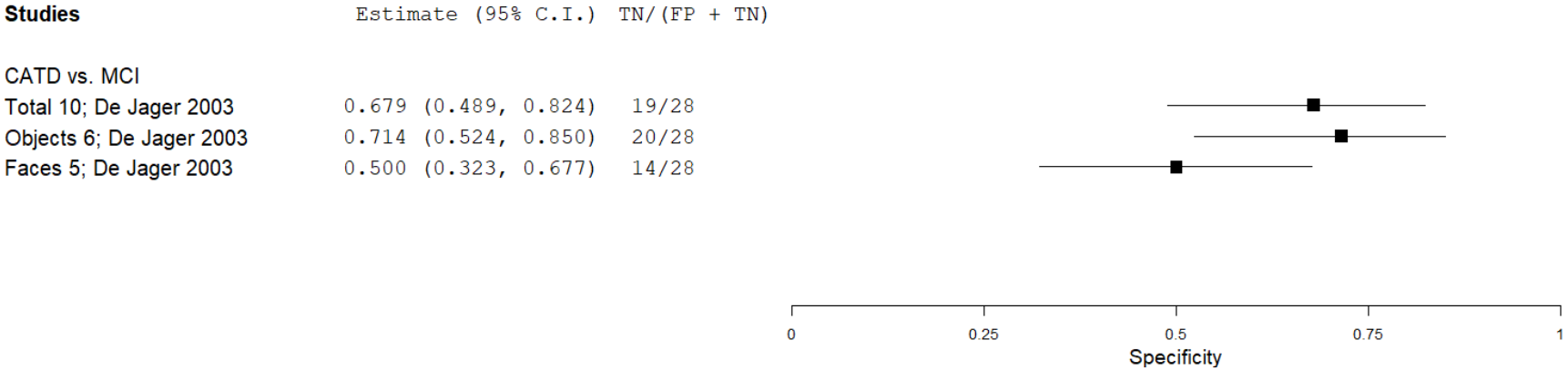
Abbrevations: aMCI=amnestic mild cognitive impairment; CATD=Clinical Alzheimer's type dementia; NAB=Neuropsychological Assessment Battery; NC=normal control

Figure C.49. Sensitivity results of TPT in eligible studies with low-moderate risk of bias



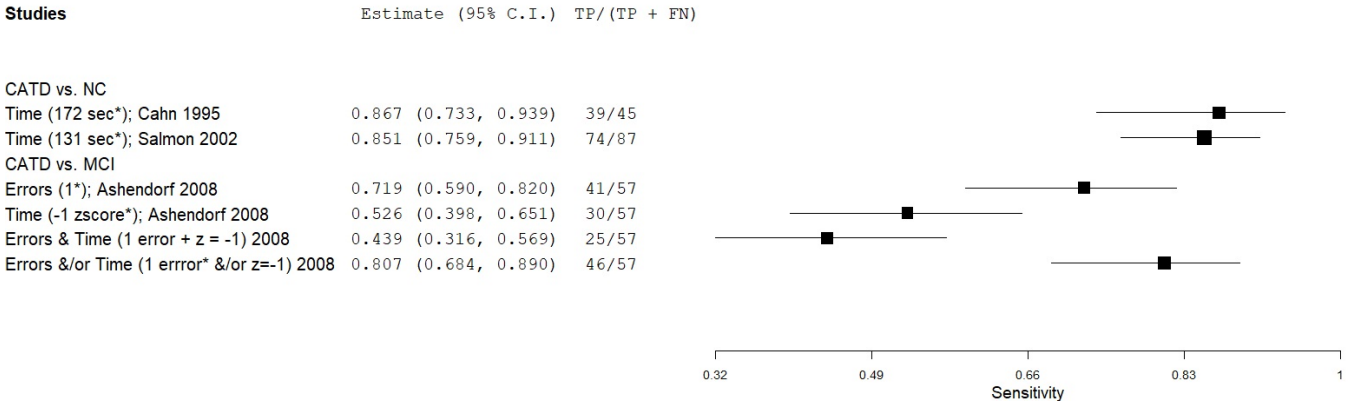
Abbrevations: CATD=Clinical Alzheimer's type dementia; MCI=Mild Cognitive Impairment; TPT=The Placing Test

Figure C.50. Specificity results of TPT in eligible studies with low-moderate risk of bias



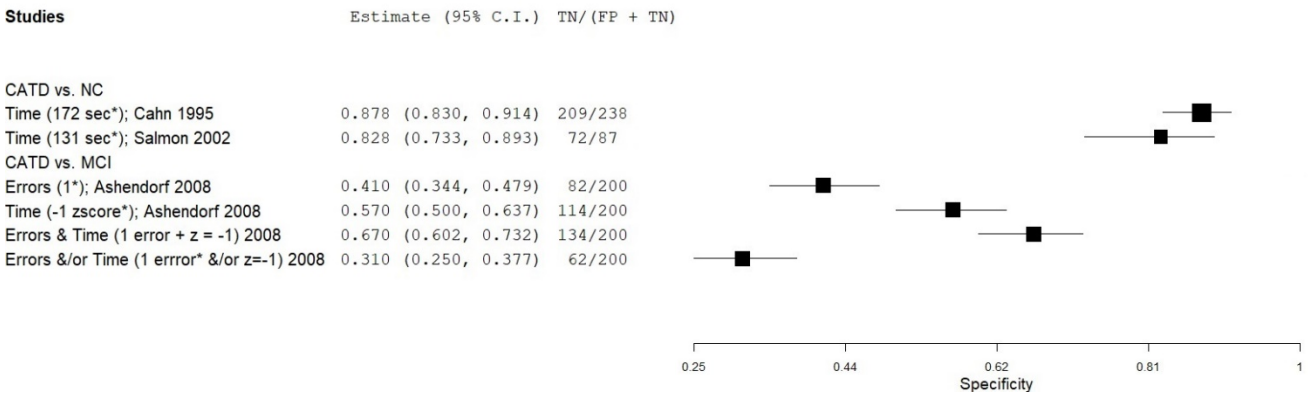
Abbrevations: CATD=Clinical Alzheimer's type dementia; MCI=Mild Cognitive Impairment; TPT=The Placing Test

Figure C.51. Sensitivity results of Trail Making Test part B in eligible studies with low-moderate risk of bias



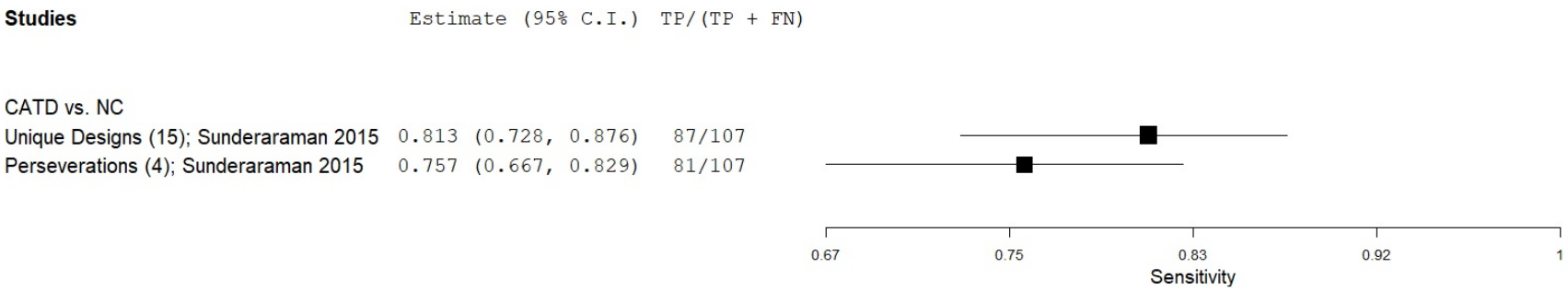
Abbrevations: CATD=Clinical Alzheimer's type dementia; MCI=mild cognitive impairment; NC=normal control

Figure C.52. Specificity results of Trail Making Test part B in eligible studies with low-moderate risk of bias



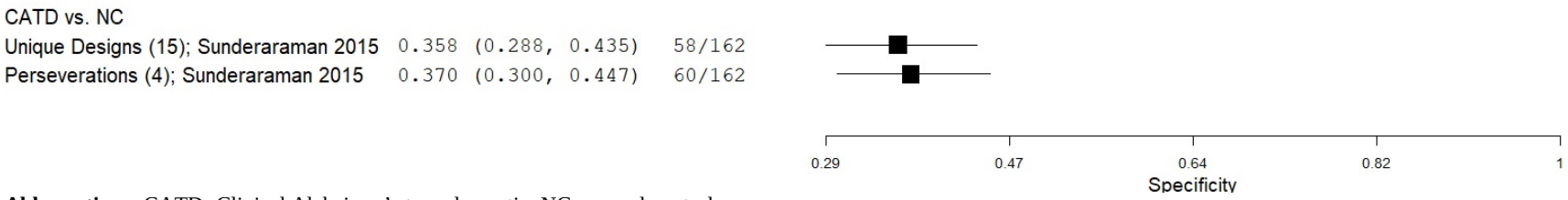
Abbrevations: CATD=Clinical Alzheimer's type dementia; MCI=mild cognitive impairment; NC=normal control

Figure C.53. Sensitivity results of Graphic Pattern Generation test in eligible studies with low-moderate risk of bias



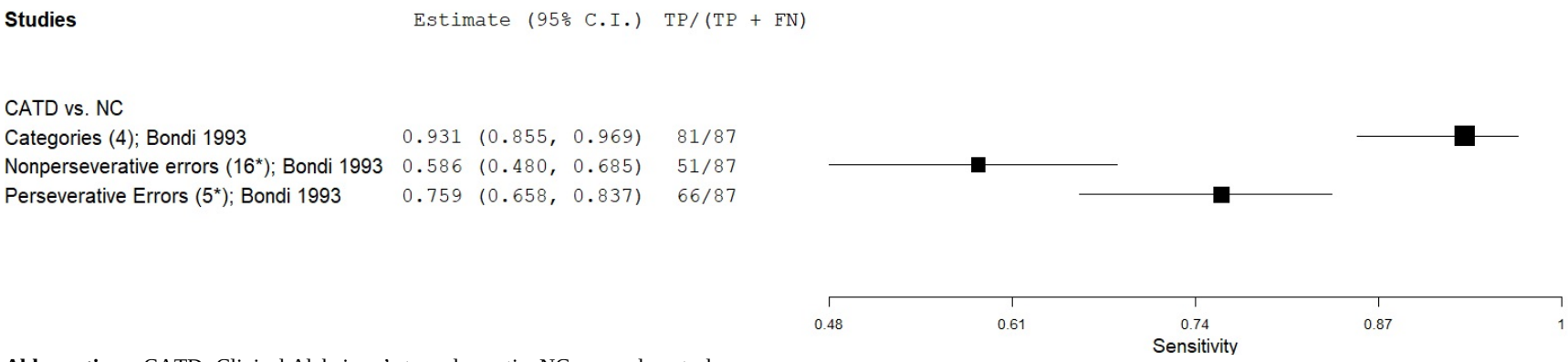
Abbrevations: CATD=Clinical Alzheimer's type dementia; NC=normal control

Figure C.54. Specificity results of Graphic Pattern Generation test in eligible studies with low-moderate risk of bias



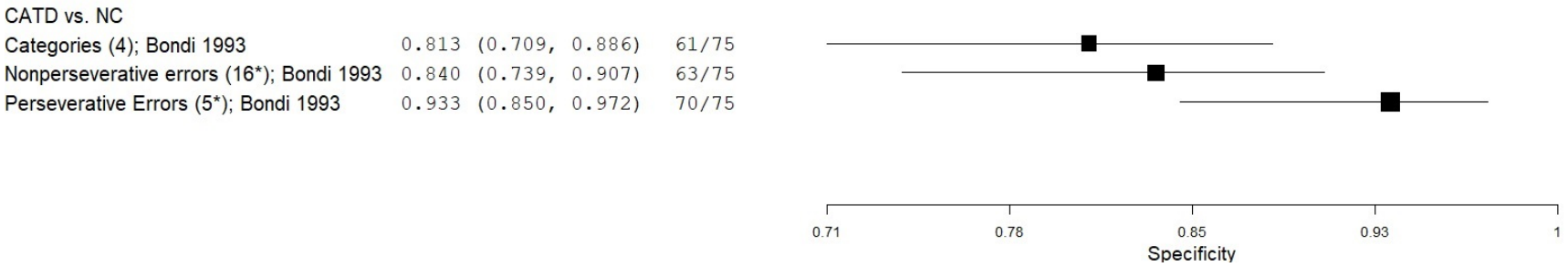
Abbrevations: CATD=Clinical Alzheimer's type dementia; NC=normal control

Figure C.55. Sensitivity results of Wisconsin Card Sorting test in eligible studies with low-moderate risk of bias



Abbrevations: CATD=Clinical Alzheimer's type dementia; NC=normal control

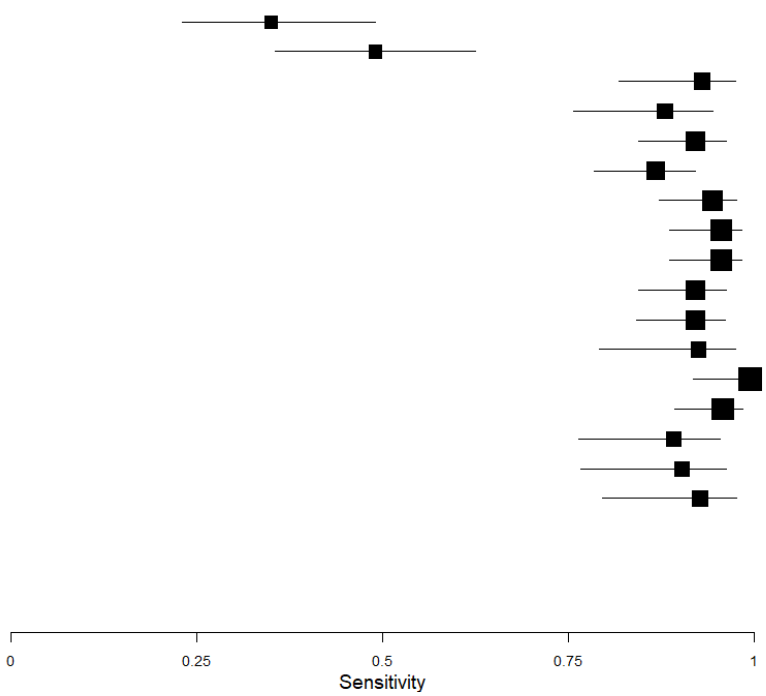
Figure C.56. Specificity results of Wisconsin Card Sorting test in eligible studies with low-moderate risk of bias



Abbrevations: CATD=Clinical Alzheimer's type dementia; NC=normal control

Figure C.57. Sensitivity results of semantic fluency in eligible studies with low-moderate risk of bias

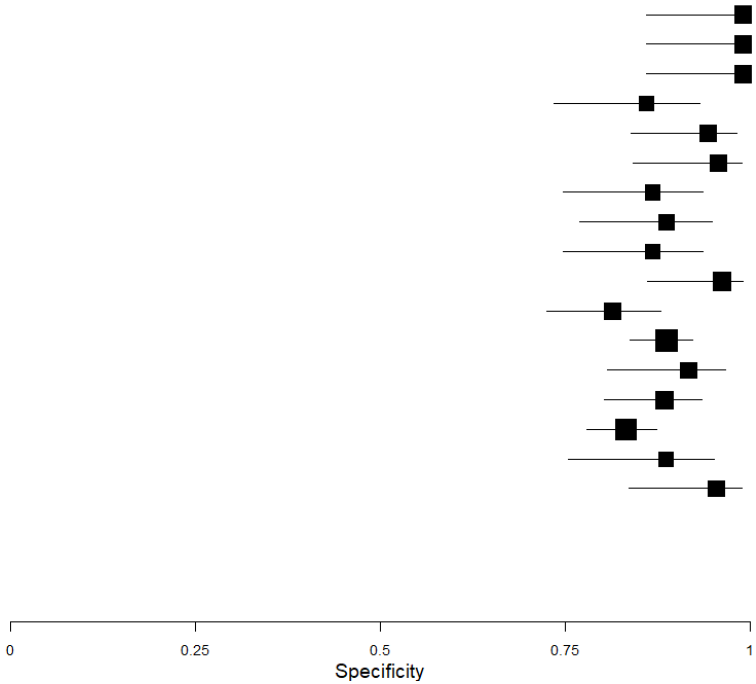
Studies	Estimate (95% C.I.)	TP/(TP + FN)
CATD vs. NC		
Animals (9.2) [Mild]; Welsh 1991/ 1992	0.350 (0.231, 0.491)	17/49
Animals (9.2) [Moderate]; Welsh 1991/ 1992	0.490 (0.356, 0.626)	24/49
Animals (9.2) [Severe]; Welsh 1991/ 1992	0.930 (0.818, 0.975)	46/49
Animals (12); Connor 2005	0.880 (0.758, 0.945)	44/50
Animals (13); Monsch 1992	0.921 (0.844, 0.962)	82/89
Animals (14); Canning 2004	0.867 (0.785, 0.921)	85/98
First names (15); Monsch 1992	0.944 (0.872, 0.976)	84/89
Fruits (10); Monsch 1992	0.955 (0.886, 0.983)	85/89
Vegetables (9); Monsch 1992	0.955 (0.886, 0.983)	85/89
Supermarket (15); Monsch 1992	0.921 (0.844, 0.962)	82/89
Supermarket (NR); Kalbe 2004	0.920 (0.842, 0.962)	81/88
Total (animals, fruits, vegetables) (28); Cerhan 2002	0.925 (0.792, 0.976)	37/40
Total (animals, fruits, vegetables) (37); Monsch 1992	0.994 (0.917, 1.000)	89/89
Total (animals, fruits, vegetables) (37); Salmon 2002	0.958 (0.893, 0.984)	91/95
Total (unspecified) (31); Cahn 1995	0.891 (0.764, 0.954)	41/46
Combined model (NR); Clark a) 2014	0.902 (0.767, 0.963)	37/41
Combined model (NR); Clark b) 2014	0.927 (0.796, 0.976)	38/41



Abbrevations: CATD=Clinical Alzheimer's type dementia; NC=normal control; OS=optimal score

Figure C.58. Specificity results of semantic fluency in eligible studies with low-moderate risk of bias

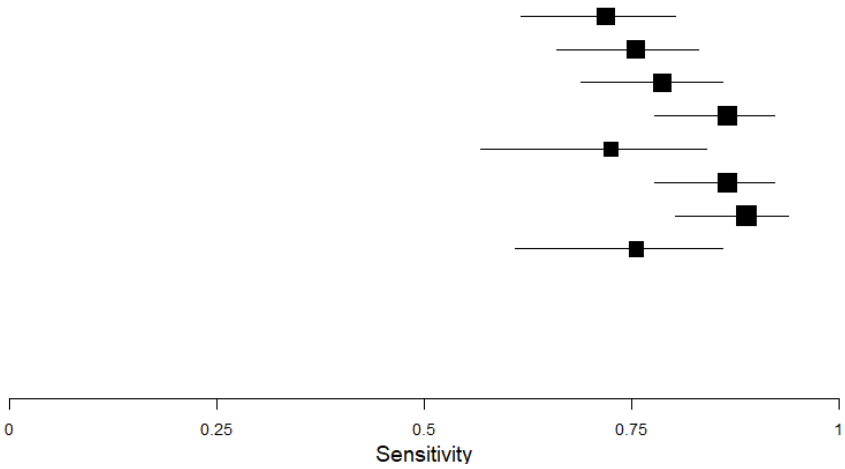
Studies	Estimate (95% C.I.)	TN/(FP + TN)
CATD vs. NC		
Animals (9.2) [Mild]; Welsh 1991/ 1992	0.990 (0.859, 0.999)	49/49
Animals (9.2) [Moderate]; Welsh 1991/ 1992	0.990 (0.859, 0.999)	49/49
Animals (9.2) [Severe]; Welsh 1991/ 1992	0.990 (0.859, 0.999)	49/49
Animals (12); Connor 2005	0.860 (0.734, 0.932)	43/50
Animals (13); Monsch 1992	0.943 (0.839, 0.982)	50/53
Animals (14); Canning 2004	0.957 (0.842, 0.989)	44/46
First names (15); Monsch 1992	0.868 (0.748, 0.936)	46/53
Fruits (10); Monsch 1992	0.887 (0.770, 0.948)	47/53
Vegetables (9); Monsch 1992	0.868 (0.748, 0.936)	46/53
Supermarket (15); Monsch 1992	0.962 (0.861, 0.991)	51/53
Supermarket (NR); Kalbe 2004	0.814 (0.725, 0.880)	79/97
Total (animals, fruits, vegetables) (28); Cerhan 2002	0.887 (0.838, 0.922)	196/221
Total (animals, fruits, vegetables) (37); Monsch 1992	0.917 (0.807, 0.967)	49/53
Total (animals, fruits, vegetables) (37); Salmon 2002	0.884 (0.803, 0.935)	84/95
Total (unspecified) (31); Cahn 1995	0.832 (0.779, 0.874)	198/238
Combined model (NR); Clark a) 2014	0.886 (0.755, 0.952)	39/44
Combined model (NR); Clark b) 2014	0.955 (0.836, 0.989)	42/44



Abbrevations: CATD=Clinical Alzheimer's type dementia; NC=normal control; OS=optimal score

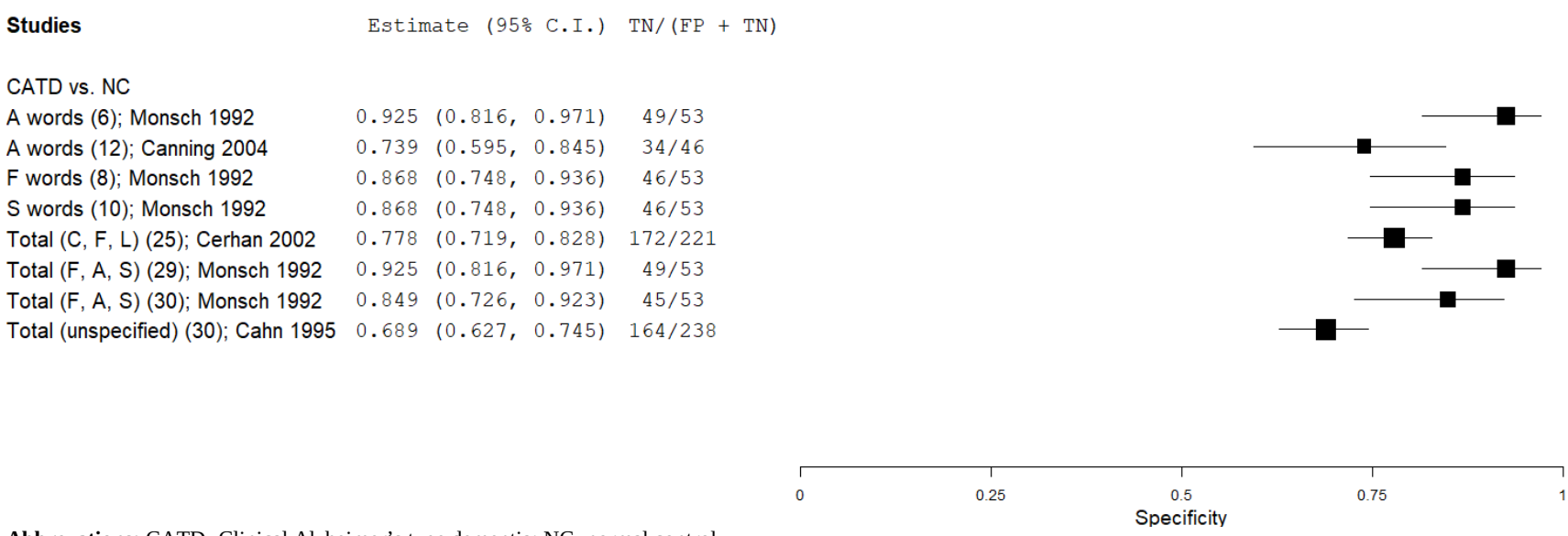
Figure C.59. Sensitivity results of phonemic fluency in eligible studies with low-moderate risk of bias

Studies	Estimate (95% C.I.)	TP/(TP + FN)
CATD vs. NC		
A words (6); Monsch 1992	0.719 (0.617, 0.803)	64/89
A words (12); Canning 2004	0.755 (0.661, 0.830)	74/98
F words (8); Monsch 1992	0.787 (0.689, 0.859)	70/89
S words (10); Monsch 1992	0.865 (0.777, 0.922)	77/89
Total (C, F, L) (25); Cerhan 2002	0.725 (0.568, 0.841)	29/40
Total (F, A, S) (29); Monsch 1992	0.865 (0.777, 0.922)	77/89
Total (F, A, S) (30); Monsch 1992	0.888 (0.804, 0.938)	79/89
Total (unspecified) (30); Cahn 1995	0.756 (0.610, 0.859)	34/45



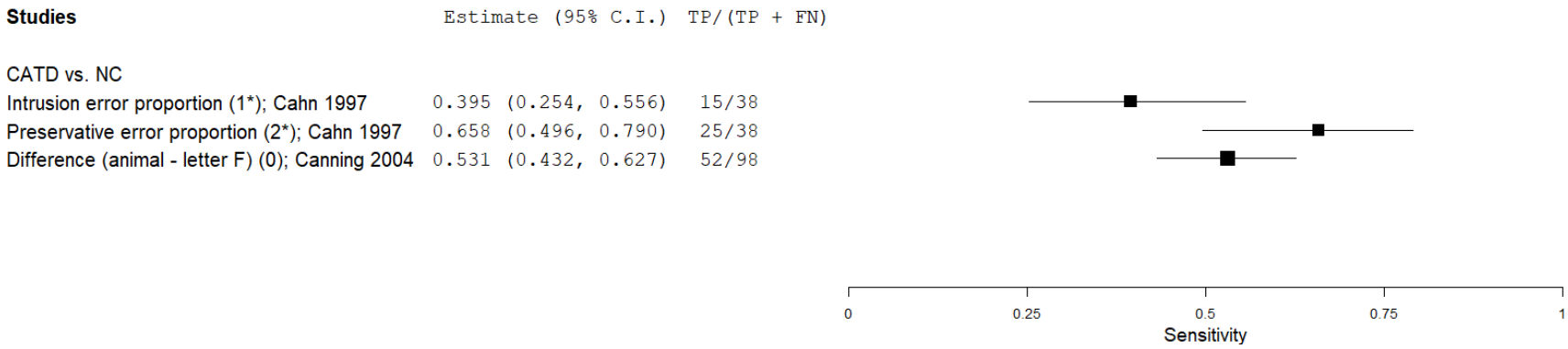
Abbrevations: CATD=Clinical Alzheimer's type dementia; NC=normal control

Figure C.60. Specificity results of phonemic fluency in eligible studies with low-moderate risk of bias



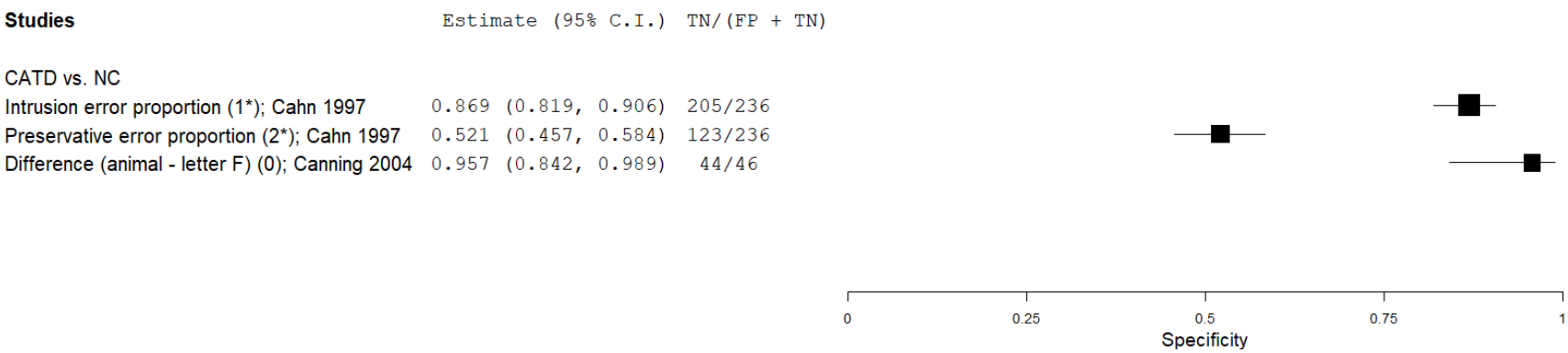
Abbrevations: CATD=Clinical Alzheimer's type dementia; NC=normal control

Figure C.61. Sensitivity results of mixed fluency in eligible studies with low-moderate risk of bias



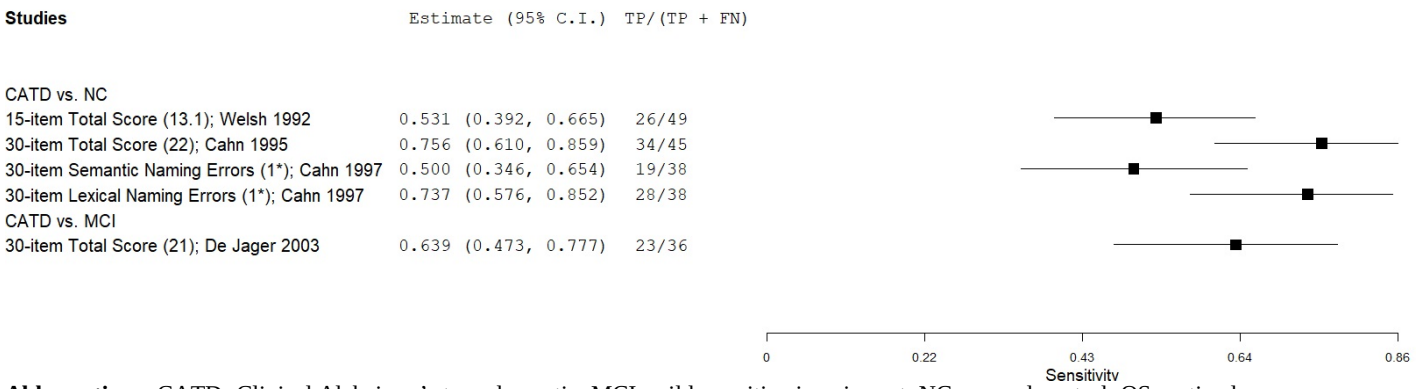
Abbrevations: CATD=Clinical Alzheimer's type dementia; NC=normal control

Figure C.62. Specificity results of mixed fluency in eligible studies with low-moderate risk of bias



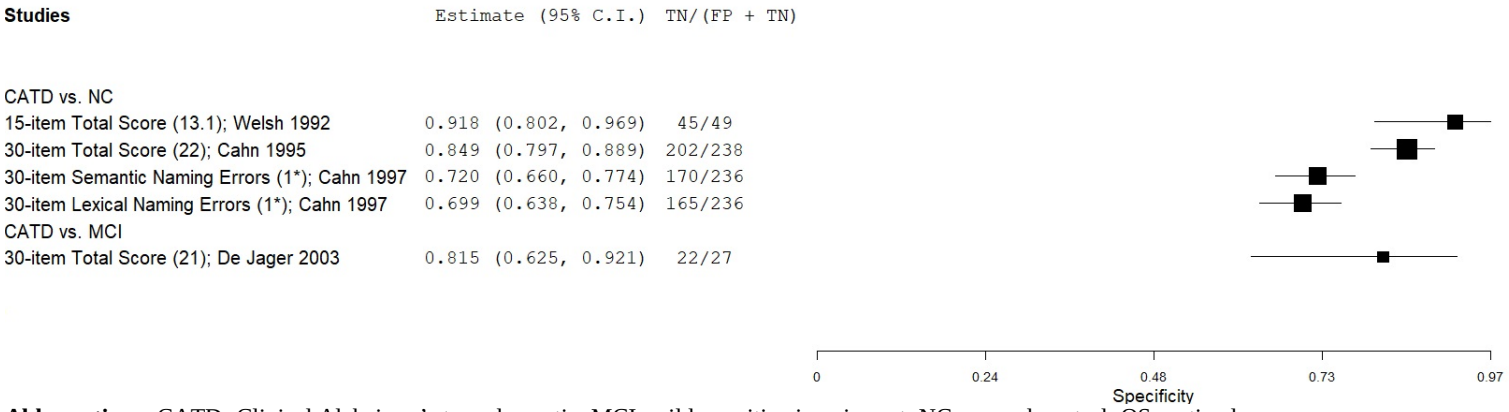
Abbrevations: CATD=Clinical Alzheimer's type dementia; NC=normal control

Figure C.63. Sensitivity results of Boston Naming Test in eligible studies with low-moderate risk of bias



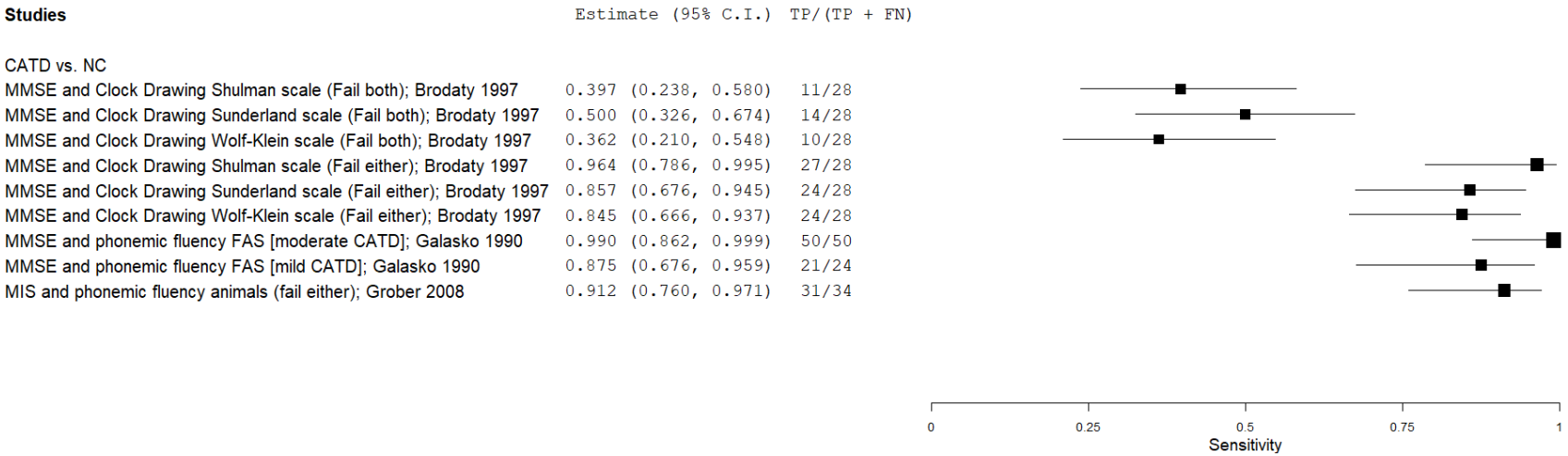
Abbrevations: CATD=Clinical Alzheimer's type dementia; MCI=mild cognitive impairment; NC=normal control; OS=optimal score

Figure C.64. Specificity results of Boston Naming Test in eligible studies with low-moderate risk of bias



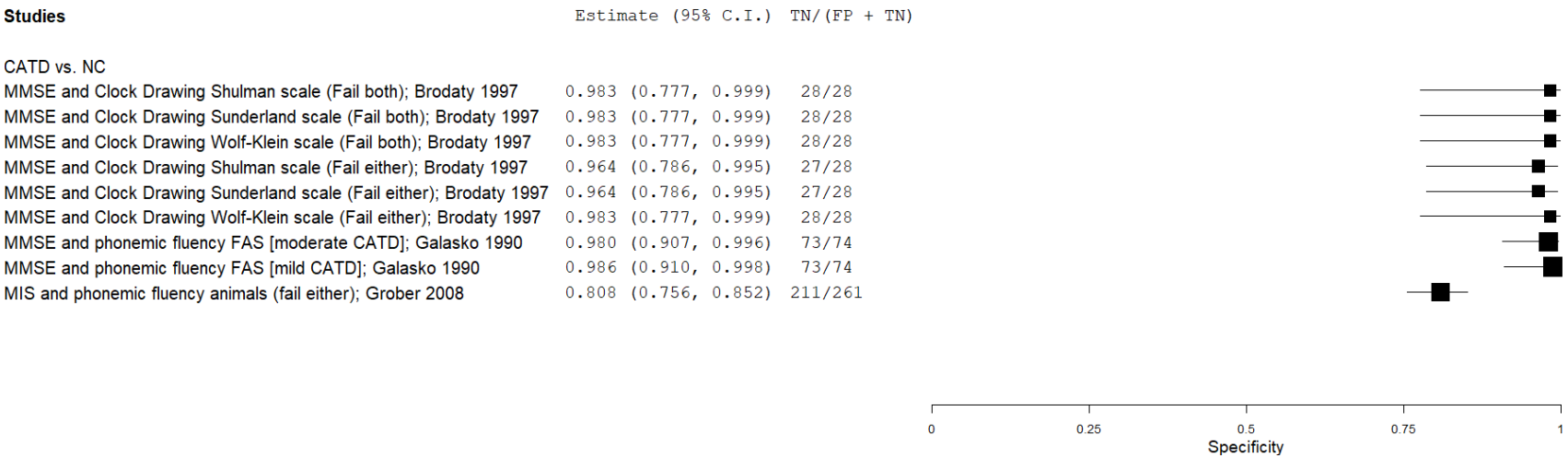
Abbrevations: CATD=Clinical Alzheimer's type dementia; MCI=mild cognitive impairment; NC=normal control; OS=optimal score

Figure C.65. Sensitivity results of brief stand-alone test + another cognitive test in eligible studies with low-moderate risk of bias



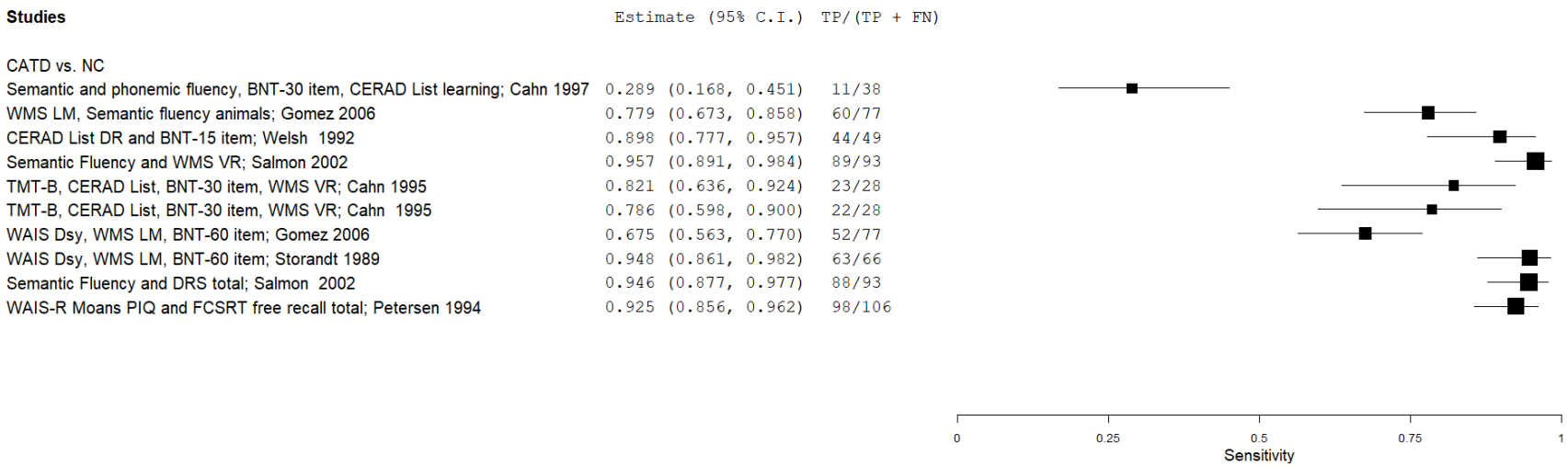
Abbrevations: CATD=Clinical Alzheimer's type dementia; MIS=Memory Impairment Screen; MMSE=Mini Mental State Examination; NC=normal control;

Figure C.66. Specificity results of brief stand-alone test + another cognitive test in eligible studies with low-moderate risk of bias



Abbrevations: CATD=Clinical Alzheimer's type dementia; MIS=Memory Impairment Screen; MMSE=Mini Mental State Examination; NC=normal control

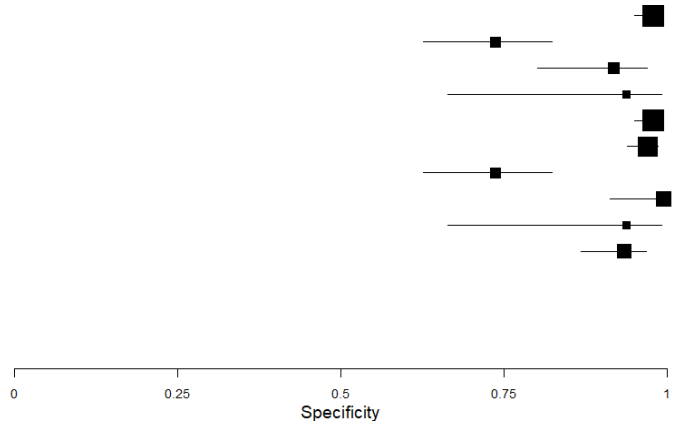
Figure C.67. Sensitivity results of other combination tests in eligible studies with low-moderate risk of bias



Abbrevations: BNT=Boston Naming Test; CATD=Clinical Alzheimer's type dementia; CERAD=Constortium to Establish Registry for Alzheimer's Diease; DR=Delayed Recall; DRS=Dementia Rating Scale; Dsy=Digit Symbol; FCSRT=Free and Cued Selective Reminding Test; LM=Logical Memory; MCI=mild cognitive impairment; MMSE=Mini Mental State Examination; NC=normal control; OS=optimal score; PIQ=Performance Intelligence Quotient; TMT-B=Trail Making Test part B; VR=visual reproduction; WAIS=Wechsler Adult Intelligence Scale; WMS=Wechsler Memory Scale

Figure C.68. Specificity results of other combination tests in eligible studies with low-moderate risk of bias

Studies	Estimate (95% C.I.)	TN/(FP + TN)
CATD vs. NC		
Semantic and phonemic fluency, BNT-30 item, CERAD List learning; Cahn 1997	0.979 (0.950, 0.991)	231/236
WMS LM, Semantic fluency animals; Gomez 2006	0.737 (0.627, 0.823)	56/76
CERAD List DR and BNT-15 item; Welsh 1992	0.918 (0.802, 0.969)	45/49
Semantic Fluency and WMS VR; Salmon 2002	0.938 (0.665, 0.991)	15/16
TMT-B, CERAD List, BNT-30 item, WMS VR; Cahn 1995	0.979 (0.949, 0.991)	228/233
TMT-B, CERAD List, BNT-30 item, WMS VR; Cahn 1995	0.970 (0.938, 0.986)	226/233
WAIS Dsy, WMS LM, BNT-60 item; Gomez 2006	0.737 (0.627, 0.823)	56/76
WAIS Dsy, WMS LM, BNT-60 item; Storandt 1989	0.994 (0.912, 1.000)	83/83
Semantic Fluency and DRS total; Salmon 2002	0.938 (0.665, 0.991)	15/16
WAIS-R Moans PIQ and FCSRT free recall total; Petersen 1994	0.934 (0.868, 0.968)	99/106



Abbrevations: BNT=Boston Naming Test; CATD=Clinical Alzheimer's type dementia; CERAD=Constortium to Establish Registry for Alzheimer's Diease; DR=Delayed Recall; DRS=Dementia Rating Scale; Dsy=Digit Symbol; FCSRT=Free and Cued Selective Reminding Test; LM=Logical Memory; MCI=mild cognitive impairment; MMSE=Mini Mental State Examination; NC=normal control; OS=optimal score; PIQ=Performance Intelligence Quotient; TMT-B=Trail Making Test part B; VR=visual reproduction; WAIS=Wechsler Adult Intelligence Scale; WMS=Wechsler Memory Scale

Appendix D. Key Question 2: Accuracy, Comparative Accuracy, and Harms of Biomarkers for Identifying Pathologically Confirmed AD

Appendix Table D.1. Risk of bias ratings: imaging classification accuracy studies

Study	Risk of Bias: Patient Selection *(0=low, 1=high or unclear)*	Risk of Bias: Index Test *(0=low, 1=high or unclear)*	Risk of Bias: Reference Standard *(0=low, 1=high or unclear)*	Risk of Bias: Flow and Timing *(0=low, 1=high or unclear)*	Applicability Concerns: Patient Selection *(0=low, 1=high or unclear)*	Applicability Concerns: Index Test *(0=low, 1=high or unclear)*	Applicability Concerns: Reference Standard *(0=low, 1=high or unclear)*	Total Score	ROB Rating
Barkhof 2007[71]	0	0	0	0	0	1	0	1	Low
Bonte 2011[72]	1	1	1	0	0	0	0	3	Medium
Burton 2009[73]	1	1	0	0	0	0	0	2	Medium
Clark 2012[74]	1	0	0	0	1	0	0	2	Medium
Foster 2007[75]	0	1	0	1	0	0	0	2	Medium
Harper 2016[76]	1	1	0	0	0	0	0	2	Medium
Jagust 2001[77]	1	0	0	0	1	0	0	2	Medium
Jagust 2007[78]	0	0	0	1	0	0	0	1	Low
La Joie 2019[79]	1	1	1	0	0	0	0	3	Medium
Rollin-Sillaire 2012[80]	0	0	0	1	0	0	0	1	Low
Rusina 2010[81]	1	1	0	1	0	0	0	3	Medium
Sabri 2015[82]	1	1	0	0	1	0	0	3	Medium
Salloway 2017[83]	1	0	0	0	1	0	0	2	Medium
Silverman 2001[84]	1	0	0	1	0	0	0	2	Medium

Study	Risk of Bias: Patient Selection *(0=low, 1=high or unclear)*	Risk of Bias: Index Test *(0=low, 1=high or unclear)*	Risk of Bias: Reference Standard *(0=low, 1=high or unclear)*	Risk of Bias: Flow and Timing *(0=low, 1=high or unclear)*	Applicability Concerns: Patient Selection *(0=low, 1=high or unclear)*	Applicability Concerns: Index Test *(0=low, 1=high or unclear)*	Applicability Concerns: Reference Standard *(0=low, 1=high or unclear)*	Total Score	ROB Rating
Vemuri 2011[85]	1	1	1	0	0	0	0	3	Medium

Abbreviations: ROB=Risk of Bias.

Appendix Table D.2. PET amyloid imaging studies with low or moderate risk of bias

Author Year	Participants' Clinical Diagnosis (Criteria)	Classification Question	Comparator Population: Neurodegenerative Dementia	Comparator Population: Other Neuropathology	PET Amyloid Classification Criteria	Neuropathological Criteria
Clark 2012[74, 86]	AD, other dementing disorders, MCI, normal cognition (physician evaluation)	AD vs. non-AD	No AD, possible AD	No AD	Visual judgment AD: tracer retention in cortical gray matter or intense uptake in at least one cortical region Quantitative AD: SUVR cutoff 1.10	AD: CERAD, NIA-Reagan Non-AD: did not meet AD criteria, including beta-amyloid negative
Sabri 2015[82,87, 88]	AD, other dementing disorders, and non-dementia (not specified)	AD vs. non-AD	FTLD, multisystem glial, neuronal tauopathy, no neurodegenerative pathology, PD (analysis based on beta-amyloid + vs. -)	No neurodegenerative pathology	Visual judgment AD: moderate or pronounced regional cortical tracer uptake Raters trained via in-person training or e-training Quantitative AD: SUVR cutoff 0.78, 0.96, 1.47, 1.48	AD: CERAD, BSS or IHC Non-AD: beta-amyloid negative

Author Year	Participants' Clinical Diagnosis (Criteria)	Classification Question	Comparator Population: Neurodegenerative Dementia	Comparator Population: Other Neuropathology	PET Amyloid Classification Criteria	Neuropathological Criteria
Salloway 2017[83] [89-91]	AD, other dementing disorders, memory loss, normal cognition (reported medical history)	AD vs. non-AD	Absence of AD neuropathology	Absence of AD neuropathology	Visual judgment AD: regional presence of amyloid	AD: CERAD, mCERAD, Thal phasing, NIA-Reagan, ADNC Non-AD: did not meet AD criteria
La Joie 2019[79] **(Villeneuve 2015**[92, 93]	AD, other dementing disorders, MCI, normal cognition (standard research criteria)	AD vs. non-AD	Absence of AD neuropathology	Absence of AD neuropathology	Quantitative AD: SUVR cutoff 1.20 and 1.21; DVR cutoff 1.06 and 1.08; and Centiloid 12.2, 23.5, 24.4	AD: CERAD, Thal phase, ADNC Non-AD: did not meet AD criteria

Abbreviations: AD=Alzheimer's disease; BSS=Bielschowsky silver staining; CERAD=Consortium to Establish a Registry for Alzheimer's Disease; DVR=distribution volume ratio; mCERAD=modified CERAD=Consortium to Establish a Registry for Alzheimer's Disease; FTLD=frontotemporal lobar degeneration; IHC=immunohistochemistry; MCI=mild cognitive impairment; NIA-AA=National Institute on Aging-Alzheimer's Association; PD=Parkinson's disease; PET=positron emission tomography; SUVR=standardized uptake value ratio.

Appendix Table D.3. FDG-PET imaging studies with low to moderate risk of bias

Author Year	Participants' Clinical Diagnoses (Criteria)	Classification Question	Comparator Population: Neurodegenerative Dementia	Comparator Population: Other Neuropathology	FDG-PET Classification Criteria	Neuropathological Criteria
Foster 2007[75]	Dementia (Consensus panel record review)	AD vs. FTLD	FTLD	none	Visual judgment AD: Hypometabolism posterior > anterior. FTLD: Hypometabolism frontal, anterior, or anterior temporal > posterior.	AD: NIA-R FTLD: Any of several findings

Author Year	Participants' Clinical Diagnoses (Criteria)	Classification Question	Comparator Population: Neurodegenerative Dementia	Comparator Population: Other Neuropathology	FDG-PET Classification Criteria	Neuropathological Criteria
Jagust 2007[78]	Dementia, cognitive impairment, or normal cognition (Clinical evaluation with consensus conference)	AD vs. non-AD	Alcoholic encephalopathy with Korsakoff syndrome, CVD without AD, CVD with AD, LBD, FTLD, normal brain, possible AD, unidentified leukoencephalopathy	Normal brain, CVD without AD, alcoholic encephalopathy with Korsakoff syndrome, unidentified leukoencephalopathy	Visual judgment; AD: Hypometabolism of bilateral temporal or parietal, posterior cingulate, or highly asymmetric temporoparietal	AD: CERAD, NIA-R Non-AD: Not meeting AD neuropathological criteria
Silverman 2001[84]	Clinically referred for possible dementia; categorized as progressive vs. nonprogressive cognitive impairment (Clinical evaluation with consensus diagnosis)	AD vs. non-AD	FTLD, LBD, CJD, PSG, PSP, lipofuscinosis Kufs disease, no neurodegenerative dementia	No neurodegenerative dementia	Visual judgement AD: Hypometabolism in parietal, temporal, and/or frontal lobes; diffuse hypometabolism in cortex w/relative sparing in sensorimotor cortex; pattern of cerebral metabolism for AD associated with cognitive decline	AD: "Accepted research criteria," but specific criteria varied between study sites Other: "Methods and criteria standard for each institution at the time pathological examination was conducted"

Abbreviations: AD=Alzheimer's disease; CERAD=Consortium to Establish a Registry for Alzheimer's Disease; CJD= Creutzfeldt-Jakob disease; CVD=cerebrovascular disease; FDG PET=fluorodeoxyglucose positron emission tomography; FTLD=frontotemporal lobar degeneration; LBD=Lewy body disease; NIA-R=National Institute on Aging-Reagan Institute; PET=positron emission tomography; PSG=progressive subcortical gliosis; PSP=progressive supranuclear palsy

Appendix Table D.4. SPECT imaging studies with low to moderate risk of bias

Author Year	Participants' Clinical Diagnosis (Criteria)	Classification Question	Comparator Population: Neurodegenerative Dementia	Comparator Population: Other Neuropathology	SPECT Classification Criteria	Neuropathological Criteria
Bonte 2011[72, 94, 95]	Possible dementia (physician evaluation)	AD vs. non-AD	Not specified for full sample, includes FTLD, multisystem degeneration, adult polyglucosan body disease, Pick disease, progressive supranuclear palsy, dysphasic dementia	Not specified for full sample	Visual judgment AD: diminished RCBF in inferior medial aspects of the temporal lobes, reduced RCBF in limbic structures and posterior temporal lobes, parietal lobes, and frontal regions	AD: CERAD Non-AD: Not specified
Jagust 2001[77]	Dementia and no cognitive impairment (Full clinical evaluation)	AD vs. non-AD	CVD, FTLD, ischemia/vascular disease, nonspecific changes/unknown, normal, PD, PSP (may not be comprehensive due to limited reporting)	Normal, CVD, nonspecific changes/unknown (may not be comprehensive due to limited reporting)	Visual judgment AD: bilateral or asymmetric temporal or parietal lobe hypoperfusion or both	AD: CERAD, criteria described by Khachaturian Non-AD: Standard criteria for other dementia etiologies
Rollin-Sillaire 2012[80]	Dementia (Consensus record review and current international diagnostic criteria)	AD vs. non-AD	LBD, FTLD, VaD	VaD	Visual and semi-quantitative judgment AD: temporoparieto-occipital hypoperfusion	AD: NIA-R Non-AD: Consensus criteria (FTLD), 3rd report of the DLB consortium (DLB), International Society of Neuropathology (VaD)
Rusina 2010[81]	AD and ALS (AD: NINCDS-ADRDA and DSM-IV)	AD vs. ALS	ALS	none	Image analysis AD: <57.11 watershed regions in the parietal lobe	AD: CERAD, NIA-R ALS: No significant AD related pathology

Abbreviations: AD=Alzheimer's disease; ALS=amyotrophic lateral sclerosis; CERAD=Consortium to Establish a Registry for Alzheimer's Disease; CVD=cerebrovascular disease; DLB=Dementia with Lewy bodies; DSM-IV=Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition); FTLD=frontotemporal lobar degeneration;

LBD=Lewy body disease; NIA-R=National Institute on Aging-Reagan Institute; NINCDS-ADRDA=National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders; PD=Parkinson's disease; PSP=progressive supranuclear palsy; SPECT=single-photon emission computerized tomography; VaD= vascular dementia.

Appendix Table D.5. MRI MTA imaging studies with low to moderate risk of bias

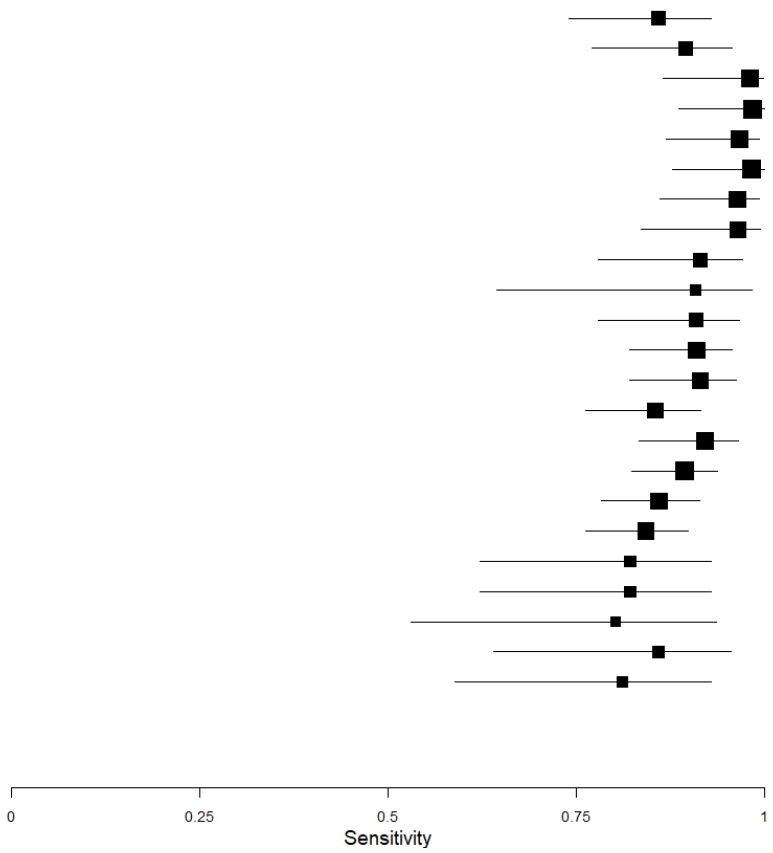
Author Year	Clinical Diagnosis (criteria)	Question	Comparator Population: Neurodegenerative Dementia	Comparator Population: Other Neuropathology	MRI MTA Classification Criteria	Neuropathological Criteria
Vemuri 2011[85]	NINCDS-ADRDA, DSM-IV, McKeith 2005 [96]	AD vs. non-AD	LBD, FTLD	none	Measured grey matter volume in multiple regions of interest, clustered participants by atrophy pattern	AD: NIA-R, CERAD Other: Mackenzie 2010, Whitwell 2009 , McKeith 2005
Burton 2009[73]	NINCDS-ADRDA, NINDS-AIRENS, Harmonization Criteria [97]	AD vs. non-AD	LBD, VCI	VCI	ROC curve analysis of 5-point MTA visual rating scale[98]	AD: CERAD, Braak staging, Newcastle diagnostic criteria Other: McKeith 1996
Barkhof 2007[71]	DSM-III-R or health/social work records	AD vs. L-rP AD vs. borderline AD	L-rP, no significant pathology	No significant pathology	Cutoff chosen from previously published criteria[98]	AD: CERAD, Braak staging L-rP: At least one a-synuclei positive neurite present in the Ammon's horn of the hippocampus and a Lewy body in at least one cortical sample orderline AD: did not fulfill AD or normal aging criteria
Harper 2016[76]	Unspecified dementia diagnosis	AD vs. LBD AD vs. FTLD	LBD, FTLD	none	ROC curve analysis of 5-point MTA visual rating scale [98]	All: "According to standard histopathological processes and criteria in use at the time of assessment"

Abbreviations: AD=Alzheimer's disease; CERAD=Consortium to Establish a Registry for Alzheimer's Disease; DSM-III-R=Diagnostic and Statistical Manual of Mental Disorders (Third Edition, Revised); DSM-IV= Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition); FTLD=frontotemporal lobar degeneration; LBD=Lewy body disease; L-rP=Lewy-related pathology; mCERAD=modified Consortium to Establish a Registry for Alzheimer's Disease; MRI=magnetic resonance imaging; MTA=medial temporal lobe atrophy; NIA-AA=National Institute of Aging – Alzheimer's Association; NIA-R=National Institute on Aging-Reagan Institute; NINCDS-ADRDA= National

Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders; NINCDS-AIRENS=National Institute of Neurologic Disorders and Stroke/Association Internationale pour la Recherche et I'Enseignement en Neurosciences; TDP43=TAR DNA-binding protein 4; VCI=vascular cognitive impairment

Figure D.1. Sensitivity results of PET amyloid in eligible studies with low-moderate risk of bias*

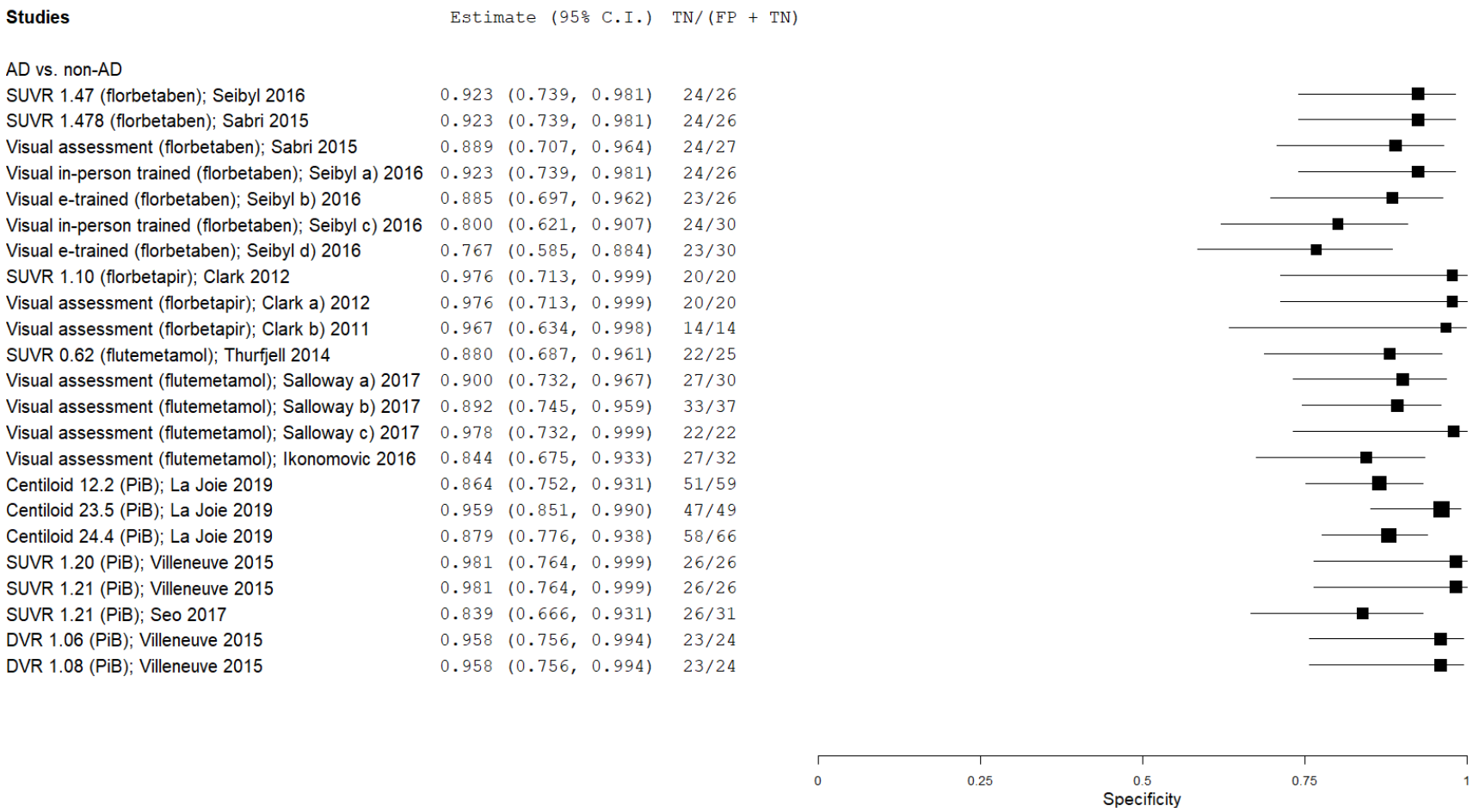
Studies	Estimate (95% C.I.)	TP/(TP + FN)
AD vs. non-AD		
SUVR 1.47 (florbetaben); Seibyl 2016	0.857 (0.739, 0.927)	48/56
SUVR 1.478 (florbetaben); Sabri 2015	0.894 (0.769, 0.955)	42/47
Visual assessment (florbetaben); Sabri 2015	0.979 (0.864, 0.997)	46/47
Visual in-person trained (florbetaben); Seibyl a) 2016	0.982 (0.884, 0.997)	55/56
Visual e-trained (florbetaben); Seibyl b) 2016	0.964 (0.868, 0.991)	54/56
Visual in-person trained (florbetaben); Seibyl c) 2016	0.981 (0.876, 0.997)	51/52
Visual e-trained (florbetaben); Seibyl d) 2016	0.962 (0.859, 0.990)	50/52
SUVR 1.10 (florbetapir); Clark 2012	0.963 (0.834, 0.992)	38/39
Visual assessment (florbetapir); Clark a) 2012	0.912 (0.777, 0.969)	36/39
Visual assessment (florbetapir); Clark b) 2011	0.906 (0.643, 0.981)	14/15
SUVR 0.62 (flutemetamol); Thurfjell 2014	0.907 (0.777, 0.965)	39/43
Visual assessment (flutemetamol); Salloway a) 2017	0.908 (0.819, 0.955)	69/76
Visual assessment (flutemetamol); Salloway b) 2017	0.913 (0.820, 0.960)	63/69
Visual assessment (flutemetamol); Salloway c) 2017	0.853 (0.761, 0.914)	72/84
Visual assessment (flutemetamol); Ikonomovic 2016	0.919 (0.831, 0.963)	68/74
Centiloid 12.2 (PiB); La Joie 2019	0.892 (0.822, 0.936)	107/120
Centiloid 23.5 (PiB); La Joie 2019	0.858 (0.781, 0.911)	97/113
Centiloid 24.4 (PiB); La Joie 2019	0.841 (0.761, 0.897)	95/113
SUVR 1.20 (PiB); Villeneuve 2015	0.820 (0.622, 0.927)	20/24
SUVR 1.21 (PiB); Villeneuve 2015	0.820 (0.622, 0.927)	20/24
SUVR 1.21 (PiB); Seo 2017	0.800 (0.530, 0.934)	12/15
DVR 1.06 (PiB); Villeneuve 2015	0.857 (0.639, 0.953)	18/21
DVR 1.08 (PiB); Villeneuve 2015	0.810 (0.588, 0.927)	17/21



Abbrevations: AD=Alzheimer's disease; DVR= distribution volume ratio; PET= positron emission tomography; PiB=Pittsburgh compound B; SUVR=standardized uptake value ratio

* The forest plot does not show sensitivity and specificity results when we could not calculate true positive, true negative, false positive, and false negative. Complete diagnostic accuracy results can be found in Appendix Table D.6.

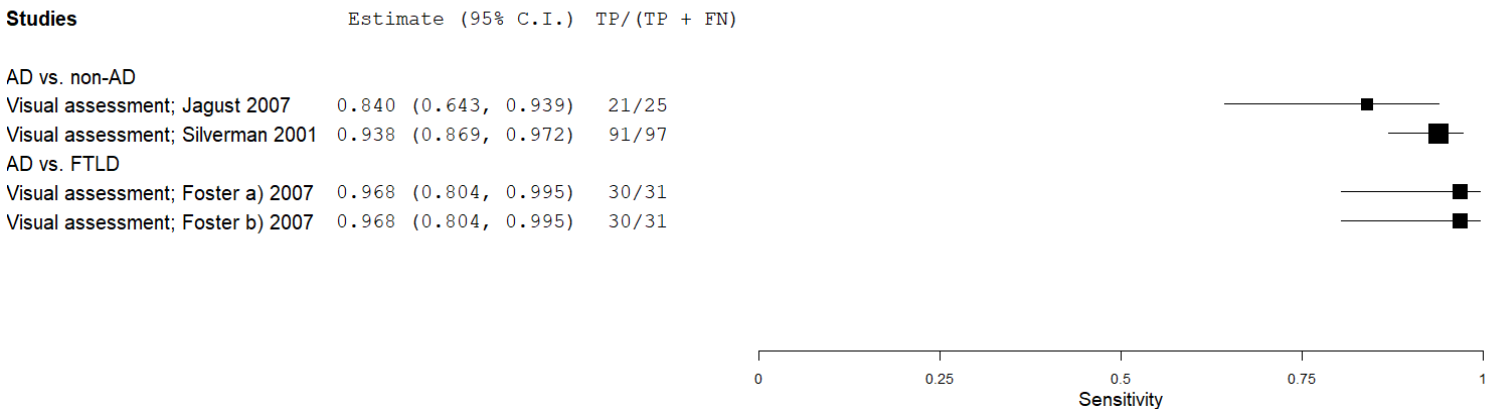
Figure D.2. Specificity results of PET amyloid in eligible studies with low-moderate risk of bias*



Abbrevations: AD=Alzheimer's disease; DVR= distribution volume ratio; PET= positron emission tomography; PiB=Pittsburgh compound B; SUVR=standardized uptake value ratio

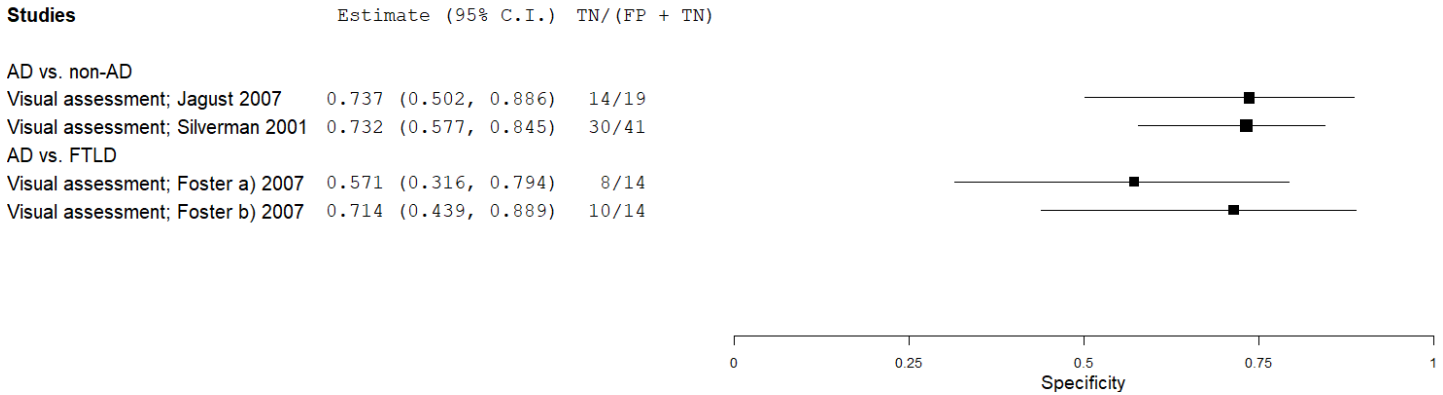
* The forest plot does not show sensitivity and specificity results when we could not calculate true positive, true negative, false positive, and false negative. Complete diagnostic accuracy results can be found in Appendix Table D.6.

Figure D.3. Sensitivity results of FDG-PET in eligible studies with low-moderate risk of bias



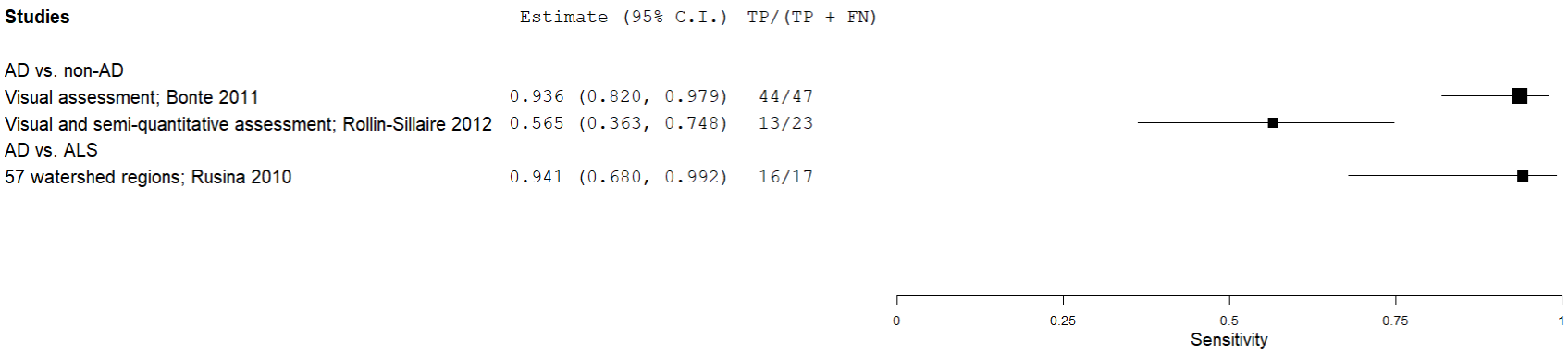
Abbrevations: AD=Alzheimer's disease; DVR= distribution volume ratio; FTLD=frontotemporal lobar degeneration

Figure D.4. Specificity results of FDG-PET in eligible studies with low-moderate risk of bias



Abbrevations: AD=Alzheimer's disease; DVR= distribution volume ratio; FTLD=frontotemporal lobar degeneration

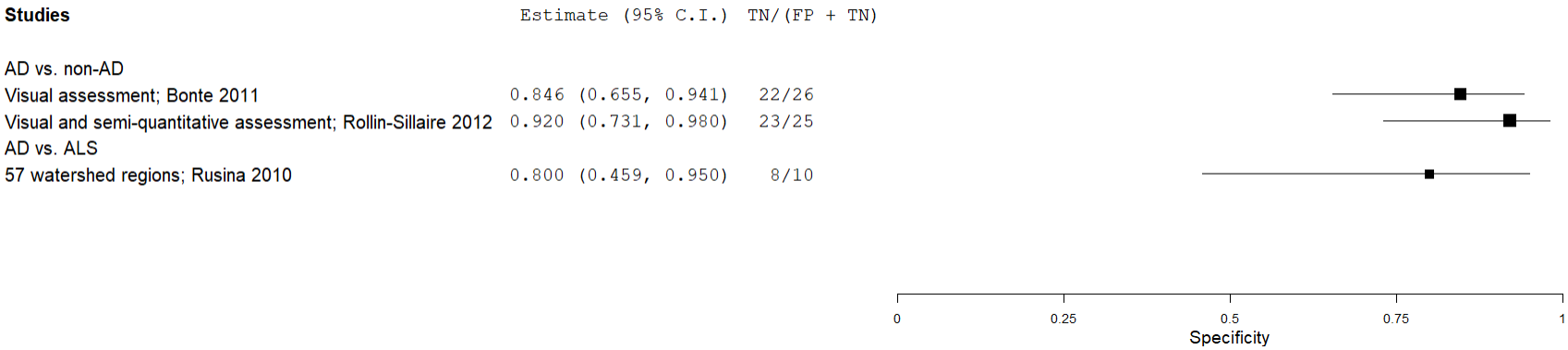
Figure D.5. Sensitivity results of SPECT in eligible studies with low-moderate risk of bias*



Abbrevations: AD=Alzheimer's disease; ALS=Amyotrophic lateral sclerosis; SPECT=single-photon emission computerized tomography

* The forest plot does not show sensitivity and specificity results when we could not calculate true positive, true negative, false positive, and false negative. Complete diagnostic accuracy results can be found in Appendix Table D.6.

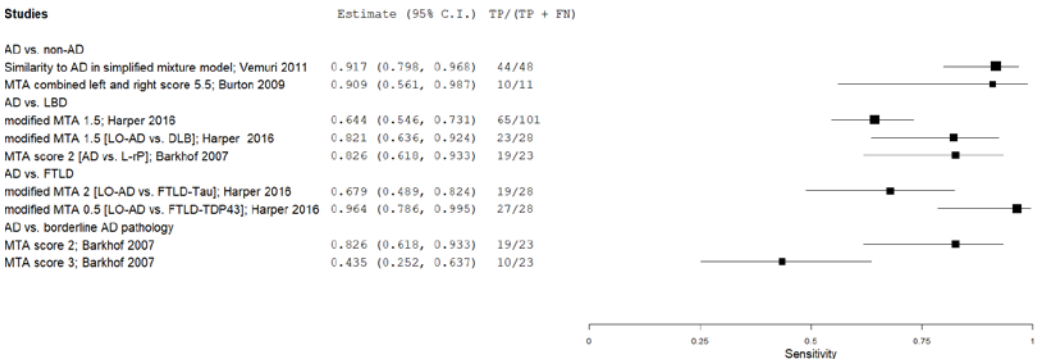
Figure D.6. Specificity results of SPECT in eligible studies with low-moderate risk of bias



Abbrevations: AD=Alzheimer's disease; ALS=Amyotrophic lateral sclerosis; SPECT=single-photon emission computerized tomography

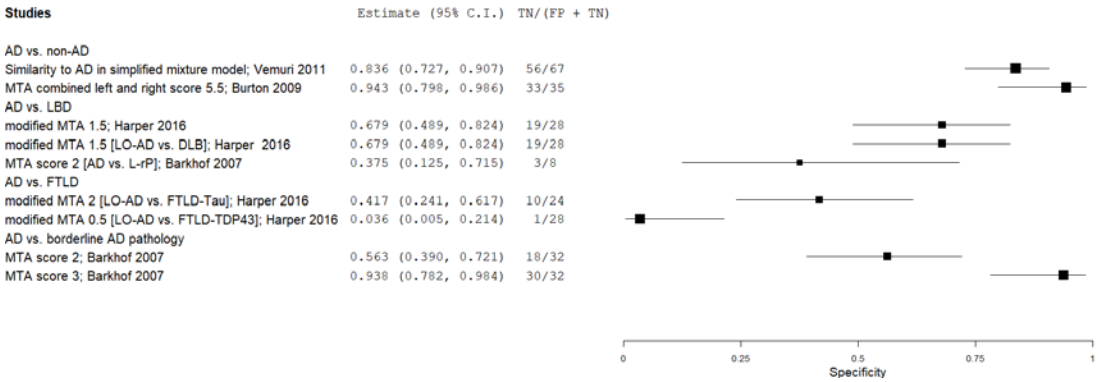
* The forest plot does not show sensitivity and specificity results when we could not calculate true positive, true negative, false positive, and false negative. Complete diagnostic accuracy results can be found in Appendix Table D.6.

Figure D.7. Sensitivity results of MRI MTA in eligible studies with low-moderate risk of bias



Abbrevations: AD=Alzheimer's disease; FTLD=frontotemporal lobar degeneration; LBD=lewy body dementia; MRI=magnetic resonance imaging; MTA=medial temporal atrophy

Figure D.8. Specificity results of MRI MTA in eligible studies with low-moderate risk of bias



Abbrevations: AD=Alzheimer's disease; FTLD=frontotemporal lobar degeneration; LBD=lewy body dementia; MRI=magnetic resonance imaging; MTA=medial temporal atrophy

Appendix Table D.6. Imaging studies: Classification accuracy results in eligible and low-moderate risk of bias imaging studies

Imaging Technique	Comparator	Chosen Cutoff	Author Year	AD N	Comparator N	Mean Age at Imaging (years)	Mean Interval Between Imaging and Autopsy (months)	Cutoff Determined by	Se (%)*	Sp (%)*	PPV (%)*	NPV (%)*	AD Base Rate
PET Florbetapir	non-AD: 15 no AD 5 possible AD	SUVR 1.10	Clark 2012[74]	39	20	NR	7	Derived in a separate group	0.97	1.00	1.00	0.95	0.66
PET Florbetapir	non-AD: 15 no AD 5 possible AD	Visual assessment	Clark 2012[74]	39	20	NR	7	Proposed clinical method	0.92	1.00	1.00	0.87	0.66
PET Florbetapir	non-AD: 14 no AD 4 possible AD	Visual assessment	Clark 2012[74]	28	18	NR	4	Proposed clinical method	0.96	1.00	1.00	0.95	0.61
PET Florbetapir	Non-AD: 14 no, possible, or low likelihood of AD	Visual assessment	Clark 2011[99]	15	14	NR	3	A priori criteria	0.93	1.0	1.0	0.93	0.52
PET PiB	non-AD: 26 beta-amyloid negative by CERAD	SUVR 1.20	Villeneuve 2015[92]	24	26	69.8	37	ROC analysis	0.83	1.00	1.00	0.87	0.48
PET PiB	non-AD: 26 beta-amyloid negative by CERAD	SUVR 1.21	Villeneuve 2015[92]	24	26	69.8	37	Derived in a separate group	0.83	1.00	1.00	0.87	0.48
PET PiB	non-AD: 24 beta-amyloid negative by CERAD	DVR 1.06	Villeneuve 2015[92]	21	24	69.8	37	ROC analysis	0.86	0.96	0.95	0.88	0.47
PET PiB	non-AD: 24 beta-amyloid negative by CERAD	DVR 1.08	Villeneuve 2015[92]	21	24	69.8	37	Derived in a separate group	0.81	0.96	0.94	0.85	0.47
PET PiB	Non-AD: 59 beta-amyloid negative by CERAD	CL 12.2	La Joie 2019[79]	120	59	73.0	40	ROC analysis	0.89	0.86	0.93	0.79	0.67
PET PiB	Non-AD: 49 beta-amyloid negative by Thal	CL 23.5	La Joie 2019[79]	113	49	73.0	40	ROC analysis	0.86	0.96	0.98	0.75	0.70
PET PiB	Non-AD: 66 none to low ADNC levels	CL 24.4	La Joie 2019[79]	113	66	73.0	40	ROC analysis	0.84	0.88	0.92	0.76	0.63
PET PiB	Non-AD: 31 not to low ADNC levels	SUVR 1.21	Seo 2017[93]	15	31	68.1	37	ROC analysis	0.80	0.82	0.69	0.89	0.33

Imaging Technique	Comparator	Chosen Cutoff	Author Year	AD N	Comparator N	Mean Age at Imaging (years)	Mean Interval Between Imaging and Autopsy (months)	Cutoff Determined by	Se (%)*	Sp (%)*	PPV (%)*	NPV (%)*	AD Base Rate
PET Florbetaben	non-AD: ** FTLD, PD, multisystem glial, neuronal tauopathy, no pathology	SUVR 1.478	Sabri 2015[82]	47	26	NR	11	ROC analysis	0.89	0.92	0.95	0.83	0.64
PET Florbetaben	Non-AD: 26 beta-amyloid negative by BSS and IHC	SUVR 1.47	Seibyl 2016[88]	56	26	NR	11	ROC analysis	0.86	0.92	0.96	0.75	0.68
PET Florbetaben	Non-AD: ** Beta-amyloid negative by BSS and IHC	SUVR 0.96 (composite/WCER)	Bullich 2017[87]	NR	NR	NR	11	Derived in a separate group	0.92	0.96	NR	NR	NR
PET Florbetaben	Non-AD: ** Beta-amyloid negative by BSS and IHC	SUVR 0.78 (composite/pons)	Bullich 2017[87]	NR	NR	NR	11	Derived in a separate group	0.92	0.96	NR	NR	NR
PET Florbetaben	non-AD: 23 pathologies other than AD (FTLD, PD, multisystem glial, neuronal tauopathy) 4 no pathology	Visual assessment	Sabri 2015[82]	47	27	NR	11	Previously described	0.98	0.89	0.94	0.96	0.64
PET Florbetaben	Non-AD: 26 beta-amyloid negative by BSS and IHC	Visual assessment (in-person training)	Seibyl 2016[88]	56	26	NR	11	A priori criteria	0.98	0.92	0.96	0.96	0.68
PET Florbetaben	Non-AD: 26 beta-amyloid negative by BSS and IHC	Visual assessment (e-training)	Seibyl 2016[88]	56	26	NR	11	A priori criteria	0.96	0.89	0.95	0.91	0.68
PET Florbetaben	Non-AD: 30 beta-amyloid negative by CERAD/ BSS staining	Visual assessment (in-person training)	Seibyl 2016[88]	52	30	NR	11	A priori criteria	0.98	0.80	0.89	0.96	0.63
PET Florbetaben	Non-AD: 30 beta-amyloid negative by CERAD/ BSS staining	Visual assessment (e-training)	Seibyl 2016[88]	52	30	NR	11	A priori criteria	0.96	0.76	0.87	0.92	0.63

Imaging Technique	Comparator	Chosen Cutoff	Author Year	AD N	Comparator N	Mean Age at Imaging (years)	Mean Interval Between Imaging and Autopsy (months)	Cutoff Determined by	Se (%)*	Sp (%)*	PPV (%)*	NPV (%)*	AD Base Rate
PET Flutemetamol	Non-AD: 25 beta-amyloid negative by mCERAD	SUVR 0.62 (pons/small)	Thurfjell 2014[91]	43	25	NR	3.5	ROC analysis	0.91	0.88	0.93	0.85	0.63
PET Flutemetamol	non-AD: 30 beta-amyloid negative by mCERAD	Visual assessment	Salloway 2017[83]	76	30	NR	8	Previously described	0.91	0.90	0.96	0.79	0.72
PET Flutemetamol	non-AD: 37 beta-amyloid negative by CERAD	Visual assessment	Salloway 2017[83]	69	37	NR	8	Previously described	0.92	0.88	0.93	0.86	0.65
PET Flutemetamol	non-AD: 22 beta-amyloid negative by Thal	Visual assessment	Salloway 2017[83]	84	22	NR	8	Previously described	0.86	1.00	1.0	0.65	0.79
PET Flutemetamol	non-AD: ** beta-amyloid negative	Visual assessment	Salloway 2017[83]	NR	NR	NR	≤12	Previously described	0.89	0.89	NR	NR	NR
PET Flutemetamol	Non-AD: 32 beta-amyloid negative by mCERADmode	Visual assessment	Ikonomovic 2016[90]	74	32	NR	8	A priori criteria	0.92	0.84	0.93	0.82	0.70
PET Flutemetamol	Non-AD: ** Less than intermediate likelihood of AD by NIA-Reagan	Visual assessment	Ikonomovic 2016[90]	NR	NR	NR	8	A priori criteria	0.79	0.91	NR	NR	NR
PET Flutemetamol	Non-AD: ** None to low ADNC levels	Visual assessment	Ikonomovic 2016[90]	NR	NR	NR	8	A priori criteria	0.88	0.82	NR	NR	NR
FDG-PET	non-AD: 4 possible AD 2 DLB 2 FTLD 5 cerebrovascular disease 2 mixed AD and cerebrovascular pathology 2 normal 1 leukoencephalo-pathy 1 alcoholic	Visual assessment	Jagust 2007[78]	25	19	NR	43	A priori criteria	0.84	0.74	0.81	0.78	0.57

Imaging Technique	Comparator	Chosen Cutoff	Author Year	AD N	Comparator N	Mean Age at Imaging (years)	Mean Interval Between Imaging and Autopsy (months)	Cutoff Determined by	Se (%)*	Sp (%)*	PPV (%)*	NPV (%)*	AD Base Rate
	encephalopathy with Korsakoff syndrome												
FDG-PET	non-AD: ** possible AD, DLB, FTLD, cerebrovascular disease, mixed AD and cerebrovascular pathology, normal, leukoencephalo-pathy, alcoholic encephalopathy with Korsakoff syndrome	Visual assessment	Jagust 2007[78]	NR	NR	NR	NR	A priori criteria	0.81	0.73	0.76	0.79	NR
FDG-PET	non-AD: ** possible AD, DLB, FTLD, cerebrovascular disease, mixed AD and cerebrovascular pathology, normal, leukoencephalo-pathy, alcoholic encephalopathy with Korsakoff syndrome	Visual assessment	Jagust 2007[78]	NR	NR	NR	NR	A priori criteria	0.82	0.79	0.75	0.85	NR
FDG-PET	non-AD: 7 FTD 6 DLB 5 CJD 3 PSG 1 PSP 1 lipofuscinosis Kufs disease 18 no neurodegenerative dementia	Visual assessment	Silverman 2001[84]	97	41	NR	35	A priori criteria	0.94	0.73	0.89	0.83	0.70
FDG-PET	non-AD: ** FTD, DLB, CJD, PSG, PSP, lipofuscinosis Kufs disease, no neurodegenerative dementia	Visual assessment	Silverman 2001[84]	41	14	NR	NR	A priori criteria	0.95	0.71	0.91	0.83	0.75

Imaging Technique	Comparator	Chosen Cutoff	Author Year	AD N	Comparator N	Mean Age at Imaging (years)	Mean Interval Between Imaging and Autopsy (months)	Cutoff Determined by	Se (%)*	Sp (%)*	PPV (%)*	NPV (%)*	AD Base Rate
FDG-PET	FTD	Visual assessment	Foster 2007[75]	31	14	65.6	56	A priori criteria	0.96	0.59	0.91	0.68	0.69
FDG-PET	FTD	Visual assessment	Foster 2007[75]	31	14	65.6	56	A priori criteria	0.98	0.73	0.89	0.93	0.69
SPECT cerebral perfusion	non-AD: ** Not specified, includes FTD, multisystem degeneration, adult polyglucosan body disease, Pick disease, progressive supranuclear palsy, dysphasic dementia	Visual assessment	Bonte 2011[72]	47	26	NR	71	A priori criteria	0.94	0.85	0.92	0.88	0.64
SPECT cerebral perfusion	non-AD: ** CVD, FTLD, ischemia/vascular disease, nonspecific changes/unknown, normal, PD, PSP	Visual assessment	Jagust 2001[77]	NR	NR	NR	29	Previously agreed upon	0.64	0.76	0.83	0.54	NR
SPECT cerebral perfusion	non-AD: ** CVD, FTLD, ischemia/vascular disease, nonspecific changes/unknown, normal, PD, PSP	Visual assessment	Jagust 2001[77]	NR	NR	NR	28	Previously agreed upon	0.63	0.82	0.81	0.65	NR
SPECT cerebral perfusion	non-AD: 18 FTLD 4 DLB 3 VaD	Visual and semi-quantitative	Rollin-Sillaire 2012[80]	23	25	67.3	58	Previously described	0.57	0.92	0.87	0.70	0.48
SPECT cerebral perfusion	ALS	57 watershed regions	Rusina 2010[81]	17	10	NR	NR	Optimal, per authors	0.94	0.80	0.89	0.89	0.63
MRI MTA	non-AD: LBD 20 FTLD 47	Similarity to AD cluster	Vemuri 2011[85]	48	67	NR	NR	Simplified mixture model	0.91	0.84	0.80	0.93	0.42
MRI MTA	non-AD: DLB 23 VCI 12	MTA combined score 5.5	Burton 2009[73]	11	35	79.0	20	ROC analysis	0.91	0.94	0.83	0.97	0.24

Imaging Technique	Comparator	Chosen Cutoff	Author Year	AD N	Comparator N	Mean Age at Imaging (years)	Mean Interval Between Imaging and Autopsy (months)	Cutoff Determined by	Se (%)*	Sp (%)*	PPV (%)*	NPV (%)*	AD Base Rate
MRI MTA	DLB	Modified MTA 1.5	Harper 2016[76]	101	28	63.1	62	Maximum balanced accuracy	0.64	0.68	0.88	0.35	0.78
MRI MTA	DLB	Modified MTA 1.5	Harper 2016[76]	28	28	72.5	56	Maximum balanced accuracy	0.82	0.68	0.72	0.79	0.50
MRI MTA	L-rP	MTA score 2	Barkhof 2007[71]	23	8	NR	NR	Highest accuracy	0.83	0.38	0.79	0.43	0.74
MRI MTA	FTLD-Tau	Modified MTA 2.0	Harper 2016[76]	28	24	69.6	66	Maximum balanced accuracy	0.68	0.42	0.58	0.53	0.54
MRI MTA	FTLD-TDP43	Modified MTA 0.5	Harper 2016[76]	28	28	67.7	69	Maximum balanced accuracy	0.96	0.04	0.50	0.50	0.50
MRI MTA	borderline AD	MTA score 2	Barkhof 2007[71]	23	32	NR	NR	Highest accuracy	0.83	0.56	0.58	0.82	0.42
MRI MTA	borderline AD	MTA score 3	Barkhof 2007[71]	23	32	NR	NR	Previously proposed	0.43	0.94	0.83	0.70	0.42

Abbreviations: AD=Alzheimer's disease; ADNC=Alzheimer's disease neuropathologic change; ALS=amyotrophic lateral sclerosis; BSS=Bielschowsky silver staining; CERAD=Consortium to Establish a Registry for Alzheimer's Disease; CJD= Creutzfeldt-Jakob disease; CL=centiloid; CT=computed tomography; CVD=cerebrovascular disease; DLB=dementia with Lewy bodies; DVR=distribution volume ratio; FDG-PET=fluorodeoxyglucose positron emission tomography; FTD=frontotemporal dementia; FTLD=frontotemporal lobar degeneration; IHC=immunohistochemistry; L-rP=Lewy-related pathology; MRI=magnetic resonance imaging; MTA=medial temporal atophy; NR=not reported; NPV=negative predictive value; PA=posterior atrophy; PD=Parkinson's disease; PET=positron emission tomography; PiB=Pittsburgh compound-B; PPV=positive predictive value; PSG=progressive subcortical gliosis; PSP=progressive supranuclear palsy; SE=sensitivity; SP=specificity; SPECT=single-photon emission computerized tomography; SUVR=standardized uptake value ratio; rWTH=radial width of the temporal horn; VaD= vascular dementia; VCI=vascular cognitive impairment; WCER=whole cerebellum

*indicates some Se, Sp, PPV, and NPV values were hand calculated

** indicates sample sizes per diagnostic group could not be determined

Appendix Table D.7. Risk of bias ratings: CSF classification accuracy studies

Study	Patient Selection Risk of Bias *(0=low, 1=high or unclear)*	Index Test Risk of Bias *(0=low, 1=high or unclear)*	Reference Standard Risk of Bias *(0=low, 1=high or unclear)*	Flow and Timing Risk of Bias *(0=low, 1=high or unclear)*	Patient Selection Applicability Concerns *(0=low, 1=high or unclear)*	Index Test Applicability Concerns *(0=low, 1=high or unclear)*	Reference Standard Applicability Concerns *(0=low, 1=high or unclear)*	Total Score	ROB Rating
Bian 2008[100]	1	1	1	0	0	0	0	3	Medium
Clark 2003 [101]	1	1	0	1	0	0	0	3	Medium
Engelborghs 2008[102]	1	1	0	1	1	0	0	4	High
Irwin 2012[103]	1	1	1	0	0	0	0	3	Medium
Koopman 2009 [104]	1	1	0	1	0	0	0	3	Medium
Le Bastard 2013[105]	1	1	0	1	1	0	0	4	High
Roher 2009[106]	1	1	0	1	0	1	0	4	High
Seeburger 2015[107]	1	1	1	1	0	0	0	4	High
Slaets 2013[108]	1	1	0	0	0	1	0	3	Medium
Slaets 2013[109]	1	1	0	0	0	1	0	3	Medium
Slaets 2014[110]	1	1	0	1	0	1	0	4	High
Strufys 2015[111]	1	1	0	0	0	1	0	3	Medium
Tapiola 2009[112]	1	1	0	0	0	0	0	2	Medium
Toledo 2012 [113]	1	1	1	0	0	0	0	3	Medium

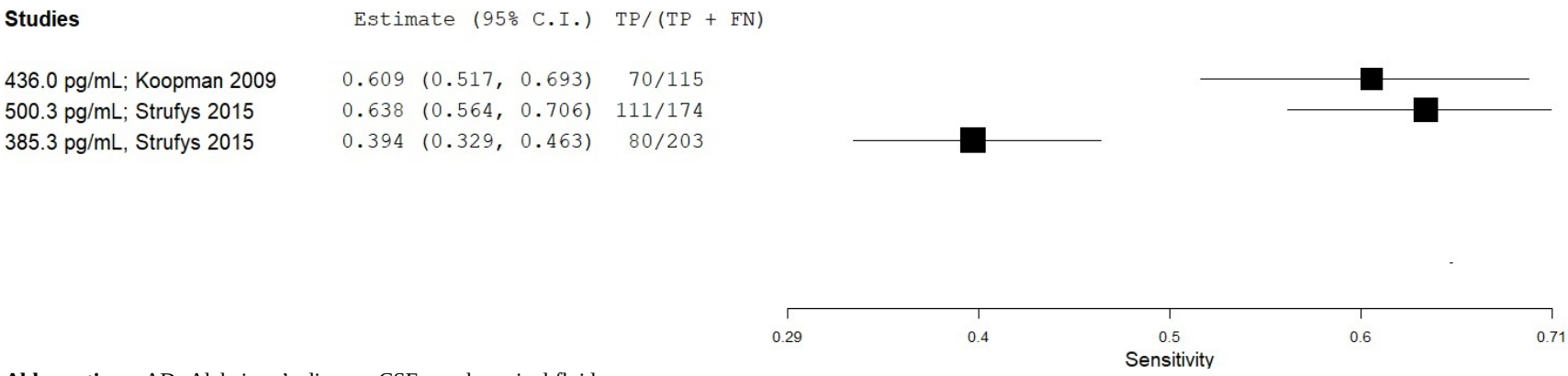
Appendix Table D.8. CSF studies with low to moderate risk of bias

Author Year	Clinical Dementia Criteria	Classification Question	Aß42	t-tau	p-tau	t-tau/ Aß42 ratio	p-tau/ Aß42 ratio	Combination and Assays	AD Autopsy Criteria	Comparator Population Autopsy Criteria
Bian 2008[100]	Neurologist clinical evaluation, consensus process; no specific criteria stated	AD vs. FTLD		x		x			NR	FTLD-Workgroup on Frontotemporal Dementia and Pick's Disease
Clark 2003[101]	Standard neurologic evaluation, including cognitive testing; no specific criteria stated	AD vs. non-AD dementia		x					NR	NR
Irwin 2012[103]	Patients followed in Alzheimer Disease Center (ADC) or Frontotemporal Degeneration Center	AD vs. FTLD				x			NIA-R	FTLD-Mackenzie 2010[114], McKeith 2005[96]
Koopman 2009[104]	NR	AD vs. non-AD dementia, including individually vs. LBD, FTLD, VaD, or CJD	x	x	x				BS	FTLD-Jackson 1996[115] FTLD, CJD, VaD-Markesberry 1998[116] LBD-Kosaka 1988[117]
Slaets 2013[108]	NINCDS-ADRDA, NINDS-AIREN	AD vs. non-AD dementia						AB42/AB40 ratio + AB42 + AB40 + p-tau	BS	LBD-McKeith 2005[96], FTLD-Jackson 1996[115], FTLD, VaD-Markesberry 1998[116]
Slaets 2013[109]	"Presented with a dementia;" no specific criteria stated	AD vs. LBD		x	x				BS	LBD-McKeith 2005[96]
Strufys 2015[111]	NR	AD vs. non-AD dementia, including individually vs. LBD, FTLD, or VaD	x	x	x	x	x		NIA-AA	FTLD-Cairns 2007[118] LBD, VaD-Montine 2012[119] FTLD*-Mackenzie[114]
Tapiola 2009[112]	NINCDS-ADRA for AD, "consensus criteria" for DLB, DSM-IV for VaD, Lund-Manchester for FTD	AD vs. non-AD dementia						Aß42 + t-tau	CERAD, BS	LBD-McKeith 2005[96]

Author Year	Clinical Dementia Criteria	Classification Question	Aß42	t-tau	p-tau	t-tau/ Aß42 ratio	p-tau/ Aß42 ratio	Combination and Assays	AD Autopsy Criteria	Comparator Population Autopsy Criteria
Toledo 2012 [113]	NINCDS-ADRA for AD, Rascovsky 2011 [120]for bv-FTD, Grossman 2007 [121] for CBS, McKeith 2005[96] for LBD	AD vs. FTLD						ELISA immunoassay, Luminex immunossay	CERAD, NIA-R, BS	FTLD-Mackenzie 2010[114], McKeith 2005[96]

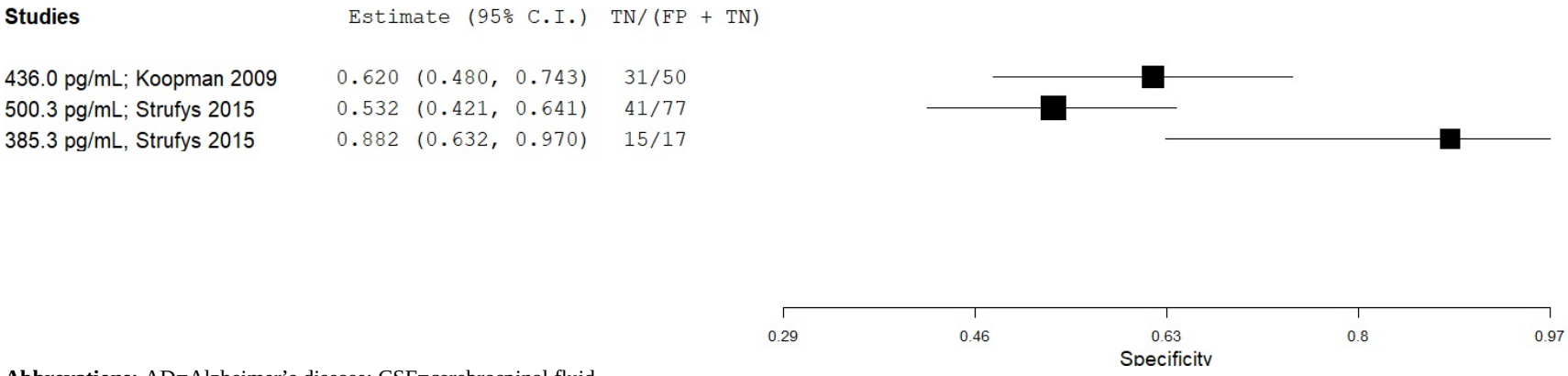
Abbreviations: BS=Braak staging criteria; CERAD=Consortium to Establish a Registry for Alzheimer's disease criteria; CJD=Creutzfeldt-Jakob disease; FTD=Frontotemporal dementia; FTLD=Frontotemporal lobar degeneration; LBD=Lewy body disease; NIA-R=National Institute on Aging and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease; NPH=normal pressure hydrocephalus; NR=not reported; PSP=progressive nuclear palsy; SCA=spinocerebellar ataxia; VaD=Vascular dementia

Figure D.9. Sensitivity results of CSF AB42 levels in eligible studies with low-moderate risk of bias



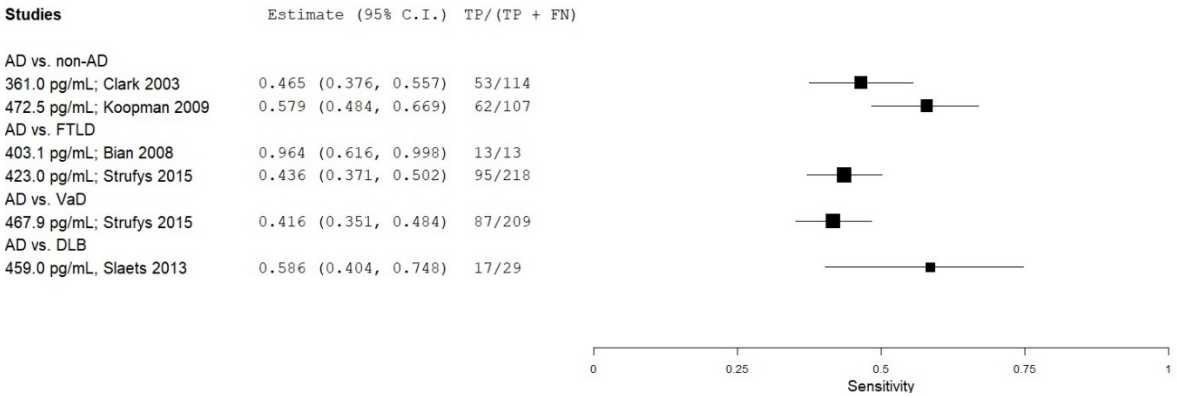
Abbrevations: AD=Alzheimer's disease; CSF=cerebrospinal fluid

Figure D.10. Specificity results of CSF AB42 levels in eligible studies with low-moderate risk of bias



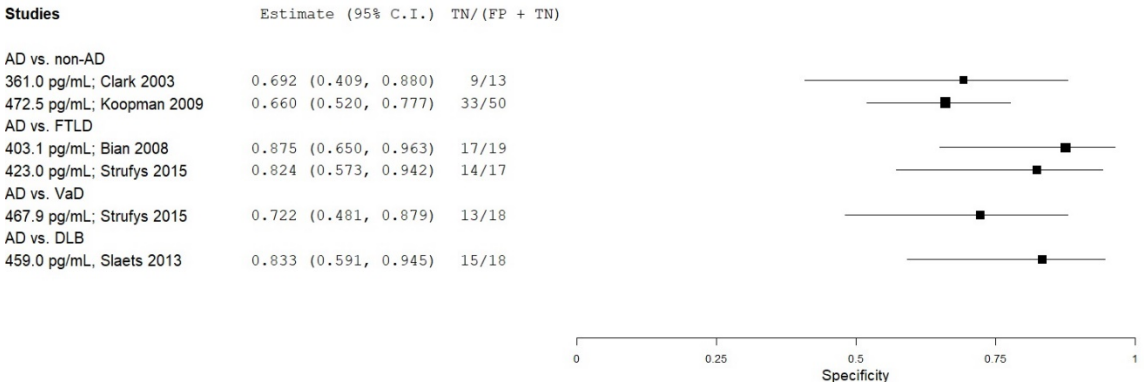
Abbrevations: AD=Alzheimer's disease; CSF=cerebrospinal fluid

Figure D.11. Sensitivity results of CSF t-tau levels in eligible studies with low-moderate risk of bias



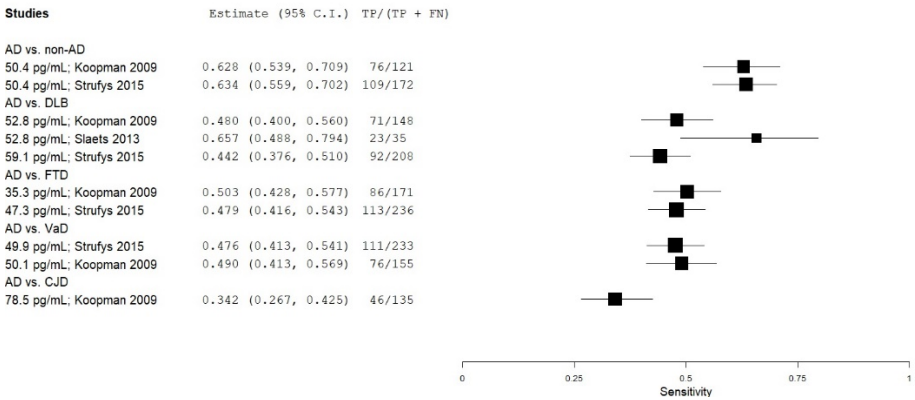
Abbrevations: AD=Alzheimer's disease; CSF=cerebrospinal fluid; DLB=dementia with lewy bodies; FTLD=frontotemporal lobar degeneration; VaD=vascular dementia

Figure D.12. Specificity results of CSF t-tau levels in eligible studies with low-moderate risk of bias



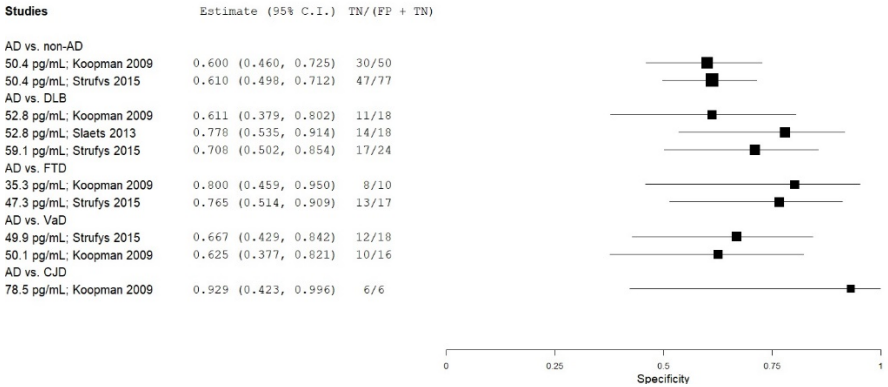
Abbrevations: AD=Alzheimer's disease; CSF=cerebrospinal fluid; DLB=dementia with lewy bodies; FTLD=frontotemporal lobar degeneration; VaD=vascular dementia

Figure D.13. Sensitivity results of CSF p-tau levels in eligible studies with low-moderate risk of bias



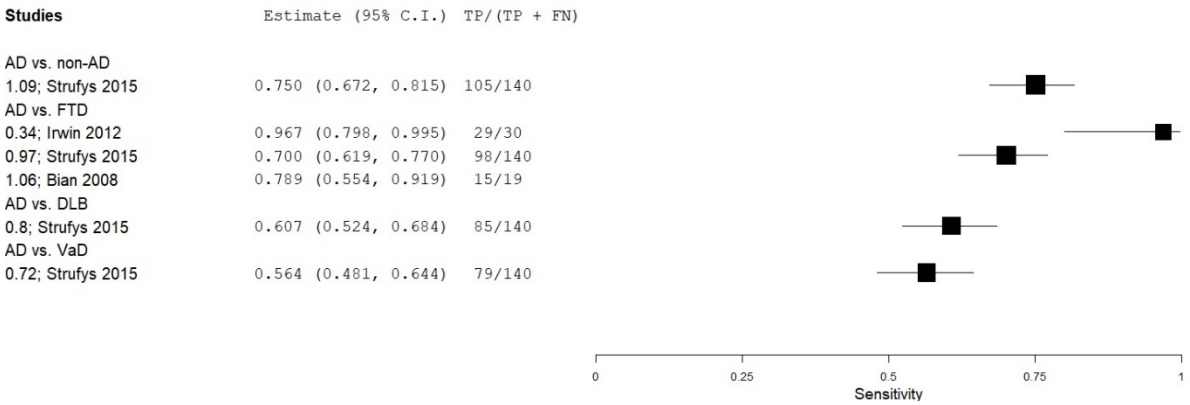
Abbrevations: AD=Alzheimer's disease; CJD=Crutzfeldt-Jacob Disease; CSF=cerebrospinal fluid; DLB=dementia with lewy bodies; FTLD=frontotemporal lobar degeneration; VaD=vascular dementia

Figure D.14. Specificity results of CSF p-tau levels in eligible studies with low-moderate risk of bias



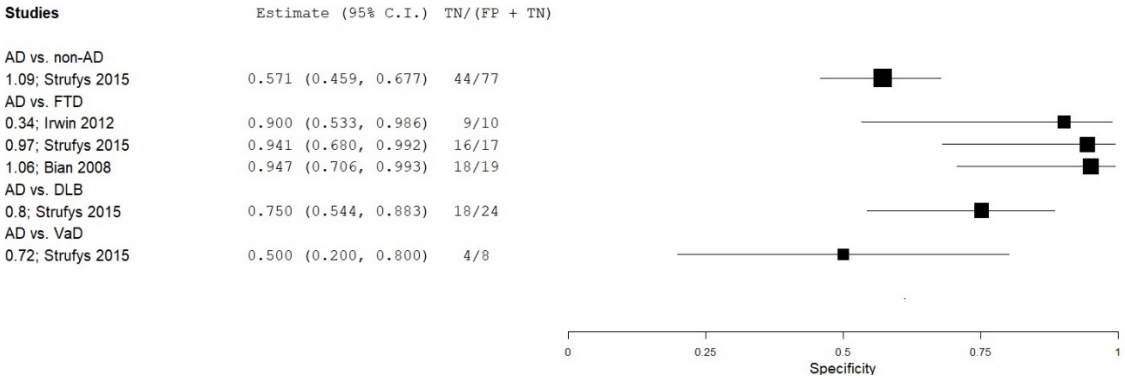
Abbrevations: AD=Alzheimer's disease; CJD=Crutzfeldt-Jacob Disease; CSF=cerebrospinal fluid; DLB=dementia with lewy bodies; FTD=frontotemporal dementia; VaD=vascular dementia

Figure D.15. Sensitivity results of CSF t-tau/AB42 ratio in eligible studies with low-moderate risk of bias



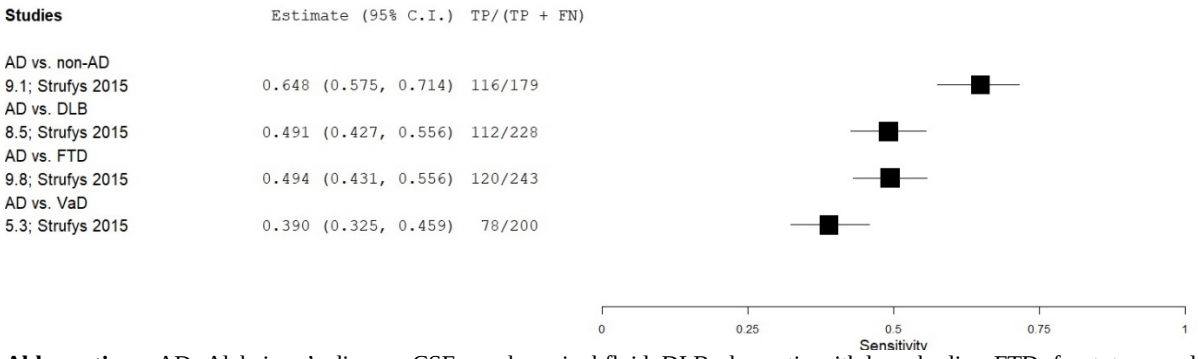
Abbrevations: AD=Alzheimer's disease; CSF=cerebrospinal fluid; DLB=dementia with lewy bodies; FTD=frontotemporal dementia; VaD=vascular dementia

Figure D.16. Specificity results of CSF t-tau/AB42 ratio in eligible studies with low-moderate risk of bias



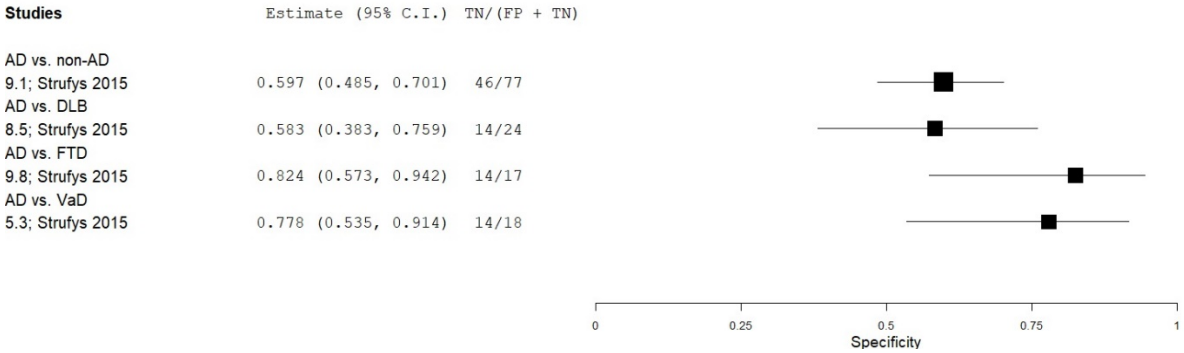
Abbrevations: AD=Alzheimer's disease; CSF=cerebrospinal fluid; DLB=dementia with lewy bodies; FTD=frontotemporal dementia; VaD=vascular dementia

Figure D.17. Sensitivity results of CSF p-tau/AB42 ratio in eligible studies with low-moderate risk of bias



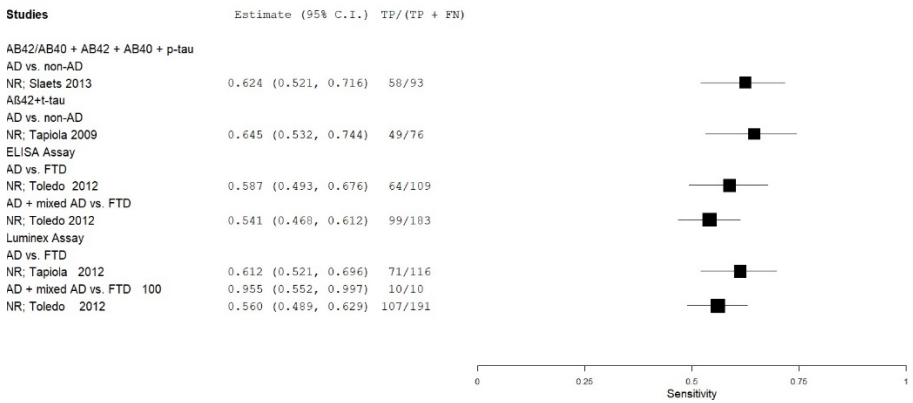
Abbrevations: AD=Alzheimer's disease; CSF=cerebrospinal fluid; DLB=dementia with lewy bodies; FTD=frontotemporal dementia; VaD=vascular dementia

Figure D.18. Specificity results of CSF p-tau/AB42 ratio in eligible studies with low-moderate risk of bias



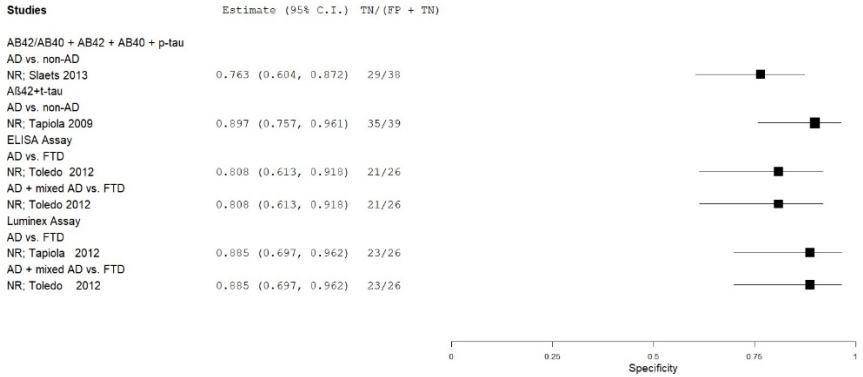
Abbrevations: AD=Alzheimer's disease; CSF=cerebrospinal fluid; DLB=dementia with lewy bodies; FTD=frontotemporal dementia; VaD=vascular dementia

Figure D.19. Sensitivity results of CSF combination tests in eligible studies with low-moderate risk of bias



Abbrevations: AD=Alzheimer's disease; CSF=cerebrospinal fluid; DLB=dementia with lewy bodies; FTD=frontotemporal dementia; NR=not reported; VaD=vascular dementia

Figure D.20. Specificity results of CSF combination tests in eligible studies with low-moderate risk of bias



Abbrevations: AD=Alzheimer's disease; CSF=cerebrospinal fluid; DLB=dementia with lewy bodies; FTD=frontotemporal dementia; NR=not reported; VaD=vascular dementia

Appendix Table D.9. CSF studies: Classification accuracy results in eligible and low-moderate risk of bias CSF studies

CSF Subtest	Comparator	Chosen Cutoff	Author Year	AD N	Comparator N	Mean Age at CSF (years)	Mean Interval between CSF and autopsy (months)	Cutoff Determined By	Se (%)	Sp (%)	PPV (%)*	NPV (%)*	AD Base Rate
Aß42	Mixed non-AD: 18 DLB 10 FTD 16 VaD 6 CJD	436 pg/ml	Koopman 2009 [104]	95	50	76	NR	ROC analysis	0.57	0.88	0.79	0.56	0.66
Aß42	Mixed non-AD: 24 DLB 17 FTD 18 VaD 13 CJD 3 PSP 1 SCA 1 NPH with VaD	500.27 pg/ml	Strufys 2015[111]	140	77	74.5	0	ROC analysis	0.74	0.62	0.75	0.59	0.65
Aß42	FTD	385.31 pg/ml	Strufys 2015[111]	140	17	74.5	0	ROC analysis	0.79	0.53	0.98	0.2	0.89
t-tau	Mixed non-AD: 3 DLB 10 FTD	361 pg/mL	Clark 2003[101]	74	13	68.8	NR	ROC analysis	0.72	0.69	0.93	0.3	0.85
t-tau	Mixed non-AD: 18 DLB 10 FTD 16 VaD 6 CJD	472.5 pg/ml	Koopman 2009[104]	95	50	76	NR	ROC analysis	0.65	0.66	0.78	0.5	0.66
t-tau	FTLD	403.05 pg/mL	Bian 2008 [100]	19	19	NR	NR	ROC analysis	0.68	0.90	0.87	0.74	0.5

CSF Subtest	Comparator	Chosen Cutoff	Author Year	AD N	Comparator N	Mean Age at CSF (years)	Mean Interval between CSF and autopsy (months)	Cutoff Determined By	Se (%)	Sp (%)	PPV (%)*	NPV (%)*	AD Base Rate
t-tau	FTD	423 pg/ml	Strufys 2015[111]	140	17	74.5	0	ROC analysis	0.68	0.82	0.97	0.24	0.89
t-tau	VaD	467.93 pg/ml	Strufys 2015[111]	140	18	74.5	0	ROC analysis	0.62	0.72	0.95	0.2	0.89
t-tau	DLB	459 pg/ml	Slaets 2013[109]	30	18	76	3.6	ROC analysis	0.57	0.83	0.85	0.54	0.63
p-tau	Mixed non-AD: 24 DLB 17 FTD 18 VaD 13 CJD 3 PSP 1 SCA 1 NPH with VaD	50.35 pg/ml	Strufys 2015[111]	140	77	74.5	0	ROC analysis	0.78	0.61	0.78	0.6	0.65
p-tau	Mixed non-AD: 18 DLB 10 FTD 16 VaD 6 CJD	50.4 pg/ml	Koopman 2009 [104]	95	50	76	NR	ROC analysis	0.80	0.60	0.79	0.61	0.66
p-tau	DLB	52.8 pg/ml	Koopman 2009 [104]	95	18	75.5	NR	ROC analysis	0.75	0.61	0.91	0.32	0.84

CSF Subtest	Comparator	Chosen Cutoff	Author Year	AD N	Comparator N	Mean Age at CSF (years)	Mean Interval between CSF and autopsy (months)	Cutoff Determined By	Se (%)	Sp (%)	PPV (%)*	NPV (%)*	AD Base Rate
p-tau	DLB	52.8 pg/ml	Slaets 2013 [109]	30	18	76	3.6	ROC analysis	0.77	0.78	0.85	0.67	0.63
p-tau	DLB	59.05 pg/ml	Strufys 2015[111]	140	24	74.5	0	ROC analysis	0.66	0.71	0.93	0.26	0.85
p-tau	FTD	35.3 pg/ml	Koopman 2009 [104]	95	10	75.1	NR	ROC analysis	0.91	0.80	0.98	0.48	0.9
p-tau	FTD	47.25 pg/ml	Strufys 2015[111]	140	17	74.5	0	ROC analysis	0.81	0.77	0.97	0.33	0.89
p-tau	VaD	49.85 pg/ml	Strufys 2015[111]	140	18	74.5	0	ROC analysis	0.79	0.67	0.95	0.29	0.89
p-tau	VaD	50.1 pg/ml	Koopman 2009 [104]	95	16	76	NR	ROC analysis	0.80	0.63	0.93	0.35	0.86
p-tau	CJD	78.5 pg/ml	Koopman 2009 [104]	95	6	75.7	NR	ROC analysis	0.48	1.00	1	0.11	0.94

CSF Subtest	Comparator	Chosen Cutoff	Author Year	AD N	Comparator N	Mean Age at CSF (years)	Mean Interval between CSF and autopsy (months)	Cutoff Determined By	Se (%)	Sp (%)	PPV (%)*	NPV (%)*	AD Base Rate
t-tau/Aß42 ratio	FTLD	0.34	Irwin 2012 [103]	30	10	68	75.4	ROC analysis	0.97	0.90	0.97	0.9	0.75
t-tau/Aß42 ratio	FTD	0.97	Strufys 2015[111]	140	17	74.5	0	ROC analysis	0.70	0.94	0.99	0.28	0.89
t-tau/Aß42 ratio	FTLD	1.06	Bian 2008[100]	19	19	NR	NR	ROC analysis	0.79	0.97	0.96	0.82	0.5
t-tau/Aß42 ratio	DLB	0.8	Strufys 2015[111]	140	24	74.5	0	ROC analysis	0.61	0.75	0.93	0.25	0.85
t-tau/Aß42 ratio	VaD	0.72	Strufys 2015[111]	140	18	74.5	0	ROC analysis	0.56	0.78	0.95	0.19	0.89
t-tau/Aß42 ratio	Mixed non-AD: 24 DLB 17 FTD 18 VaD 13 CJD 3 PSP 1 SCA 1 NPH with VaD	1.08	Strufys 2015[111]	140	77	74.5	0	ROC analysis	0.75	0.57	0.76	0.56	0.65

CSF Subtest	Comparator	Chosen Cutoff	Author Year	AD N	Comparator N	Mean Age at CSF (years)	Mean Interval between CSF and autopsy (months)	Cutoff Determined By	Se (%)	Sp (%)	PPV (%)*	NPV (%)*	AD Base Rate
p-tau/Aß42 ratio	Mixed non-AD: 24 DLB 17 FTD 18 VaD 13 CJD 3 PSP 1 SCA 1 NPH with VaD	9.11	Strufys 2015[111]	140	77	74.5	0	ROC analysis	0.83	0.60	0.79	0.66	0.65
p-tau/Aß42 ratio	DLB	8.46	Strufys 2015[111]	140	24	74.5	0	ROC analysis	0.80	0.58	0.92	0.33	0.85
p-tau/Aß42 ratio	FTD	9.77	Strufys 2015[111]	140	17	74.5	0	ROC analysis	0.86	0.82	0.98	0.42	0.89
p-tau/Aß42 ratio	VaD	5.3	Strufys 2015[111]	140	18	74.5	0	ROC analysis	0.56	0.78	0.95	0.18	0.89
Aß42/Aß40 ratio + Aß42 + Aß40 + p-tau	Mixed non-AD: 15 DLB 12 FTLD 11 VaD	NR	Slaets 2013 [108]	73	38	74	18	Decision Tree model	0.79	0.76	0.86	0.65	0.66
Aß42 + t-tau	Mixed non-AD: 11 NIA-R low likelihood of AD 7 FTD 9 vascular pathology	NR	Tapiola 2009 [112]	66	39	75.8	24.6	ROC analysis	0.74	0.90	0.92	0.67	0.63

CSF Subtest	Comparator	Chosen Cutoff	Author Year	AD N	Comparator N	Mean Age at CSF (years)	Mean Interval between CSF and autopsy (months)	Cutoff Determined By	Se (%)	Sp (%)	PPV (%)*	NPV (%)*	AD Base Rate
	5 vascular dementia 2 DLB 2 PD w/dementia 1 CBD 1 PSP 1 CJD												
LR Model (ELISA) [AD + mixed AD vs. FTD]	FTLD	NR	Toledo 2012 [113]	71	26	67.6	62.1	Logistic regression model	0.90	0.82	0.93	0.75	0.73
LR Model (Luminex)	FTLD	NR	Toledo 2012 [113]	71	26	67.6	62.1	Logistic regression model	1.00	0.88	0.96	1	0.73
LR Model (ELISA) [AD + mixed AD vs. FTD]	FTLD	NR	Toledo 2012 [113]	110	26	68.1	63.5	Logistic regression model	0.90	0.81	0.95	0.66	0.81
LR Model (Luminex) [AD + mixed AD vs. FTD]	FTLD	NR	Toledo 2012 [113]	110	26	68.1	63.5	Logistic regression model	0.97	0.88	0.97	0.86	0.81

Abbreviations: AD=Alzheimer's disease; CJD= Creutzfeldt-Jakob disease, DLB=Lewy body dementia, CBD=corticobasal degeneration; FTD=frontotemporal dementia; FTLD= Frontotemporal lobar degeneration, NIA-R= National Institute on Aging and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease, NPH= normal pressure hydrocephalus, NPV=negative predictive value; NR=not reported; PSP= progressive nuclear palsy; PD=Parkinson's disease predictive value; PPV=positive predictive value; SCA=spinocerebellar ataxia, SE=sensitivity; SP=specificity; VaD=Vascular dementia
*indicate some PPV and NPV values were hand calculated

Appendix E. Key Question 3: Efficacy and Harms of Prescription Drug Treatment Versus Placebo for Cognition, Function, and Quality of Life

Donepezil Versus Placebo and Donepezil Dose Comparisons

Appendix Table E.1. Characteristics of systematic reviews: donepezil versus placebo and donepezil versus donepezil

Review Characteristics: Author/year Country AMSTAR Rating	Number of Studies N=	Population Characteristics	Intervention: Intervention Mode, Components, Frequency, Duration	Comparison: Comparison Mode, Components, Frequency, Duration	Outcome Timing	Outcome Domain [Instrument]
Birks 2018[122] **UK** **Low**	30 studies in included in the review 17 placebo-controlled trials contributed data N=4445 2 trials compared high-dose donepezil to standard-dose donepezil N=1818	**Versus Placebo** CATD severity Mild: 1 trials Mild and moderate: 10 trials Moderate and severe: 1 trial Severe: 4 trials Any severity: 1 trial Age (mean) 75 years (reported in all trials) % Female 66 (reported in all trials) Baseline MMSE (mean) 15 (reported in 16 trials) % White 94 (reported in 6 trials) **High- vs. Standard-dose** CATD severity Moderate and severe: 1 trial Severe: 1 trial Age (mean) 74 years (reported in all trials) % Female	Donepezil oral (tablet) 5, 10, or 23 mg/day	Donepezil 5-10 mg/day versus placebo Donepezil 23 mg/day versus 10 mg/day	Weeks 24-26, 52, and 54	Cognitive Tests ADAS-Cog MMSE SIB Function ADCS-ADL DAD IDDD Global Impression of Change GDS CGIC CIBIC-Plus CDR Harms Adverse events associated with cholinesterase inhibitors Dropouts due to adverse events Withdrawals due to an adverse event Withdrawals Serious adverse events Deaths

Review Characteristics: Author/year Country AMSTAR Rating	Number of Studies N=	Population Characteristics	Intervention: Intervention Mode, Components, Frequency, Duration	Comparison: Comparison Mode, Components, Frequency, Duration	Outcome Timing	Outcome Domain [Instrument]
		64 (reported in all trials) Baseline MMSE (mean) 12 (reported in all trials) % White 74 (reported in 1 trial)				

Appendix Table E.2. Characteristics of eligible studies not included in a systematic review: donepezil versus placebo

Study Design Country	N=	Population AD Severity Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome Timing	Outcome Domain [Instrument]
Maher-Edwards 2015[123] **RCT** **Multinational**	297 This trial also included 2 arms of experimental treatment SB742457, a potent and selective 5-HT6 receptor antagonist	Mild to Moderate AD Mean Age 72 65% Female Race NR Education, yrs 11 Baseline Cognition: MMSE mean 18.5 MMSE medians 18-19 (range 10-26)	Donepezil 5-10 mg/day	Placebo	24 weeks	Cognitive Tests ADAS-Cog Function ADCS-ADL Harms SAEs Withdrawal due to AE All-cause mortality

Appendix Table E.3. Quality assessments of previous systematic reviews (AMSTAR II critical domains): donepezil versus placebo and donepezil versus donepezil

Topic (Author, Year)	A Priori Design	Search Strategy	Excluded Studies Justified	Study RoB	MA Methods	MA Considered Study RoB	Publication Bias	Comments	Overall Assessment
Donepezil Birks, 2018[122]	Presumed yes based on previously published protocol	Yes	Yes	Yes	Yes	Partial yes (no included trial noted to have high RoB)	No (no primary outcome had ≥10 trials for funnel plot asymmetry analysis)	Of the 30 trials in this review, x did not meet our inclusion criteria, based on duration (<24 weeks), study design (meeting abstracts)	Low

Abbreviations: COI=conflict of interest; MA=meta-analysis; PICO=population, intervention, comparison, outcomes; RoB=risk of bias; SoE=strength of evidence

Appendix Table E.4. Risk of bias assessment from systematic reviews: donepezil versus placebo and donepezil versus donepezil

Study	Random sequence generation	Allocation concealment	Blinding, participants/ personnel	Blinding, outcomes assessment	Incomplete outcome data	Selective outcomes reporting	Other bias	Notes
Courtney 2004[124]	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	High risk	Very high attrition, study excluded*
Black 2007[125]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	
Burns 1999[126]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	
Farlow 2010[127]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	
Feldman 2001[128]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	
Homma 2000[129]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk	
Homma 2008[130]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	
Homma 2016**[131]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	
Jia 2017[132]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	
Krishnan 2003[133]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	
Maher-Edwards 2011[134]	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	
Mazza 2006[135]	Low risk	High risk	Low risk	Low risk	Low risk	High risk	Low risk	Not all outcomes reported
Mohs 2001[136]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	High attrition
Moraes 2006[137]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	
Rogers 1998[138]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	
Seltzer 2004[139]	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	High risk	Participants were withdrawn if unable to tolerate 10 mg dose
Tariot 2001[140]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	

Study	Random sequence generation	Allocation concealment	Blinding, participants/ personnel	Blinding, outcomes assessment	Incomplete outcome data	Selective outcomes reporting	Other bias	Notes
Tune 2003[141]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	
Winblad 2001[142]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	
Winblad 2006[143]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	

*Excluded from the trials evaluated in the present report
**High vs. standard-dose trials (all other compared with placebo)

Appendix Table E.5. Risk of bias assessment of eligible studies not included in a systematic review: donepezil versus placebo

Study	Random sequence generation	Allocation concealment	Blinding, participants/ personnel	Blinding, outcomes assessment	Incomplete outcome data	Selective outcomes reporting	Other bias	Notes
Maher-Edwards (Study 1) 2015	Unclear risk	Low risk	Low risk	Low risk	Moderate risk	Low risk	Low risk	Attrition 16%

Appendix Table E.6. Outcome instruments used in low/medium risk of bias studies:* donepezil versus placebo

Study RoB*	AD Severity	Global- Brief Stand-Alone Tests	Global- Brief Multidomain Batteries	Individual Domain Level Tests Typically Part of a Larger Battery**	Function	Quality of Life	Staging or Clinical Impression
Black 2007[125]	Severe	MMSE	NR	NR	ADCS-ADL	NR	CIBIC
Burns 1999[126]	Mild to Moderate	NR	ADAS-cog	NR	IDDD	Patient-rated, not further details	CDR; CIBIC
Feldman 2001[128]	Moderate to Severe	MMSE	NR	NR	DAD	NR	CIBIC
Homma 2000[129]	Mild to Moderate	NR	ADAS-cog	NR	NR	NR	CDR; CGIC
Homma 2008[130]	Severe	NR	NR	NR	ADCS-ADL	NR	CIBIC
Jia 2017[132]	Severe	MMSE	NR	NR	NR	NR	CIBIC
Krishnan 2003[133]	Mild to Moderate	NR	NR	NR	NR	NR	NR
Maher-Edwards 2011[134]	Mild to Moderate	NR	ADAS-cog	NR	DAD	NR	CIBC

Study RoB*	AD Severity	Global- Brief Stand-Alone Tests	Global- Brief Multidomain Batteries	Individual Domain Level Tests Typically Part of a Larger Battery**	Function	Quality of Life	Staging or Clinical Impression
Maher-Edwards 2015[123] **Mild to Moderate**	MMSE	ADAS-cog	NR	ADCS-ADL	NR	CIBIC	Maher-Edwards 2015[123] Mild to Moderate
Mazza 2006[135]	Mild to Moderate	MMSE	NR	NR	NR	NR	CGIC
Mohs 2001[136]	Mild to Moderate	NA	NR	NR	NA	NR	NA
Moraes 2006[137]	Mild to Moderate	NR	ADAS-cog	NR	NR	NR	NR
Rogers 1998[138]	Mild to Moderate	MMSE	ADAS-cog	NR	NR	Patient-rated, 7-item scale	CDR; CIBIC
Seltzer 2004[139]	Mild	NR	ADAS-cog	Memory: Computerized Memory Battery Test	NR	NR	CDR
Tariot 2001[140]	All CATD	MMSE	NR	NR	NR	NR	CDR
Tune 2003[141]	Mild to Moderate	NR	ADAS-cog	NR	NR	NR	NR
Winblad 2001[142]	Mild to Moderate	NR	NR	NR	NR	NR	NR
Winblad 2006[143]	Severe	MMSE	NR	NR	ADCS-ADL	NR	CGIC
TOTAL		8	8	1 (subscales only)	4 ADCS-ADL (3 others)	2	CDR 5 CIBIC 8 CGIC 1

***** RoB was assessed by the authors of the prior systematic review and reported individual risk of bias items (eg allocation concealment, blinding, attrition) but did not derive an aggregate risk of bias for each trial. See Appendix Table E.3. Domain level tests typically part of a larger battery are tests of memory, executive function, language and/or attention: [a]Memory; [b]Executive Function; [c]Language; [d]Attention

ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive subscale; ADCS-ADL=Alzheimer Disease Cooperative Study-Activities of Daily Living; CGIC=Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change; CATD=clinical Alzheimer-type dementia; CDR= Clinical Dementia Rating Scale; CIBIC-Plus=Clinician Interview Based Impression of Change incorporating caregiver information scale; DAD=Disability Assessment for Dementia; GDS=Global Deterioration Scale; IDDD= Interview for Deterioration in Daily living activities in Dementia; MMSE=Mini-Mental State Examination; NR=Not Reported; ROB=risk of bias;

Appendix Table E.7. Outcome instruments used in low/medium risk of bias studies:* donepezil versus donepezil

Study	AD Severity	Global Brief Stand-Alone Tests	Global Multidomain Tests	Domain Level Tests Typically Part of a Larger Battery**	Function	Quality of Life	Global Assessment of Change
Farlow 2010[127]	Moderate to Severe (mostly severe)	MMSE	SIB	NR	ADCS-ADL	NR	CIBIC
Homma 2016[131]	Severe	NR	SIB	NR	NR	NR	CIBIC
TOTAL		1	2	0	1	0	2

* RoB was assessed by the authors of the prior systematic review and reported individual risk of bias items (eg allocation concealment, blinding, attrition) but did not derive an aggregate risk of bias for each trial. See Appendix Table E.3.

**Domain level tests typically part of a larger battery are tests of memory, executive function, language and/or attention: [a]Memory; [b]Executive Function; [c]Language; [d]Attention

ADCS-ADL=Alzheimer Disease Cooperative Study-Activities of Daily Living; MMSE=Mini-Mental State Examination; NR=Not Reported; ROB=risk of bias; SIB=Severe Impairment Battery

Appendix Table E.8. Summary of strength of evidence: donepezil (5-10 mg/day) versus placebo

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations *	Consistency	Directness	Precision	Overall Grade/ Conclusion
Cognition Global- Brief Stand-Alone Tests	CATD (moderate to severe 62%)	24-26 weeks	8 RCT (n=1662)	Mild to moderate: SMD on MMSE=0.30 (95% CI 0.16 to 0.44) Moderate to severe: SMD on MMSE=0.29 (95% CI 0.17 to 0.40)	Medium	Consistent	Direct	Precise	Low for both severity groups
Cognition Global- Brief Multi-Domain Batteries	Mild-moderate CATD	24 weeks	8 RCT (n=1654)	SMD on ADAS-cog= -0.39 (95% CI -0.54 to -0.25)	Medium	Consistent	Direct	Imprecise	Low
Function	Severe CATD	24-26 weeks	4 RCT (n=979)	Mild to moderate: SMD on ADCS-ADL=0.02 (95% CI -0.27 to 0.23) Severe: SMD on ADCS-ADL=0.18 (95% CI 0.03 to 0.32)	Medium	Mild to moderate: Unknown Severe: Consistent	Direct	Imprecise	Mild to moderate: Insufficient Severe: Low

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations *	Consistency	Directness	Precision	Overall Grade/ Conclusion
Quality of Life	Mild-moderate CATD	24 weeks	2 RCT (n=815)	SMD on participant-rated quality of life= -0.07 (95% CI -0.21 to 0.06)	Medium	Consistent	Direct	Imprecise	Insufficient (downgraded due to reporting bias)
Staging	Mild-moderate CATD	24 weeks	4 RCT (n=1256)	SMD on CDR= -0.38 (95% CI -0.50 to -0.25)	Medium	Consistent	Direct	Precise	Moderate
Clinical Impression	CATD (moderate to severe 58%)	24-26 weeks	8 RCT (n=2737)	Mild to moderate: RR any improvement on CIBIC-plus or CGIC=1.89 (95% CI 1.46 to 2.45) Moderate to severe: RR any improvement on CIBIC-plus or CGIC=1.34 (95% CI 1.13 to 1.58)	Medium	Consistent	Direct	Precise	Mild to moderate: Moderate Severe: Low
Serious Adverse Events	CATD (moderate to severe 52%)	24-54 weeks	12 RCT (n=3674)	Mild to moderate: RR=1.32 (95% CI 1.03 to 1.68 Moderate to severe: RR=0.87 (95% CI 0.66 to 1.15)	Medium	Consistent	Direct	Imprecise	Low for both severity groups
Withdrawals Due to Adverse Events	CATD (moderate to severe 61%)	24-54 weeks	16 RCT (n=4676)	Mild to moderate: RR=1.22 (95% CI 0.93 to 1.62 Moderate to severe: RR=1.54 (95% CI 1.13 to 2.10)	Medium	Inconsistent	Direct	Imprecise	Low for both severity groups

Abbreviations: ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive subscale; CATD=clinical Alzheimer-type dementia; CDR= Clinical Dementia Rating Scale; CGIC=Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change; CI=confidence interval; CIBIC-Plus=Clinician Interview Based Impression of Change incorporating caregiver information scale; GDS=Global Deterioration Scale; MMSE=Mini-Mental State Examination; NR=not reported; PDS=Progressive Deterioration Scale; RCT=randomized controlled trial; RR=risk ratio; SMD= standardized mean difference

*Based on assessment for the systematic review by Birks [122]. Limitations noted were lack of information on allocation concealment and on the blinding of outcome assessment.

Appendix Table E.9. Summary of strength of evidence: donepezil (23 mg/day) versus donepezil (10 mg/day)

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations*	Consistency	Directness	Precision	Overall Grade/ Conclusion
Cognition Global- Brief Stand-Alone Tests	Moderate to severe CATD	24 weeks	1 RCT (n=1370)	SMD on MMSE=0.04 (95% CI -0.07 to 0.15)	Medium	Unknown	Direct	Precise	Low
Cognition Global- Brief Multi-Domain Batteries	Moderate to severe CATD	24 weeks	2 RCT (n=1704)	SMD on SIB = 0.10 (95% CI -0.02 to 0.21)	Medium	Consistent	Direct	Imprecise	Low
Function	Severe CATD	24 weeks	1 RCT (n=1369)	SMD on ADCS-ADL=0.00 (95% CI -0.11 to 0.11)	Medium	Unknown	Direct	Precise	Low
Quality of Life	NR	NR	NR	NR	NR	NR	NR	NR	Insufficient
Staging	NR	NR	NR	NR	NR	NR	NR	NR	Insufficient
Clinical Impression	Moderate to severe CATD	24 weeks	2 RCT (n=1704)	RR on CIBIC-plus=0.90 (95% CI 0.58 to 1.40)	Medium	Consistent	Direct	Imprecise	Low
Serious Adverse Events	Moderate to severe CATD	24 weeks	2 RCT (n=1785)	RR=1.06 (95% CI 0.64 to 1.74)	Medium	Consistent	Direct	Imprecise	Low
Withdrawals Due to Adverse Events	Moderate to severe CATD	24 weeks	2 RCT (n=1818)	RR=2.22 (95% CI 1.67 to 2.96)	Medium	Consistent	Direct	Precise	Moderate

Abbreviations: ADCS-ADL-severe=Alzheimer Disease Cooperative Study–Activities of Daily Living–severe version; CATD=clinical Alzheimer-type dementia; CI=confidence interval; CIBIC-Plus=Clinician Interview Based Impression of Change incorporating caregiver information scale; MMSE=Mini-Mental State Examination; NR=not reported; RCT=randomized controlled trial; RR=risk ratio; SMD= standardized mean difference; SIB=Severe Impairment Battery

*Based on assessment for the systematic review by Birks [122]. Limitations noted were lack of information on allocation concealment and on the blinding of outcome assessment.

Appendix Table E.10. Summary of strength of evidence: donepezil (10 mg/day) versus donepezil (5 mg/day)

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations*	Consistency	Directness	Precision	Overall Grade/ Conclusion
Cognition Global- Brief Stand-Alone Tests	Mild to moderate CATD	24 weeks	1 RCT (n=303)	SMD on MMSE=0.04 (95% CI -0.29 to 0.16)	Low	Unknown	Direct	Imprecise	Low
Cognition Global- Brief Stand-Alone Tests	Moderate to severe CATD	NR	NR	NR	NR	NR	NR	NR	Insufficient
Cognition Global- Brief Multi-Domain Batteries	Mild to moderate CATD	24 weeks	1 RCT (n=311)	RR on ADAS-cog (improvement in scores ≥4 points)=1.42 (95% CI 1.11 to 1.82)	Low	Unknown	Direct	Imprecise	Low
Cognition Global- Brief Multi-Domain Batteries	Moderate to severe CATD	24 weeks	1 RCT (n=188)	SMD on SIB=0.20 (95% CI -0.09 to 0.48)	Low	Unknown	Direct	Imprecise	Low
Function	Mild to moderate CATD	NR	NR	NR	NR	NR	NR	NR	Insufficient
Function	Moderate to severe CATD	24 weeks	1 RCT (n=188)	SMD on ADCS-ADL-severe scale= -0.03 (95% CI -0.32 to 0.250	Low	Unknown	Direct	Imprecise	Low
Quality of Life	All severities	NR	NR	NR	NR	NR	NR	NR	Insufficient
Staging	All severities	NR	NR	NR	NR	NR	NR	NR	Insufficient
Clinical Impression	Mild to moderate to CATD	24 weeks	1 RCT (n=298)	RR on CIBIC-plus=0.95 (95% CI 0.64 to 1.40)	Low	Unknown	Direct	Imprecise	Low
Clinical Impression	Moderate to severe CATD	24 weeks	1 RCT (n=188)	RR on CIBIC-plus=1.45 (95% CI 1.01 to 2.08)	Low	Unknown	Direct	Imprecise	Low
Serious Adverse Events	Mild to moderate to CATD	24 weeks	2 RCT (n=855)	RR=1.67 (95% CI 1.04 to 2.66)	Low	Consistent	Direct	Imprecise	Low

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations*	Consistency	Directness	Precision	Overall Grade/ Conclusion
Serious Adverse Events	Moderate to severe CATD	24 weeks	1 RCT (n=197)	RR=0.88 (95% CI 0.40 to 1.93)	Low	Unknown	Direct	Very imprecise	Insufficient
Withdrawals Due to Adverse Events	Mild to moderate to CATD	24 weeks	2 RCT (n=855)	RR=2.24 (95% CI 1.52 to 3.29)	Low	Consistent	Direct	Precise	Moderate
Withdrawals Due to Adverse Events	Moderate to severe CATD	24 weeks	1 RCT (n=197)	RR=1.71 (95% CI 0.74 to 3.94)	Low	Consistent	Direct	Very imprecise	Insufficient

Abbreviations: ADCS-ADL-severe=Alzheimer Disease Cooperative Study–Activities of Daily Living–severe version; CATD=clinical Alzheimer-type dementia; CI=confidence interval; CIBIC-Plus=Clinician Interview Based Impression of Change incorporating caregiver information scale; MMSE=Mini-Mental State Examination; NR=not reported; RCT=randomized controlled trial; RR=risk ratio; SMD= standardized mean difference; SIB=Severe Impairment Battery

*Based on assessment for the systematic review by Birks [122]. Limitations noted were lack of information on allocation concealment and on the blinding of outcome assessment.

Galantamine Versus Placebo

Appendix Table E.11. Characteristics of eligible studies: galantamine versus placebo

Study Characteristics: Author/Year Country Risk of Bias	N=	Population: AD Severity Mean Age % Female % White Education (mean yrs.) Baseline Cognition	Intervention: Intervention Mode, Components, Frequency, Duration	Comparison: Comparison Mode, Components, Frequency, Duration	Outcome Timing	Outcome Domain [Instrument]
Hager 2014[144] **RCT** **Multinational** **High** **Hager 2016[145]**	2,051	Mild to Moderate AD Mean Age 73 65% Female 99.8% White Education NR Baseline Cognition: MMSE 19	Galantamine ER, 8-24 mg/day	Placebo	24 months	<u>Cognitive Tests</u> MMSE <u>Function</u> DAD <u>Harms</u> SAEs Withdrawal due to AE All-cause mortality
Kano 2013[146] **RCT**	34	Mild to Moderate AD Mean Age 71 44% Female	Galantamine, 16 mg/day	Galantamine, 24 mg/day	28 weeks	<u>Cognitive Tests</u> MMSE

Study Characteristics: Author/Year Country Risk of Bias	N=	Population: AD Severity Mean Age % Female % White Education (mean yrs.) Baseline Cognition	Intervention: Intervention Mode, Components, Frequency, Duration	Comparison: Comparison Mode, Components, Frequency, Duration	Outcome Timing	Outcome Domain [Instrument]
Japan **Medium**		Race NR Education NR Baseline Cognition: MMSE 17				Function DAD
Burns 2009[147] **RCT** **Multinational** **Medium**	407	Probable AD with severe dementia Mean Age 84 81% Female Race NR Education NR Baseline Cognition: MMSE 8.9	Galantamine, 8-24 mg/day	Placebo	26 weeks	Cognitive Tests SIB, Total Score SIB, Memory Subscale SIB, Attention Subscale SIB, Language Function MDS ADL Self-Performance Scale, 7-items MDS ADL Self-Performance Scale, 11-items SIB, Praxis Subscale Harms SAEs Withdrawal due to AEs Falls Mortality
Suh 2008[148] **CCT** **South Korea** **High**	138	Mild to Moderate AD Mean Age 75 75% Female Race NR Years Formal Education 4.0 Baseline Cognition: MMSE 16	Galantamine, 8-24 mg/day	No treatment (community control group)	52 weeks	Cognitive Tests ADAS-cog/11 (Korean Version) Function DAD (Korean Version) Global Staging GDS
Broadty 2005[149] **RCT** **Multinational** **High** **Dunbar 2006**[150]	965	Mild to Moderate AD Mean Age 77 64% Female 91% White Education NR	Galantamine or Galantamine ER, 16 or 24 mg/day	Placebo	26 weeks	Cognitive Tests ADAS-Cog/11 ADAS-Cog/13 Nonmemory ADAS-cog Memory ADAS-cog

Study Characteristics: Author/Year Country Risk of Bias	N=	Population: AD Severity Mean Age % Female % White Education (mean yrs.) Baseline Cognition	Intervention: Intervention Mode, Components, Frequency, Duration	Comparison: Comparison Mode, Components, Frequency, Duration	Outcome Timing	Outcome Domain [Instrument]
		Baseline Cognition: MMSE 18				Function ADCS-ADL Clinical Impression of Change CIBIC-plus Harms Withdrawals due to AEs Mortality
Raskind 2000[151] **RCT** **US** **High**	636	Mild to Moderate AD Mean Age 75 62% Female Race NR Education NR Baseline Cognition: MMSE 19	Galantamine, 24 or 32 mg/day	Placebo	6 months	Cognitive Tests ADAS-Cog/11 ADAS-Cog/13 Function DAD Clinical Impression of Change CIBIC-plus Harms SAEs Withdrawal due to AEs Mortality
Wilcock 2000[152] **Multinational** **RCT** **Medium**	653	Mild to Moderate AD Mean Age 72 Race NR Education NR 63% Female Baseline Cognition: MMSE 19.3	Galantamine 24 or 32 mg/day	Placebo	6 months	Cognitive Tests ADAS-Cog/11 ADAS-Cog/13 Function DAD Clinical Impression of Change CIBIC-plus Harms Withdrawal due to AEs

Abbreviations: AD=Alzheimer's Disease; ADAS-Cog= Alzheimer's Disease Assessment Cognitive Subscale; ADCS-ADL=Alzheimer's Disease Cooperative Study-Activities of Daily Living; AEs=Adverse Events; CIBIC-plus= Clinician's Interview-Based Impression of Change-Plus Caregiver Input; DAD= Disability Assessment for Dementia;

ER=Extended Release; GDS=Global Deterioration Scale; MDS ADL=Minimum Data Set Activities of Daily Living; MMSE=Mini-Mental State Examination; RCT=Randomized Controlled Trial; RoB=Risk of Bias; SAEs=Serious Adverse Events; SIB=Severe Impairment Battery

Appendix Table E.12. Risk of bias ratings: galantamine versus placebo

Study	Time	Selection Bias	Attrition Bias	Performance Bias	Detection Bias	Reporting Bias	Overall Rating*
Hager 2014[144] **Hager 2016**[145]	24 months	Low	High	Low	Low	Low	High
Kano 2013[146]	26 weeks	Medium	Low	Medium	Low	Medium	Medium
Burns 2009[147]	26 weeks	Low	Medium	Low	Low	Medium	Medium
Suh 2008[148]	52 weeks	High	High	Low	Low	Low	High
Broadty 2005[149] **Dunbar 2006** [150]	26 weeks	Low	High	Low	Low	Low	High
Raskind 2000[151]	6 months	Low	High	Low	Low	Low	High
Wilcock 2000[152]	6 months	Low	Medium	Low	Low	Low	Medium

Appendix Table E.13. Outcome instruments used in low/medium risk of bias studies: galantamine versus placebo

Study	RoB	AD Severity	Cognition-Brief Stand-Alone Tests	Cognition-Brief Multidomain Batteries	Cognition-Domain Level Tests Typically Part of a Larger Battery*	Function	Quality of Life	Global Staging	Clinical Impression of Change
Burns 2009[147]	Medium	Severe	NR	SIB, Total Score	SIB, Memory Subscale[a] SIB, Language Subscale[c] SIB, Attention Subscale[d]	MDS ADL Self-Performance Scale, 7-items MDS ADL Self-Performance Scale, 11-items SIB, Praxis Subscale	NR	NR	NR
Wilcock 2000[152]	Medium	Mild to Moderate	NR	ADAS-Cog/11 ADAS-Cog/13	NR	DAD	NR	NR	CIBIC-plus
TOTAL			0	2	3	4	0	0	1

Appendix Table E.14. Primary outcomes summary low and medium risk of bias studies: galantamine versus placebo

Drug Comparison	AD Severity	Study Characteristics: Author/Year Followup N Risk of Bias	Cognition	Function	QoL	Global Staging	Clinical Impression of Change	Harms
Galantamine vs. Placebo	Mild to Moderate AD	Wilcock 2000[152] 6 months N=653 Medium	ADAS-Cog/11 24 mg/day Number (%) ≥4 points improvement I: 64/220 (29%) C: 32/215 (15%) ARD (95% CI) 14.0% (6.0, 22.0) Between-group difference (95% CI) 2.9 (1.6, 4.1) SMD (95% CI) 0.50 (0.31,0.69) 32 mg/day Number (%) ≥4 points improvement I: 70/217 (32%) C: 32/215 (15%) ARD (95% CI) 17.0% (9.0, 17.0) Between-group difference (95% CI) 3.1 (1.9, 4.4) SMD (95% CI) 0.52 (0.33, 0.71)	DAD 24 mg/day Mean Change from Baseline (SE) I: -3.2 (1.02) C: -6.0 (1.08) Between-group difference (95% CI) 2.8 (-0.6, 6.1) SMD (95% CI) 0.18 (-0.01, 0.37) 32 mg/day Mean Change from Baseline (SE) I: −2.5 (1.07) C: -6.0 (1.08) Between-group difference (95% CI) 3.4 (0.1, 6.7) SMD (95% CI) 0.22 (0.03, 0.41)	NR	NR	CIBIC-plus Percent Minimally to Much Improved 24 mg/day I: 17% (36/206) C: 16% (33/203) p<0.05 32 mg/day I: 24% (48/198) C: 16% (33/203) p<0.001	SAEs 12-13% across all groups Withdrawal due to AEs 24 mg/day I: 14% (31/220) 32 mg/day I: 22% (48/218) C: 8.8% (19/215)

Drug Comparison	AD Severity	Study Characteristics: Author/Year Followup N Risk of Bias	Cognition	Function	QoL	Global Staging	Clinical Impression of Change	Harms
Galantamine vs. Placebo	Severe AD	Burns 2009[147] 26 weeks N=407 Medium	<u>SIB Total Score</u> Mean at 26 Weeks (SD) I: 69.1 (23.4) C: 66.9 (23.6) Between Group LS Mean Difference (95% CI) 4.36 (1.3, 7.5) <u>SMD</u> 0.29 (0.10, 0.49) <u>SIB, Memory Subscale</u> Favors galantamine p=0.006 <u>SIB, Attention Subscale</u> No difference between groups p=0.08 <u>SIB, Language Subscale</u> No difference between groups p=0.06	<u>Minimum Data Set ADL Self-Performance Scale, 7-items</u> Mean at 26 Weeks (SD) I: 13.0 (7.7) C: 13.6 (8.0) Between Group LS Mean Difference (95% CI) -0.41 (-1.3, 0.5) <u>Minimum Data Set ADL Self-Performance Scale, 11-items</u> No overall scale score reported. Significant difference only for locomotion on unit (p = 0.021), favoring galantamine, differences for other 10 sub-scales were not significant. <u>SIB, Praxis Subscale</u> Favors galantamine p=0.01	NR	NR	NR	<u>SAEs</u> I: 18.0% C: 21.0% <u>Withdrawal due to AEs</u> I: 14.5% (30/207) C: 15.5% (31/200) <u>Falls</u> I: 11.6% (24/207) C: 11.0% (22/200) <u>Mortality (All Cause)</u> I: 4.0% C: 11.0% p=0.01
Galantamine vs. Galantamine	Mild to Moderate AD	Kano 2013[146] 28 weeks N=34 Medium	<u>MMSE</u> No difference between galantamine dosages.	<u>DAD</u> No difference between galantamine dosages.	NR	NR	NR	NR

Abbreviations: AD=Alzheimer's Disease; ADAS-Cog=Alzheimer's Disease Assessment Cognitive Subscale; AEs=Adverse Events; CI=Confidence Interval; CIBIC-plus= Clinician's Interview-Based Impression of Change-Plus Caregiver Input; DAD= Disability Assessment for Dementia; LS=Least Squares; MDS ADL=Minimum Data Set Activities of Daily Living; MMSE=Mini-Mental State Examination; NR=Not Reported; RoB=Risk of Bias; SAEs=Serious Adverse Events; SD=Standard Deviation; SIB=Severe Impairment Battery; SMD=Standardized Mean Difference

Appendix Table E.15. Summary of strength of evidence: galantamine versus placebo

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Cognition Global- Brief Stand-Alone Tests	NA	NR	NR	NA	NA	NA	NA	NA	NA
Cognition Global- Brief Multidomain Batteries	CATD (62% mild to moderate, 38% severe)	6 months	2 RCTs[147, 152] (n=1,060)	In mild to moderate CATD, increased likelihood of ≥4-point improvement in ADAS-cog with galantamine versus placebo (24 mg/day: 29% vs. 15%, ARD 14% [95% CI 6 to 20]; 32 mg/day: 32% vs. 15%, ARD 17% [95% CI 9 to 17]). Also, increased mean change in ADAS-cog score versus placebo (24 mg/day: SMD 0.50 [95% CI 0.31 to 0.69]; 32 mg/day: SMD 0.52 [95% CI 0.33 to 0.71]). In severe CATD, increased mean change in SIB score (SMD 0.29 [95% CI 0.10 to 0.49]).	Medium	Consistent	Direct	Imprecise	Low (Favors Intervention)
Cognition- Domain Level Tests Typically Part of a Larger Battery	Severe CATD	6 months	1 RCT[147] (n=407)	Difference in memory change scores between groups appeared larger for galantamine versus placebo (p<0.05).No statistically significantly differences for language or attention scores (p>0.05).	Medium	Unknown	Direct	Imprecise	Insufficient

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Function	CATD (62% mild to moderate, 38% severe)	6 months	2 RCTs[147, 152] (n=1,060)	Inconsistent findings about the efficacy of galantamine compared with placebo on function.	Medium	Inconsistent	Direct	Imprecise	Insufficient
Quality of Life	NA	NR	NR	NA	NA	NA	NA	NA	NA
Global Staging	NA	NR	NR	NA	NA	NA	NA	NA	NA
Clinical Impression of Change	Mild to Moderate CATD	6 months	1 RCT[152] (n=653)	Statistically significant difference in the distribution of CIBIC-plus ratings between both galantamine groups compared with placebo ($p<0.05$).	Medium	Unknown	Direct	Imprecise	Insufficient
Serious Adverse Events	CATD (62% mild to moderate, 38% severe)	6 months	2 RCTs[147, 152] (n=1,060)	No difference in serious adverse events between galantamine and placebo in either trial.[152]	Medium	Consistent	Direct	Imprecise	Low (No Difference)
Withdrawals due to Adverse Events	CATD (62% mild to moderate, 38% severe)	6 months	2 RCTs[147, 152] (n=1,060)	Inconsistent findings about differences in withdrawals due to adverse events.	Medium	Inconsistent	Direct	Imprecise	Insufficient

Abbreviations: AD=Alzheimer's Disease; ADAS-Cog=Alzheimer's Disease Assessment Cognitive Subscale; CI=Confidence Interval; CIBIC-plus: Clinician's Interview-Based Impression of Change-Plus Caregiver Input; NR=Not Reported; NA=Not Applicable; RCT=Randomized Controlled Trial; SIB=Severe Impairment Battery; SMD=Standardized Mean D

Rivastigmine Versus Placebo and Rivastigmine Versus Rivastigmine

Appendix Table E.16. Characteristics of systematic reviews: rivastigmine versus placebo and rivastigmine versus rivastigmine

Study Characteristics: Author/Year Country AMSTAR Rating	Number of Studies N=	Population: AD Severity Mean Age % Female % White Education (mean yrs.) Baseline Cognition	Intervention: Intervention Mode, Components, Frequency, Duration	Comparison: Comparison Mode, Components, Frequency, Duration	Outcome Timing	Outcome Domain [Instrument]
Birks 2015[153] **UK** **Low**	13 eligible trials 9 placebo-controlled trials contributed data N=5,591 1 trial compared 9.5 mg/day rivastigmine patch with 6-12 mg/day rivastigmine oral N=590	**Versus Placebo** CATD severity Mild and moderate CATD: 8 trials Moderate and severe CATD: 1 trial Age (mean) 73.2 years (reported in 9 trials) % Female 62.6 (reported in 9 trials) Baseline MMSE (mean) 17.9 (reported in 8 trials) % White 87 (reported in 4 trials) Education (mean) 10.2 years (reported in 2 trials) **9.5 mg/day patch versus 6-12 mg/day oral** CATD severity Mild and moderate CATD: 1 trial Age (mean) 73.2 years (reported in 1 trial) % Female	Rivastigmine, oral 1-4 mg/day and 6-12 mg/day Rivastigmine, patch 4.6 mg/day, 9.5 mg/day, and 17.4 mg/day	Rivastigmine versus placebo Rivastigmine patch 9.5 mg/day versus rivastigmine oral 6-12 mg/day	12 weeks and 24-26 weeks	Cognition ADAS-Cog ADAS-J Cog MMSE SIB Clock Drawing Cognition (Attention) TMT-A Function ADCS-ADL PDS DAD Global Change GDS CGIC CIBIC-Plus CIBIC-Plus J MENFIS Behavioral Symptoms NPI-10 or NPI-12 BEHAVE-AD Caregiver Distress NPI-D Harms Adverse events (decreased

Study Characteristics: Author/Year Country AMSTAR Rating	Number of Studies N=	Population: AD Severity Mean Age % Female % White Education (mean yrs.) Baseline Cognition	Intervention: Intervention Mode, Components, Frequency, Duration	Comparison: Comparison Mode, Components, Frequency, Duration	Outcome Timing	Outcome Domain [Instrument]
		66.8 (reported in 1 trial) Baseline MMSE (mean) 16.5 (reported in 1 trial) % White 75.0 (reported in 1 trial) Education (mean) 9.9 years (reported in 1 trial)				appetite, weight decrease, nausea, vomiting, diarrhea, anorexia, headache, insomnia, syncope, abdominal pain, dizziness, bone fracture, asthenia, application site erythema, application site pruritis, application site edema, application site exfoliation, dermatitis contact, nasopharyngitis) Dropouts due to adverse events Withdrawals due to an adverse event Withdrawals Serious adverse events Deaths

Abbreviations: ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive subscale; ADAS-J Cog=Japanese version of Alzheimer's Disease Assessment Scale-Cognitive subscale; ADCS-ADL= Alzheimer Disease Cooperative Study-Activities of Daily Living; BEHAVE-AD= Behavioral Pathology in AD; CATD=clinical Alzheimer-type dementia; CGIC=Clinical Global Impression of Change; CIBIC-Plus=Clinician Interview Based Impression of Change incorporating caregiver information scale; CIBIC-Plus J=Japanese version of the Clinician Interview Based Impression of Change incorporating caregiver information scale; DAD=Disability Assessment for Dementia; GDS=Global Deterioration Scale; MENFIS=Mental Function Impairment; MMSE=Mini-Mental State Examination; NPI=Neuropsychiatric Inventory; NPI-D=Neuropsychiatric Inventory-Caregiver Distress; PDS=Progressive Deterioration Scale; SIB=Severe Impairment Battery; TMT-A=Trail Making Test Part A

Appendix Table E.17. Characteristics of eligible studies:* rivastigmine versus placebo and rivastigmine versus rivastigmine

Study Characteristics: Design Country RoB	N=	Population Characteristics	Intervention: Intervention Mode Components Frequency Duration	Comparison: Comparison Mode Components Frequency Duration	Outcome Timing	Outcome Domain [Instrument]
Cummings 2012[154] **RCT** **USA, Canada, Italy, Germany, France, Switzerland, Spain** **Medium (24 weeks)** **High (48 weeks)**	567 (double-blind phase)	Mild to Moderate CATD Mean Age: 75.7 % Female: 64.7 % White: 96.6 Mean Education: 10.6 Baseline Cognition: MMSE 14.2	Rivastigmine, patch 13.3 mg/day	Rivastigmine, patch 9.5 mg/day	24-48 weeks open-label and 48 weeks double-blind	Cognition ADAS-Cog Cognition (Executive Function) TMT-B Cognition (Attention) TMT-A Function ADCS-IADL Harms Serious adverse events Withdrawals due to adverse events Mortality Confusion/Delirium Falls
Farlow 2013[155] **RCT** **USA** **High**	716	Severe CATD Mean Age: 77.0 % Female: 64.4 % White: 87.3 Mean Education: NR Baseline Cognition: MMSE 8.8	Rivastigmine, patch 13.3 mg/day	Rivastigmine, patch 4.6 mg/day	24 weeks	Cognition SIB Function ADCS-ADL-SIV Global Change ADCS-CGIC Harms Serious adverse events Withdrawals due to adverse events Mortality Confusion/Delirium

Study Characteristics: Design Country RoB	N=	Population Characteristics	Intervention: Intervention Mode Components Frequency Duration	Comparison: Comparison Mode Components Frequency Duration	Outcome Timing	Outcome Domain [Instrument]
Moretti 2014[156] **CCT** **Italy** **High**	20	All Severity Levels CATD Mean Age: 81.3 % Female: 60.0 % White: NR Mean Education: 5.2 Baseline Cognition: MMSE 19.7	Rivastigmine, patch 9.5 mg/day	Rivastigmine, oral 12 mg/day	18 months	Cognition MMSE
Nakamura 2015[157] **RCT** **Japan** **High**	216	Mild to Moderate CATD Mean Age: 77.5 % Female: 67.4 % White: NR Mean Education: 10.6 Baseline Cognition: MMSE 17.1	Rivastigmine, patch 9.5 mg/day (1-step titration)	Rivastigmine, patch 9.5 mg/day (3-step titration)	24 weeks	Cognition ADAS-J-Cog MMSE Global Change J-CGIC Harms Serious adverse events Withdrawals due to adverse events Mortality
Zhang 2016[158] **RCT** **China** **High**	501	Mild to Moderate CATD Mean Age: 70.1 % Female: 55.7 % White: NR Mean Education: NR Baseline Cognition: MMSE 16.3	Rivastigmine, patch 9.5 mg/day	Rivastigmine, oral 12 mg/day	24 weeks	Cognition ADAS-Cog MMSE Function ADCS-ADL Global Change ADCS-CGIC Harms Serious adverse events Withdrawals due to adverse events Mortality Somnolence

Abbreviations: ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive subscale; ADAS-J Cog=Japanese version of Alzheimer's Disease Assessment Scale-Cognitive subscale; ADCS-ADL=Alzheimer Disease Cooperative Study-Activities of Daily Living; ADCS-ADL-SIV=Alzheimer's Disease Cooperative Study—Activities of Daily Living scale-Severe Impairment Version; ADCS-CGIC=Alzheimer's Disease Cooperative Study—Clinical Global Impression of Change; ADCS-IADL=Instrumental Activities of Daily Living domain (items 7-23) of the Alzheimer's Disease Cooperative Study—Activities of Daily Living; CATD=clinical Alzheimer-type dementia; CCT=controlled clinical trial; J-CGIC=Japanese Clinical Global Impression of Change; MMSE=Mini-Mental State Examination; NR=not reported; RoB=Risk of Bias; RCT=randomized controlled trial; SIB=Severe Impairment Battery; TMT-A=Trail Making Test Part A; TMT-B=Trail Making Test Part B
*This table only shows rivastigmine studies not included in the prior systematic review.

Appendix Table E.18. Quality assessments of previous systematic reviews (AMSTAR II critical domains): rivastigmine versus placebo and rivastigmine versus rivastigmine

Topic (Author, Year)	*A Priori* Design	Search Strategy	Excluded Studies Justified	Study RoB	MA Methods	MA Considered Study RoB	Publication Bias	Comments	Overall Assessment
Rivastigmine Birks 2015[153]	Yes	Yes	Yes	Yes	Yes	Yes	No	Despite not investigating publication bias, we rated the systematic review low ROB because we do not believe publication bias affected their findings. Among the trials eligible for our review, there was a similar number of trials registered on clinicaltrials.gov compared with the amount of published trials.	Low ROB

Abbreviations: MA=Meta-Analysis; RoB=Risk of Bias

Appendix Table E.19. Risk of bias ratings: rivastigmine versus placebo and rivastigmine versus rivastigmine

Study*	Time	Selection Bias	Attrition Bias	Performance Bias	Detection Bias	Reporting Bias	Overall Rating
Cummings 2012[154]	24 weeks	Low	Medium	Low	Low	Low	Medium
Cummings 2012[154]	48 weeks	Low	High	Low	Low	Low	High
Farlow 2013[155]	24 weeks	Low	High	Low	Low	High	High
Moretti 2014[156]	6 months	High	High	High	High	Low	High
Moretti 2014[156]	18 months	High	High	High	High	Low	High
Nakamura 2015[157]	24 weeks	Low	High	Low	Low	Low	High

Study*	Time	Selection Bias	Attrition Bias	Performance Bias	Detection Bias	Reporting Bias	Overall Rating
Zhang 2016[158]	24 weeks	Low	High	Low	Low	Low	High

*This table only shows rivastigmine studies not included in the prior systematic review.

Appendix Table E.20. Outcome instruments used in low/medium risk of bias* studies: rivastigmine versus placebo and rivastigmine versus rivastigmine

Study	Risk of Bias*	CATD Severity	Global Brief Stand-Alone Tests	Global Multidomain Tests	Domain Level Tests Typically Part of a Larger Battery**	Function	Quality of Life	Global Assessment of Change
Feldman 2007[159]	*	Mild and Moderate CATD	MMSE	ADAS-cog ADAS-cogA	NR	PDS	NR	CIBIC-plus GDS
Nakamura 2011[160]	*	Mild and Moderate CATD	MMSE	ADAS-J-Cog	NR	DAD	NR	CIBIC-plus-J MENFIS
Rosler 1999[161]	*	Mild and Moderate CATD	MMSE	ADAS-Cog	NR	PDS	NR	CIBIC-Plus GDS
Winblad 2007[162]	*	Mild and Moderate CATD	MMSE 10-Point Clock Drawing Test	ADAS-Cog	TMT-A[d]	ADCS-ADL	NR	ADCS-CGIC
Cummings 2012[154]	Medium (24 weeks) High (48 weeks)	Mild and Moderate CATD	NR	ADAS-cog	TMT-A[d] and TMT-B[b]	ADCS-IADL	NR	NR
Lopez-Pousa 2004[163]	*	Moderate and Severe CATD	MMSE	SIB	NR	ADCS-ADL	NR	ADCS-CGIC GDS
TOTAL			5	6	2	6	0	5

ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive subscale; ADAS-CogA=Alzheimer's Disease Assessment Scale-Cognitive subscale with an added item of attention; ADAS-J Cog=Japanese version of Alzheimer's Disease Assessment Scale-Cognitive subscale; ADCS-ADL=Alzheimer Disease Cooperative Study-Activities of Daily Living; ADCS-CGIC=Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change; ADCS-IADL=Instrumental Activities of Daily Living domain (items 7-23) of the Alzheimer's Disease Cooperative Study—Activities of Daily Living; CATD=clinical Alzheimer-type dementia; CIBIC-Plus=Clinician Interview Based Impression of Change incorporating caregiver information scale; CIBIC-Plus J=Japanese version of the Clinician Interview Based Impression of Change incorporating caregiver information scale; DAD=Disability Assessment for Dementia; GDS=Global Deterioration Scale; MENFIS=Mental Function Impairment; MMSE=Mini-Mental State Examination; NR=Not Reported; PDS=Progressive Deterioration Scale; ROB=risk of bias; SIB=Severe Impairment Battery; TMT-A=Trail Making Test Part A; TMT-B=Trail Making Test Part B

*Overall ROB was not rated for studies included in the prior systematic review. We determined if a study was high ROB or less than high ROB by reviewing the ROB domain ratings in the prior systematic review.
**Domain level tests typically part of a larger battery are tests of memory, executive function, language and/or attention: [a]Memory; [b]Executive Function; [c]Language; [d]Attention

Appendix Table E.21. Primary outcomes summary low and medium risk of bias studies: rivastigmine versus placebo and rivastigmine versus rivastigmine

Drug Comparison	CATD Severity	Study Characteristics: Author/Year Followup Risk of Bias	Cognitive	Function	QoL	Global Change	Harms
Rivastigmine vs. Placebo and Rivastigmine vs. Rivastigmine	Mild and Moderate CATD	Feldman 2007[159] 26 weeks Riv 2 doses) 12 mg/day oral in two divided doses Riv 3 doses) 12 mg/day oral in three divided doses P) placebo	MMSE Mean change from baseline (SD) Riv 2 doses: -0.6 (3.6) Riv 3 doses: 0.3 (3.6) P: -1.4 (3.6) ADAS-cog % of patients with improvement Riv 2 doses vs. P: not significantly different Riv 3 doses vs. P: significantly different (p<0.05) Mean change from baseline (SD) Riv 2 doses: 1.2 (7.2) Riv 3 doses: -0.2 (7.3) P: 2.8 (7.2) ADAS-cogA Mean change from baseline (SD) Riv 2 doses: 1.5 (7.8) Riv 3 doses: -0.1 (7.9) P: 3.2 (7.8)	PDS Mean change from baseline (SD) Riv 2 doses: -2.6 (11.1) Riv 3 doses: -1.5 (11.3) P: -4.9 (11.2)	NR	CIBIC-Plus % of patients with improvement Riv 2 doses vs. P: not significantly different Riv 3 doses vs. P: significantly different (p<0.05) Mean change from baseline (SD) Riv 2 doses: 4.1 (1.3) Riv 3 doses: 3.9 (1.3) P: 4.5 (1.3) GDS Mean change from baseline (SD) Riv 2 doses: -0.2 (0.7) Riv 3 doses: 0.0 (0.7) P: -0.3 (0.7)	Serious adverse events Riv 2 doses: 40/228 Riv 3 doses: 40/227 P: 33/222 Withdrawals due to adverse events Riv 2 doses: 39/229 Riv 3 doses: 24/227 P: 20/222 Somnolence Riv 2 doses: NR Riv 3 doses: NR P: NR Confusion/Delirium Riv 2 doses: NR Riv 3 doses: NR P: NR Falls Riv 2 doses: NR Riv 3 doses: NR P: NR Extrapyramidal symptoms Riv 2 doses: NR Riv 3 doses: NR P: NR Stroke

Drug Comparison	CATD Severity	Study Characteristics: Author/Year Followup Risk of Bias	Cognitive	Function	QoL	Global Change	Harms
							Riv 2 doses: NR Riv 3 doses: NR P: NR <u>Mortality</u> Riv 2 doses: 0/228 Riv 3 doses: 0/227 P: 0/222
	Mild and Moderate CATD	Nakamura 2011[160] 24 weeks Riv 9.5 mg) 9.5 mg/day patch Riv 4.6 mg) 4.6 mg/day patch P) placebo	<u>MMSE</u> Mean change from baseline (SD) Riv 9.5 mg: 0.0 (2.87) Riv 4.6 mg: -0.3 (3.05) P: -0.3 (2.82) <u>ADAS-J-cog</u> Mean change from baseline (SD) Riv 9.5 mg: 0.1 (5.04) Riv 4.6 mg: 0.5 (4.96) P: 1.3 (5.07)	<u>DAD</u> Mean change from baseline (SD) Riv 9.5 mg: -1.9 (10.66) Riv 4.6 mg: -3.0 (10.26) P: -4.2 (12.44)	NR	<u>CIBIC plus-J</u> % of patients with improvement Riv 9.5 mg: 22% Riv 4.6 mg: 21% P: 15% Favorable response OR (95% CI) Riv vs. P Riv 9.5 mg: 1.33 (0.98, 1.82) Riv 4.6 mg: 1.34 (.98, 1.83) <u>MENFIS</u> Mean change from baseline (SD) Riv 9.5 mg: 1.6 (5.82) Riv 4.6 mg: 2.2 (5.86) P: 2.9 (6.18)	<u>Serious adverse events</u> Riv 9.5 mg: 18/287 Riv 4.6 mg: 14/282 P: 20/286 <u>Withdrawals due to adverse events</u> Riv 9.5 mg: 34/287 Riv 4.6 mg: 38/284 P: 21/288 <u>Somnolence</u> Riv 9.5 mg: NR Riv 4.6 mg: NR P: NR <u>Confusion/Delirium</u> Riv 9.5 mg: NR Riv 4.6 mg: NR P: NR <u>Falls</u> Riv 9.5 mg: NR Riv 4.6 mg: NR P: NR <u>Extrapyramidal symptoms</u> Riv 9.5 mg: NR Riv 4.6 mg: NR P: NR

Drug Comparison	CATD Severity	Study Characteristics: Author/Year Followup Risk of Bias	Cognitive	Function	QoL	Global Change	Harms
							Stroke Riv 9.5 mg: NR Riv 4.6 mg: NR P: NR Mortality Riv 9.5 mg: 0/287 Riv 4.6 mg: 1/284 P: 1/288
	Mild and Moderate CATD	Rosler 1999[161] 26 weeks Riv 12 mg) 12 mg/day oral Riv 4 mg) 4 mg/day oral P) Placebo	MMSE Mean change from baseline (95% CI) Riv 12 mg: 0.21 (-0.24 to 0.64) Riv 4 mg: -0.62 (-1.05, -0.15) P: -0.47 (-0.96 to -0.04) ADAS-cog % of patients with ≥4 point improvement Riv 12 mg: 29% Riv 4 mg: 17% P: 19% Mean change from baseline (95% CI) Riv 12 mg: 0.26 (-0.66 to 1.06) Riv 4 mg: -1.37 (-2.27, -0.53) P: -1.34 (-2.19 to -0.41)	PDS % of patients with ≥10% improvement Riv 12 mg: 33% Riv 4 mg: 20% P: 20% Mean change from baseline (95% CI) Riv 12 mg: 0.05 (-1.57 to 1.77) Riv 4 mg: -3.37 (-4.99, -1.61) P: -2.18 (-3.91 to -0.49)	NR	CIBIC plus % of patients with improvement Riv 12 mg: 41% Riv 4 mg: 31% P: 22% Mean change from baseline (95% CI) Riv 12 mg: 3.91 (3.71 to 4.09) Riv 4 mg: 4.24 (4.02, 4.38) P: 4.38 (4.22 to 4.58) GDS Mean change from baseline (95% CI) Riv 12 mg: -0.06 (-0.2 to 0.0) Riv 4 mg: -0.22 (-0.3, -0.1) P: -0.26 (-0.4 to -0.2)	Serious adverse events Riv 12 mg: 40/242 Riv 4 mg: 29/242 P: 29/239 Withdrawals due to adverse events Riv 12 mg: 55/242 Riv 4 mg: 18/242 P: 16/239 Somnolence Riv 12 mg: NR Riv 4 mg: NR P: NR Confusion/Delirium Riv 12 mg: NR Riv 4 mg: NR P: NR Falls Riv 12 mg: NR Riv 4 mg: NR P: NR Extrapyramidal symptoms Riv 12 mg: NR Riv 4 mg: NR

Drug Comparison	CATD Severity	Study Characteristics: Author/Year Followup Risk of Bias	Cognitive	Function	QoL	Global Change	Harms
							P: NR <u>Stroke</u> Riv 12 mg: NR Riv 4 mg: NR P: NR <u>Mortality</u> Riv 12 mg: 2/242 Riv 4 mg: 0/242 P: 0/239
		Winblad 2007[162] 24 weeks Riv 9.5 mg) 9.5 mg/day patch Riv 17.4 mg) 17.4 mg/day patch Riv 12 mg) 12 mg/day oral P) Placebo	<u>MMSE</u> Mean change from baseline (SD) Riv 9.5 mg: 1.1 (3.3) Riv 17.4 mg: 0.9 (3.4) Riv 12 mg: 0.8 (3.2) P: 0.0 (3.5) <u>Clock drawing</u> Mean change from baseline (SD) Riv 9.5 mg: 0.3 (3.4) Riv 17.4 mg: 0.1 (3.1) Riv 12 mg: 0.2 (2.9) P: -0.1 (3.2) <u>ADAS-cog</u> % of patients with ≥4 point improvement Riv 9.5 mg: 27.4% Riv 17.4 mg: 32.8% Riv 12 mg: 28.5% P: 19.9% Mean change from baseline (SD) Riv 9.5 mg: -0.6 (6.4) Riv 17.4 mg: -1.6 (6.5)	<u>ADCS-ADL</u> Mean change from baseline (SD) Riv 9.5 mg: -0.1 (9.1) Riv 17.4 mg: 0.0 (11.6) Riv 12 mg: -0.5 (9.5) P: -2.3 (9.4)	NR	<u>ADCS-CGIC</u> % of patients who improved Riv 9.5 mg: 31% Riv 17.4 mg: 33% Riv 12 mg: 36% P: 28% Mean change from baseline (SD) Riv 9.5 mg: 3.9 (1.2) Riv 17.4 mg: 4.0 (1.3) Riv 12 mg: 3.9 (1.3) P: 4.2 (1.3)	<u>Serious adverse events</u> Riv 9.5 mg: 23/291 Riv 17.4 mg: 36/303 Riv 12 mg: 21/294 P: 26/302 <u>Withdrawals due to adverse events</u> Riv 9.5 mg: 28/293 Riv 17.4 mg: 30/303 Riv 12 mg: 24/297 P: 18/302 <u>Somnolence</u> Riv 9.5 mg: NR Riv 17.4 mg: NR Riv 12 mg: NR P: NR <u>Confusion/Delirium</u> Riv 9.5 mg: NR Riv 17.4 mg: NR Riv 12 mg: NR P: NR <u>Falls</u> Riv 9.5 mg: NR Riv 17.4 mg: NR Riv 12 mg: NR

Drug Comparison	CATD Severity	Study Characteristics: Author/Year Followup Risk of Bias	Cognitive	Function	QoL	Global Change	Harms
			Riv 12 mg: -0.6 (6.2) P: 1.0 (6.8) <u>TMT-A scores</u> Mean change from baseline (SD) Riv 9.5 mg: -12.3 (55.1) Riv 17.4 mg: -6.5 (55.9) Riv 12 mg: -9.8 (66.1) P: 7.7 (56.6)				P: NR <u>Extrapyramidal symptoms</u> Riv 9.5 mg: NR Riv 17.4 mg: NR Riv 12 mg: NR P: NR <u>Stroke</u> Riv 9.5 mg: NR Riv 17.4 mg: NR Riv 12 mg: NR P: NR <u>Mortality</u> Riv 9.5 mg: 4/293 Riv 17.4 mg: 5/303 Riv 12 mg: 2/297 P: 3/302
Rivastigmine vs. Placebo	Moderate and severe CATD	Lopez-Pousa 2005[163] 26 weeks Riv 12 mg) 12 mg/day oral P) Placebo	<u>MMSE</u> Data not available <u>SIB</u> Mean change from baseline (SD) Riv 12 mg: -1.37 (15) P: -5.9 (15)	<u>ADCS-ADL</u> Data not available	NR	<u>Clinical Global Impression</u> No change or worse Riv 12 mg: 81/104 P: 96/106	<u>Serious adverse events</u> Riv 12 mg: 6/104 P: 9/106 <u>Withdrawals due to adverse events</u> Riv 12 mg: 10/104 P: 5/106 <u>Somnolence</u> Data not available <u>Confusion/Delirium</u> Data not available <u>Falls</u> Data not available

Drug Comparison	CATD Severity	Study Characteristics: Author/Year Followup Risk of Bias	Cognitive	Function	QoL	Global Change	Harms
							Extrapyramidal symptoms Data not available Stroke Data not available Mortality Riv 12 mg: 1/109 P: 1/109
Rivastigmine vs. Rivastigmine	Mild and Moderate CATD	Cummings 2012 [154] 24 weeks Medium (24 weeks) High (48 weeks) Riv 13.3 mg) 13.3 mg/day patch Riv 9.5 mg) 9.5 mg/day patch	ADAS-Cog Mean change from baseline Riv 13.3 mg: 1.0 Riv 9.5 mg: 2.2 TMT-A Mean change from baseline Riv 13.3 mg: 4.2 Riv 9.5 mg: 10.2 TMT-B Mean change from baseline (SD) Riv 13.3 mg: 5.5 Riv 9.5 mg: 0.9	ADCS-IADL Mean change from baseline (SD) Riv 13.3 mg: -1.5 Riv 9.5 mg: -2.8	NR	NR	Serious adverse events Riv 13.3 mg: NR Riv 9.5 mg: NR Withdrawals due to adverse events Riv 13.3 mg: NR Riv 9.5 mg: NR Somnolence Riv 13.3 mg: NR Riv 9.5 mg: NR Confusion/Delirium Riv 13.3 mg: 5/280 Riv 9.5 mg: 6/283 Falls Riv 13.3 mg: 12/280 Riv 9.5 mg: 10/283 Extrapyramidal symptoms Riv 13.3 mg: NR Riv 9.5 mg: NR Stroke Riv 13.3 mg: NR Riv 9.5 mg: NR

Drug Comparison	CATD Severity	Study Characteristics: Author/Year Followup Risk of Bias	Cognitive	Function	QoL	Global Change	Harms
							Mortality Riv 13.3 mg: NR Riv 9.5 mg: NR

Abbreviations: ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive subscale; ADAS-CogA=Alzheimer's Disease Assessment Scale-Cognitive subscale with an added item of attention; ADCS-ADL=Alzheimer Disease Cooperative Study-Activities of Daily Living; ADCS-IADL=Instrumental Activities of Daily Living domain (items 7-23) of the Alzheimer's Disease Cooperative Study—Activities of Daily Living; ADCS-CGIC=Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change; CATD=clinical Alzheimer-type dementia; CI=confidence interval; CIBIC-Plus=Clinician Interview Based Impression of Change incorporating caregiver information scale; DAD=Disability Assessment for Dementia; GDS=Global Deterioration Scale; MENFIS=Mental Function Impairment; MMSE=Mini-Mental State Examination; NR=not reported; PDS=Progressive Deterioration Scale; QoL=quality of life; RCT=randomized controlled trial; TMT-A=Trail Making Test Part A; TMT-B=Trail Making Test Part B
*Overall ROB was not rated for studies included in the prior systematic review. We determined if a study was high ROB or less than high ROB by reviewing the ROB domain ratings in the prior systematic review.

Appendix Table E.22. Summary of strength of evidence: rivastigmine versus placebo

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Cognition Global- Brief Stand-Alone Tests	Mild-moderate CATD	24-26 weeks	4 RCT (n=2,439)	*12 mg/d PO or 9.5 mg/d patch* SMD on MMSE=0.24 (95% CI 0.14 to 0.34); 4 trials, n=2,439. Mean change on 10-Point Clock-Drawing was 0.2 12 mg/d PO or 0.3 9.5 mg/d patch vs. -0.1 placebo (p=0.15 and p=0.08 vs. placebo, respectively); 1 trial, n=760	Medium	Inconsistent	Direct	Precise	Low
Cognition Global- Brief Stand-Alone Tests	Mild-moderate CATD	24-26 weeks	2 RCT (n=968)	*4 mg/d PO or 4.6 mg/d patch* SMD on MMSE= -0.02 (95% CI, -0.15 to 0.10); 2 trials, n=968	Medium	Consistent	Direct	Precise	Moderate
Cognition Global- Brief Multi-	Mild-moderate CATD	24-26 weeks	4 RCT (n=2,470)	*12 mg/d PO or 9.5 mg/d patch* ≥4-point improvement	Medium	Consistent	Direct	Precise	Moderate

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Domain Batteries				ADAS-Cog was 25% vs. 17%; ARD, 8% (95% CI, 4% to 11%); RR, 1.47 (95% CI, 1.22 to 1.79); 3 trials, n=1,819 SMD on ADAS-cog=-0.26 (95% CI -0.34 to -0.18); 4 trials, n=2,470					
Cognition Global- Brief Multi-Domain Batteries	Mild-moderate CATD	24-26 weeks	2 RCT (n=1,011)	*4 mg/d PO or 4.6 mg/d patch* ≥4-point improvement ADAS-Cog was 17% vs. 19%; ARD, -2% (95% CI, -9% to 6%); NNTH, 50 (95% CI, NNTH 11 to ∞ to NNTB 17); RR, 0.91 (95% CI, 0.60 to 1.38); 1 trial, n=407. SMD on ADAS-Cog=-0.08 (95% CI, -0.25 to 0.10); 2 trials, n=1,011	Medium	Consistent	Direct	Imprecise	Low
Cognition Global- Brief Multi-Domain Batteries	Moderate - severe CATD	26 weeks	1 RCT (n=210)	*12 mg/d PO or 9.5 mg/d patch* SMD on SIB=0.30 (95% CI, 0.03 to 0.57); 1 trial, n=210	Medium	Unknown	Direct	Imprecise	Insufficient
Cognition-Domain Level Tests Typically Part of a Larger Battery (Attention)	Mild-moderate CATD	24 weeks	1 RCT (n=739)	*12 mg/d PO or 9.5 mg/d patch* SMD on TMT-A=-0.32 (95% CI, -0.47 to -0.16); 1 trial, n=739	Medium	Unknown	Direct	Imprecise	Insufficient
Function	Mild-moderate CATD	24-26 weeks	4 RCT (n=2469)	*12 mg/d PO or 9.5 mg/d patch* likelihood >10% PDS improvement was 33% vs. 20%; ARD, 13% (95% CI, 5% to 22%); NNTB, 8	Medium	Consistent	Direct	Imprecise	Low

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
				(95% CI, 5 to 20); RR, 1.65 (95% CI, 1.19 to 2.29); 1 trial, n=421 SMD on PDS=0.21 (95% CI 0.09 to 0.33); 2 trials, n=1,151 SMD on ADCS-ADL= 0.21 (95% CI, 0.09 to 0.33); 1 trials, n=782 SMD on DAD= 0.19 (95% CI, 0.03 to 0.37); 1 trial, n=536					
Function	Mild-moderate CATD	24-26 weeks	2 RCT (n=1,014)	*4 mg/d PO or 4.6 mg/d patch* likelihood >10% PDS improvement was 20% vs. 20%; 1 trial, n=448 SMD on PDS= -0.09 (95% CI, -0.27 to 0.09); 1 trial, n=478 SMD on DAD=0.11 (95% CI, -0.06 to 0.28); 1 trial, n=536	Medium	Consistent	Direct	Imprecise	Low
Quality of Life	Mild-moderate CATD	NR	NR	NR	NR	NR	NR	NR	Insufficient
Staging	Mild-moderate CATD	26 weeks	2 RCT (n=1158)	*12 mg/d PO or 9.5 mg/d patch* SMD on GDS=0.27 (95% CI 0.15 to 0.39); 2 trials, n=1,158	Medium	Consistent	Direct	Imprecise	Low
Staging	Mild-moderate CATD	26 weeks	1 RCT (n=480)	*4 mg/d PO or 4.6 mg/d patch* SMD on GDS= 0.05 (95% CI, -0.13 to 0.23); 1 trial, n=480	Medium	Unknown	Direct	Imprecise	Insufficient
Clinical Impression	Mild-moderate CATD	24-26 weeks	3 RCT (n=2,201)	*12 mg/d PO or 9.5 mg/d patch* Likelihood unchanged/improved was	Medium	Consistent	Direct	Precise	Moderate

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
				70% vs. 59%; ARD, 11% (95% CI, 5% to 16%); NNTB, 9 (95% CI, 6 to 20); RR, 1.16 (95% CI, 1.04 to 1.29) Likelihood improved was 31% vs. 21%; ARD, 10% (95% CI, 7% to 14%); RR, 1.47 (95% CI, 1.20 to 1.80) Likelihood moderately/markedly improved was 10% vs. 6%; ARD, 4% (95% CI, 1% to 7%); NNTB, 25 (95% CI, 14 to 100); RR, 1.46 (95% CI, 0.93 to 2.29)					
Clinical Impression	Mild-moderate CATD	24-26 weeks	2 RCT (n=931)	*4 mg/d PO or 4.6 mg/d patch* Likelihood unchanged/improved was 62% vs. 57%; ARD, 5% (95% CI, -4 to 13); NNTB, 20 (95% CI, NNTB 8 to ∞ to NNTH 25); RR, 1.08 (95% CI, 0.94 to 1.25) Likelihood improved was 25% vs. 18%; ARD, 7% (95% CI, 2 to 13); RR, 1.39 (95% CI, 1.09 to 1.78); 2 trials, n=931 Likelihood moderately/markedly improved was 4.5% vs. 2%; ARD, 2.6% (95% CI, -0.4 to 5.5); NNTB, 38 (95% CI, NNTB 18 to ∞ to NNTH 250); RR, 2.38 (95% CI, 0.85 to 6.67)	Medium	Consistent	Direct	Imprecise	Low

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Clinical Impression	Moderate - severe CATD	26 weeks	1 RCT (n=210)	*12 mg/d PO or 9.5 mg/d patch* Likelihood improved was 22% vs. 9%; RR, 2.34 (95% CI, 1.17 to 4.68); ARD, 13% (95% CI, 3 to 22); 1 trial, n=210	Medium	Unknown	Direct	Imprecise	Low
Serious Adverse Events	All severity CATD	24-26 weeks	5 RCT (n=2828)	*12 mg/d PO or 9.5 mg/d patch* 11.2% vs. 10.1%; ARD, 1% (95% CI, -1 to 3); NNTH, 100 (95% CI, NNTH 33 to ∞ to NNTB 100); RR=1.07 (95% CI 0.86 to 1.34); 5 trials, n=2,828	Medium	Inconsistent	Direct	Imprecise	Low
Serious Adverse Events	Mild-moderate CATD	24-26 weeks	2 RCT (n=1,049)	*4 mg/d PO or 4.6 mg/d patch* 8.2% vs. 9.3%; ARD, -1.1 (95% CI, -4.5 to 2.3); NNTB, 91 (95% CI, NNTB 22 to ∞ to NNTH 43); RR, 0.88 (95% CI, 0.60 to 1.30); 2 trials, n=1,049)	Medium	Consistent	Direct	Imprecise	Low
Withdrawals Due to Adverse Events	All severity CATD	24-26 weeks	5 RCT (n=2836)	*12 mg/d PO or 9.5 mg/d patch* 12.7% vs. 6.9%; ARD, 5.8% (95% CI, 3.7 to 8); NNTH, 17 (95% CI, 13 to 27); RR=1.88 (95% CI 1.35 to 2.61); 5 trials, n=2,836	Medium	Consistent	Direct	Precise	Moderate
Withdrawals Due to Adverse Events	Mild-moderate CATD	24-26 weeks	2 RCT (n=1,053)	*4 mg/d PO or 4.6 mg/d patch* 10.6% vs. 7.0%; ARD, 3.6 (95% CI, 0.2 to 7); NNTH, 28 [95% CI, 14 to 500); RR, 1.49 (95% CI, 0.92 to 2.42); 2 trials, n=1,053	Medium	Consistent	Direct	Imprecise	Low

Abbreviations: ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive subscale; ADCS-ADL=Alzheimer Disease Cooperative Study-Activities of Daily Living; ARD=Absolute Risk Difference; CATD=clinical Alzheimer-type dementia; CI=confidence interval; CIBIC-Plus=Clinician Interview Based Impression of Change incorporating caregiver information scale; DAD=Disability Assessment for Dementia; GDS=Global Deterioration Scale; MMSE=Mini-Mental State Examination; NNTB=Number Needed to Benefit; NNTH=Number Needed to Harm; NR=not reported; PDS=Progressive Deterioration Scale; RCT=randomized controlled trial; RR=risk ratio; SIB=Severe Impairment Battery; SMD=standardized mean difference; TMT-A=Trail Making Test Part A

Appendix Table E.23. Summary of strength of evidence: rivastigmine versus rivastigmine

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Cognition Global- Brief Stand-Alone Tests	Mild-moderate CATD	24-26 weeks	2 RCTs (n=966)	*Standard-dose vs. low-dose* SMD on MMSE= 0.22 (95% CI, -0.01 to 0.44) No statistical difference on 10-point clock drawing (0.3 vs. 0.2; p not reported)	Medium	Inconsistent	Direct	Imprecise	Insufficient
	Mild-moderate CATD	24 weeks	1 RCT (n=506)	*9.5 mg/day vs. 12-13.3 mg/day* SMD on MMSE= 0.09 (95% CI, -0.08 to 0.27)	Medium	Unknown	Direct	Imprecise	Insufficient
	Mild-moderate CATD	26 weeks	1 RCT (n=454)	*4 mg/day TID vs. 6 mg/day BID* SMD on MMSE= 0.25 (95% CI, 0.07 to 0.43)	Medium	Unknown	Direct	Imprecise	Insufficient
Cognition Global- Brief Multi-Domain Batteries	Mild-moderate CATD	24-26 weeks	2 RCTs (n=1,018)	*Standard-dose vs. low-dose* SMD on ADAS-Cog= -0.27 (95% CI -0.60 to 0.07) Likelihood of 4 point improvement on ADAS-Cog was 29% vs. 17% (RR, 1.70 [95% CI, 1.15 to 2.52])	Medium	Inconsistent	Direct	Imprecise	Insufficient
	Mild-moderate CATD	24 weeks	2 RCTs (n=968)	*9.5 mg/day vs. 12-13.3 mg/day* 1st trial: SMD on ADAS-Cog=0.00 (95% CI, -0.18 to 0.18). Likelihood of 4 point improvement on ADAS-Cog was 28.2% vs. 28.5%; ARD, -0.2% [95% CI, -8.1 to 7.7]; NNTH, 500 [95% CI, NNTH 12 to ∞ to NNTB	Medium	Inconsistent	Direct	Imprecise	Insufficient

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
				13]; RR, 0.99 [95% CI, 0.75 to 1.31]; 2nd trial: 13.3 mg/day worsened less compared with 9.5 mg/day on ADAS-Cog (MD, -1.2, p=0.04)					
	Mild-moderate CATD	26 weeks	1 RCT (n=455)	*4 mg/day TID vs. 6 mg/day BID* SMD on ADAS-Cog= -0.19 (95% CI, -0.38 to -0.01) Likelihood of 4 point improvement on ADAS-Cog was 23% vs. 18% (estimated from graphical data, p=NR)	Medium	Unknown	Direct	Imprecise	Insufficient
Cognition-Domain Level Tests Typically Part of a Larger Battery (attention)	NA	NR	NR	*Standard-dose vs. low-dose* NR	NR	NR	NR	NR	Insufficient
Cognition-Domain Level Tests Typically Part of a Larger Battery (attention)	Mild-moderate CATD	26 weeks	2 RCT (n=993)	*9.5 mg/day vs. 12-13.3 mg/day* 1st trial: SMD on TMT-A= 0.04 (95% CI, -0.14 to 0.22) 2nd trial: not statistically significant (p=0.11)	Medium	Consistent	Direct	Imprecise	Low
Cognition-Domain Level Tests Typically Part of a Larger	NA	NR	NR	*4 mg/day TID vs. 6 mg/day BID* NR	NR	NR	NR	NR	Insufficient

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Battery (attention)									
Cognition-Domain Level Tests Typically Part of a Larger Battery (executive function)	NA	NR	NR	*Standard-dose vs. low-dose* NR	NR	NR	NR	NR	Insufficient
Cognition-Domain Level Tests Typically Part of a Larger Battery (executive function)	Mild-moderate CATD	24 weeks	1 RCT (n=471)	*9.5 mg/day vs. 12-13.3 mg/day* not statistically significant on TMT-B (p=0.78)	Medium	Unknown	Direct	Imprecise	Insufficient
Cognition-Domain Level Tests Typically Part of a Larger Battery (executive function)	NA	NR	NR	*4 mg/day TID vs. 6 mg/day BID* NR	NR	NR	NR	NR	Insufficient
Function	Mild-moderate CATD	24-26 weeks	2 RCTs (1,020)	*Standard-dose vs. low-dose* 1st trial: SMD on PDS= 0.26 (95% CI, 0.08 to 0.44). Likelihood of >10% improvement on PDS was 29% vs. 19% (ARD, 10% [95% CI, 3 to 18]; NNTB, 10 [95% CI, 6 to 33]; RR, 1.56 [95% CI, 1.12 to 2.16])	Medium	Inconsistent	Direct	Imprecise	Insufficient

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
				2nd trial: SMD on DAD= 0.11 (95% CI, -0.06 to 0.27)					
	Mild-moderate CATD	24 weeks	2 RCTs (n=976)	*9.5 mg/day vs. 12-13.3 mg/day* 1st trial: SMD on ADCS-ADL= 0.04 (95% CI, -0.13 to 0.22) 2nd trial: 13.3 mg/day declined less than the 9.5 mg/day patch on Instrumental Activities of Daily Living domain of the ADCS-ADL (p<0.001)	Medium	Inconsistent	Direct	Imprecise	Insufficient
	Mild-moderate CATD	26 weeks	1 RCT (n=452)	*4 mg/day TID vs. 6 mg/day BID* SMD on PDS= 0.10 (95% CI, -0.09 to 0.28)	Medium	Unknown	Direct	Imprecise	Insufficient
Quality of Life	NA	NR	NR	*Standard-dose vs. low-dose* NR	NR	NR	NR	NR	Insufficient
	NA	NR	NR	*9.5 mg/day vs. 12-13.3 mg/day* NR	NR	NR	NR	NR	Insufficient
	NA	NR	NR	*4 mg/day TID vs. 6 mg/day BID* NR	NR	NR	NR	NR	Insufficient
Staging	Mild-moderate CATD	26 weeks	1 RCT (n=484)	*Standard-dose vs. low-dose* SMD on GDS= 0.20 (95% CI, 0.02 to 0.38)	Medium	Unknown	Direct	Imprecise	Insufficient
	Mild-moderate CATD	NR	NR	*9.5 mg/day vs. 12-13.3 mg/day* NR	NR	NR	NR	NR	Insufficient
	Mild-moderate CATD	26 weeks	1 RCT (n=456)	*4 mg/day TID vs. 6 mg/day BID* SMD on GDS= 0.29 (95% CI, 0.10 to 0.47)	Medium	Unknown	Direct	Imprecise	Insufficient

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Clinical Impression	Mild-moderate CATD	24-26 weeks	2 RCTs (n=892)	*Standard-dose vs. low-dose* Improvement: no difference (29% vs. 26%; ARD,3% [95% CI, -3% to 9%]; NNTB, 33 [95% CI, NNTB 11 to ∞ to NNTH 33]; RR, 1.17 [95% CI, 0.94 to 1.47])	Medium	Consistent	Direct	Imprecise	Low
	Mild-moderate CATD	24 weeks	1 RCT (n=501)	*9.5 mg/day vs. 12-13.3 mg/day* Improvement: 31% vs. 36% (ARD, -5% [95% CI, -14 to 3]; NNTH, 20 [95% CI, NNTH 7 to ∞ to NNTB 33]; RR, 0.85 [95% CI, 0.67 to 1.09] SMD on ADCS-CGIC= 0.00 (95% CI, -0.18 to 0.18)	Medium	Unknown	Direct	Precise	Low
	Mild-moderate CATD	26 weeks	1 RCT (n=444)	*4 mg/day TID vs. 6 mg/day BID* Improvement: 30% vs. 23% (estimated from graphical data, p=NR) SMD on CIBIC-Plus= -0.15 (95% CI, -0.34 to 0.03)	Medium	Unknown	Direct	Imprecise	Insufficient
Serious Adverse Events	Mild-moderate CATD	24-26 weeks	2 RCTs (n=1,053)	*Standard-dose vs. low-dose* RR= 1.34 (95% CI, 0.93 to 1.95)	Medium	Consistent	Direct	Imprecise	Low
	Mild-moderate CATD	24 weeks	1 RCT (n=585)	*9.5 mg/day vs. 12-13.3 mg/day* RR= 1.11 (95% CI, 0.63 to 2.00)	Medium	Unknown	Direct	Imprecise	Insufficient
	Mild-moderate CATD	26 weeks	1 RCT (n=455)	*4 mg/day TID vs. 6 mg/day BID* RR= 1.00 (95% CI, 0.67 to 1.50)	Medium	Unknown	Direct	Imprecise	Insufficient

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Withdrawals Due to Adverse Events	Mild-moderate CATD	24-26 weeks	2 RCTs (n=1,055)	*Standard-dose vs. low-dose* RR= 1.63 (95% CI, 0.49 to 5.50)	Medium	Inconsistent	Direct	Imprecise	Insufficient
	Mild-moderate CATD	24 weeks	1 RCT (n=590)	*9.5 mg/day vs. 12-13.3 mg/day* RR= 1.18 (95% CI, 0.70 to 1.99)	Medium	Unknown	Direct	Imprecise	Insufficient
	Mild-moderate CATD	26 weeks	1 RCT (n=455)	*4 mg/day TID vs. 6 mg/day BID* RR=0.63 (95% CI, 0.39 to 1.02)	Medium	Unknown	Direct	Imprecise	Insufficient

Abbreviations: ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS-CGIC=Alzheimer's Disease Cooperative Study—Clinical Global Impression of Change; ADCS-ADL=Alzheimer's Disease Cooperative Study—Activities of Daily Living; BID=two times a day; CATD=Clinical Alzheimer's-type dementia; CI=confidence intervals; CIBIC-Plus=Clinician Interview Based Impression of Change Incorporating Caregiver Information Scale; DAD=Disability Assessment for Dementia; GDS=Global Deterioration Scale; MD=mean difference; MMSE=Mini-Mental State Examination; NA=not applicable; NR=not reported; PDS=Progressive Deterioration Scale; RCT=randomized controlled trial; RR=risk ratio; SMD=standardized mean difference; TID=three times a day; TMT-A=Trail Making Test Part A; TMT-B=Trail Making Test Part B

Memantine Versus Placebo

Appendix Table E.24. Characteristics of eligible randomized controlled trials: memantine versus placebo monotherapy

Study Characteristics: Author/Year, Country, Risk of Bias, Post hoc analyses	Overall number randomized N=	Population: AD Severity Mean Age % Female % White Education (mean yrs.) Baseline Cognition	Intervention: Intervention mode, n/group, Maximum dose, Frequency, Duration	Comparison: Comparison mode, n/group, Dose, Frequency, Duration	Outcome Timing	Outcome Domain [Instrument]
Bakchine 2008[164] Austria, Belgium, Greece, Denmark, Finland, Spain, France, Lithuania, United Kingdom, Poland, Sweden, the Netherlands, High	470	Mild to Moderate 74 yrs. 63% female 100% white Education: NR Mean MMSE: 19 (included 11-23)	Memantine n=318 20 mg/day 24 weeks	Placebo n=152 daily 24 weeks	24 weeks	Cognition: ADAS-Cog Function: ADCS-ADL Quality of Life: NR Clinical Impression: CIBIC-Plus Harms: AE, SAE, mortality, stroke BPSD: NPI

Study Characteristics: Author/Year, Country, Risk of Bias, Post hoc analyses	Overall number randomized N=	Population: AD Severity Mean Age % Female % White Education (mean yrs.) Baseline Cognition	Intervention: Intervention mode, n/group, Maximum dose, Frequency, Duration	Comparison: Comparison mode, n/group, Dose, Frequency, Duration	Outcome Timing	Outcome Domain [Instrument]
Emre 2008[165] **Hellweg 2012[166]** **Mecocci 2009[167]** **Wilkinson 2007[168]** **Winblad 2010[169]**						
Peskind 2006[170] **United States** **Medium** **Emre 2008[165]** **Farlow 2008[171]** **Hellweg 2012[166]** **Mecocci 2009[167]** **Pomara 2007[172]** **Wilkinson 2007[168]** **Winblad 2010[169]**	403	Mild to Moderate 78 yrs. 59% female 91% white Education: NR Mean MMSE: 17 (included 10-22)	Memantine n=201 20 mg/day [=two 5 mg tabs 2x/day (4 tabs/day)] 24 weeks	Placebo n=202 (two tabs, 2x/day = 4 tabs/day) 24 weeks	24 weeks	Cognition: ADAS-Cog Function: ADCS-ADL Quality of Life: NR Clinical Impression: CIBIC-plus: Harms: TEAE, SAE, fall, somnolence, confusion, mortality, discontinued due to AE BPSD: NPI
Reisberg 2003[173] **12672860** **United States** **High** **Atri 2015[174]** **Emre 2008[165]** **Farlow 2008[171]** **Ferris 2009[175]** **Hellweg 2012[166]** **Mecocci 2009[167]** **Wilkinson 2007[168]** **Winblad 2010[169]**	252	Moderate to Severe 76 yrs. 67% female 90% white Education: 13 yrs. Mean MMSE: 8 (included 3-14)	Memantine n=126 20 mg/day 28 weeks	Placebo n=126 daily 28 weeks	28 weeks	Cognition: SIB, MMSE Function: ADCS-ADL Quality of Life: NR Global Change: CIBIC-Plus, Global Deterioration Scale Staging: FAST Harms: SAE, most common AE, mortality, discontinued due to AE BPSD: NPI Other: RUD
van Dyck 2007[176] **United States** **High** **Atri 2015[174]** **Emre 2008[165]** **Farlow 2008[171]** **Ferris 2009[175]**	350	Moderate to Severe 78 yrs. 71% female 81% white Education: NR Mean MMSE: 10 (5-14)	Memantine n=178 20 mg/day (=10 mg 2x/day) 24 weeks	Placebo n=172 daily 24 weeks	24 weeks	Cognition: SIB Function: ADCS-ADL, FAST Quality of Life: NR Global Change: CIBIC-Plus Staging: NR Harms: SAE, fall, confusion, mortality

Study Characteristics: Author/Year, Country, Risk of Bias, Post hoc analyses	Overall number randomized N=	Population: AD Severity Mean Age % Female % White Education (mean yrs.) Baseline Cognition	Intervention: Intervention mode, n/group, Maximum dose, Frequency, Duration	Comparison: Comparison mode, n/group, Dose, Frequency, Duration	Outcome Timing	Outcome Domain [Instrument]
Hellweg 2012[166] **Mecocci 2009[167]** **Winblad 2010[169]**						BPSD: NPI, BGP Other: RUD
Wang 2013[177] **China** **High**	26 (reported only 22 completers)	Moderate to Severe 65 yrs. 64% female (14/22) % white NR Education: 7 yrs. Mean MMSE: 12	Memantine n=11 20 mg/day (=10 mg 2x/day) 24 weeks	Placebo n=11 2x/day 24 weeks	24 weeks	Cognition: SIB, ADAS-Cog, MMSE Function: NR Quality of Life: NR Global Change: NR Harms: NR BPSD: NPI Other: FDG-PET, CSF

Abbreviations: AChEI= acetylcholinesterase inhibitor (donepezil, galantamine or rivastigmine); AD=Alzheimer's Disease; ADAS-Cog= Alzheimer Disease Assessment Scale–cognitive subscale score; ADCS-ADL= Alzheimer Disease Cooperative Study–Activities of Daily Living; ADL=Activities of Daily Living; AE=adverse events; BPSD= behavioral and psychological symptoms in dementia; BGP=Behavioral Rating Scale for Geriatric Patients; BADLS= Bristol Activities of Daily Living Scale; CGI-I=Clinical Global Impression-Improvement; CDR= Clinical Dementia Rating; CFT=Category Fluency Test; COWAT= Controlled Oral Word Association Test; CSF= cerebrospinal fluid; DEMQOL-Proxy=Quality of life for people with dementia; DIAM=donepezil increase vs. additional memantine; --ER=extended release; FAST=Functional Assessment Staging Tool; FDG-PET fluorodeoxyglucose positron emission tomography; GDS=Global Deterioration Scale; GHQ-12=General Health Questionnaire-12; MENFIS=Mental Function Impairment Scale); MRI=magnetic resonance imaging; mg=milligrams; NPI=Neuropsychiatric Inventory; NR=not reported; OT= Orientation test; RUD=Resource Utilization in Dementia; SIT=Stroop Interference Test; SAEs=Serious Adverse Events; SIB= Severe Impairment Battery; SMMSE= Standardized MMSE; VAMC=Veterans Affairs Medical Centers; VFT= Verbal Fluency Test; yrs.=years

Appendix Table E.25. Characteristics of randomized controlled trials: memantine versus placebo, added to stable cholinesterase inhibitor

Study Characteristics: Author/Year, Country, Risk of Bias	Overall number randomized N=	Population: AD Severity Mean Age % Female % White Education (mean yrs.) Baseline Cognition	Intervention: Intervention mode, n/group, Maximum dose, Frequency, Duration	Comparison: Comparison mode, n/group, Dose, Frequency, Duration	Outcome Timing	Outcome Domain [Instrument]
Araki 2014[178]** **Japan** **High**	37	Moderate to severe 79 yrs. 51% female % white NR Education: NR Mean Hasegawa: NR (3-16 included)	Memantine (continue concurrent donepezil) n=19 20 mg/day 24 weeks	"Non-memantine" (continue concurrent donepezil) n=18 frequency NR duration NR	24 weeks	Cognition: MMSE, CDT Function: NR Quality of Life: NR Global Change: CGI-I Harms: gait instability, discontinued due to AE BPSD: NPI

Study Characteristics: Author/Year, Country, Risk of Bias	Overall number randomized N=	Population: AD Severity Mean Age % Female % White Education (mean yrs.) Baseline Cognition	Intervention: Intervention mode, n/group, Maximum dose, Frequency, Duration	Comparison: Comparison mode, n/group, Dose, Frequency, Duration	Outcome Timing	Outcome Domain [Instrument]
Ashford 2011[179] **United States** **High**	17 (Table 1 =13; Results =10)	Mild to moderate 76 yrs. 39% female 69% white Education: 14 yrs. Mean MMSE: 21	Memantine (added to ongoing donepezil in 86%) n=7 20 mg/day (=10mg, 2x/day) 52 weeks	Placebo (added to ongoing donepezil in 67%) n=6 NR 2x/day 52 weeks	52 weeks	Cognition: ADAS-Cog Function: NR Quality of Life: NR Global Change: NR Harms: NR
Dysken 2014[180] **United States** **High** **Belitskaya-Levy 2018{Belitskaya-Levy, 2018 #466**	307 (2 of 4 RCT arms)	Mild to Moderate 79 yrs. 2% female (VAMC) 86% white Education: 57% high school or less Mean MMSE: 21 (12-26 included)	Memantine (added to ongoing donepezil 65%, galantamine 30% or rivastigmine 5%) n=155 20 mg/day [=10 mg, 2x/day] Duration varied	Placebo (added to ongoing donepezil 63%, galantamine 36% or rivastigmine 1%) n=152 2x/day Duration varied	Mean follow-up 2.1 years	Cognition: ADAS-Cog, MMSE Function: ADCS-ADL Quality of Life: NR Global Change: NR Harms: AE, SAE, mortality BPSD: NPI
Grossberg 2013[181] **Argentina, United States, Mexico, Chile** **Medium** **Atri 2015[174]** **Grossberg 2018[182]**	677 (Results= 676)	Moderate to Severe 76 yrs. 72% female 94% white (69% non-US Hispanic adults) Education: 9 yrs. Mean MMSE: 11 (3-14 included)	Memantine-ER (added to ongoing donepezil 69%, galantamine 21% or rivastigmine 9%) n=342 28 mg/day 24 weeks	Placebo (added to ongoing donepezil 68%, galantamine 20% or rivastigmine 12%) n=335 Daily 24 weeks	24 weeks	Cognition: SIB, Verbal Fluency Test Function: ADCS-ADL Quality of Life: NR Global Change: CIBIC-Plus Harms: TEAE, SAE, fall, somnolence, confusion, stroke, mortality, discontinued due to AE BPSD: NPI Other: Modified Resource Utilization, Caregiver Perceived Burden

Study Characteristics: Author/Year, Country, Risk of Bias	Overall number randomized N=	Population: AD Severity Mean Age % Female % White Education (mean yrs.) Baseline Cognition	Intervention: Intervention mode, n/group, Maximum dose, Frequency, Duration	Comparison: Comparison mode, n/group, Dose, Frequency, Duration	Outcome Timing	Outcome Domain [Instrument]
Herrmann 2013[183] **Canada** **High**	369	Moderate to Severe 75 yrs. 58% female % white NR NR Mean MMSE: 12 (8-18 included)	Memantine (added to ongoing AChEI in 95%; baseline % by drug NR) n=182 20 mg/day 24 weeks	Placebo (added to ongoing AChEI in 97%; baseline % by drug NR) n=187 daily 24 weeks	24 weeks	Cognition: SIB Function: ADCS-ADL Quality of Life: NR Global Change: CIBIC-Plus Harms: TEAE, fall, somnolence, severe AE, discontinued due to AE BPSD: NPI, CMAI
Howard 2012[184] **United Kingdom** **Medium** **Knapp 2017**[185]	295	Moderate to Severe 77 yrs. 65% female 95% white Education: NR Mean MMSE: 9 (5-13 included) All taking donepezil ≥ 3 mo. at baseline	1. Memantine & donepezil (=continue donepezil 10 mg & add memantine to 20 mg/day); n=73 2. Memantine only (= discontinue donepezil & add memantine to 20 mg/day); n=76 52 weeks	3. Donepezil only (=continue donepezil 10 mg/day & add placebo memantine); n=73 4. Neither donepezil nor memantine (=discontinue donepezil & add placebo memantine); n=73 52 weeks	30 weeks (for 2 groups); harms for 4 study arms were reported over 52 weeks	Cognition: SMMSE* Function: BADLS* Quality of Life: NR Global Change: NR Quality of Life: DEMQOL-Proxy Harms (52 weeks): SAE, stroke, fall, mortality BPSD: NPI
Lorenzi 2011[186] **Italy** **Medium**	15	Moderate to Severe 76 yrs. 87% female % white NR Mean education5 yrs. Mean MMSE: 15 All taking AChEI at baseline	Memantine (continue AChEI) n=8 20 mg/day	Placebo (continue AChEI) n=7	6 months	Cognition: MMSE, Raven's Coloured Progressive Matrices, Rey-Osterrieth complex figure copy, Trail Making Test, Verbal fluency, Token Test, Story recall, Rey-Osterrieth complex figure recall, digit span, spatial span Function: NR Quality of Life: NR Global Change: NR Harms: NR

Study Characteristics: Author/Year, Country, Risk of Bias	Overall number randomized N=	Population: AD Severity Mean Age % Female % White Education (mean yrs.) Baseline Cognition	Intervention: Intervention mode, n/group, Maximum dose, Frequency, Duration	Comparison: Comparison mode, n/group, Dose, Frequency, Duration	Outcome Timing	Outcome Domain [Instrument]
Peters 2015[187] **Germany** **High**	226 (190 reported for ITT)	Mild to Moderate 72 yrs. 64% female % white: NR Education: NR Mean MMSE: 22 (included 15-26)	Memantine 20 mg/day + galantamine 24 mg/day n=112 52 weeks	Placebo + galantamine 24 mg/day n=114 52 weeks	52 weeks	Cognition: ADAS-Cog Function: ADCS-ADL, CDR Quality of Life: NR Global Change: NR Harms: AE, SAE, fall BPSD: NPI
Porsteinsson 2008[188] **United States** **Medium** **Atri 2013**[189] **Emre 2008**[165] **Farlow 2008**[171] **Hellweg 2012**[166] **Mecocci 2009**[167] **Winblad 2010**[169]	433 (ITT=427)	Mild to Moderate 75 yrs. 52% female % white NR Education: NR MMSE: 17 10-22	Memantine (concurrent stable donepezil 71%, galantamine 14%, or rivastigmine 15%) n=217 20 mg/day 24 weeks	Placebo (concurrent stable donepezil 63%, galantamine 16%, or rivastigmine 20%) n=216 Daily 24 weeks	24 weeks	Cognition: ADAS-Cog, MMSE Function: ADCS-ADL Quality of Life: NR Global Change: CIBIC-Plus Harms: AE, fall, mortality, confusion, discontinued due to AE BPSD: NPI
Tariot 2004[190] **USA** **Medium** **Schmitt 2006**[191] **Atri 2013**[189] **Atri 2015**[174] **Farlow 2008**[171] **Feldman 2006**[192] **Emre 2008**[165] **Ferris 2009**[175] **Hellweg 2012**[166] **Mecocci 2009**[167] **Wilkinson 2007**[168] **Winblad 2010**[169]	404 (403)	Moderate to Severe 76 yrs. 65% female 91% white Education: NR MMSE: 10 (included 5-14) All taking donepezil 5-10 mg/day ≥ 6 mo. at baseline	Memantine (concurrent stable donepezil 5-10 mg/day) n=203 20 mg/day 24 weeks	Placebo (concurrent stable donepezil 5-10 mg/day) n=201 Daily 24 weeks	24 weeks	Cognition: SIB Function: ADCS-ADL Quality of Life: NR Global Change: CIBIC-Plus Harms: TEAE, discontinued due to AE, confusion, fall BPSD: NPI Other: Behavioral Rating Scale for Geriatric Patients-Care Dependency subscale

Study Characteristics: Author/Year, Country, Risk of Bias	Overall number randomized N=	Population: AD Severity Mean Age % Female % White Education (mean yrs.) Baseline Cognition	Intervention: Intervention mode, n/group, Maximum dose, Frequency, Duration	Comparison: Comparison mode, n/group, Dose, Frequency, Duration	Outcome Timing	Outcome Domain [Instrument]
Wilkinson 2012[193] France, Germany, UK, Switzerland **High**	278 (275 for cognitive outcomes)	Moderate 74 yrs. 57% female 100% white Education: NR Mean MMSE: NR (included MMSE 12-20)	Memantine [with (72%) or without concurrent AChEI] n=134 20 mg/day 52 weeks	Placebo [with (71%) or without concurrent AChEI] n=144 Daily	52 weeks	Cognition: MMSE, COWAT, Category Fluency Test, Stroop Interference Test, Orientation Test Function: NR Quality of Life: NR Global Change: NR Harms: AE, discontinued due to AE, severe AE, mortality, stroke, fall, somnolence BPSD: NPI Other: brain atrophy (MRI)

Abbreviations: ≥: greater than or equal to; AChEI= acetylcholinesterase inhibitor (donepezil, galantamine or rivastigmine); AD=Alzheimer's Disease; ADAS-Cog=Alzheimer Disease Assessment Scale–cognitive subscale score; ADCS-ADL= Alzheimer Disease Cooperative Study–Activities of Daily Living; ADL=Activities of Daily Living; AE=adverse events; APTS= all patients treated data set; BPSD= behavioral and psychological symptoms in dementia; BADLS=Bristol Activities of Daily Living Scale; CGI-I=Clinical Global Impression-Improvement; CDR= Clinical Dementia Rating; CDT=Clock Draw Test; CFT=Category Fluency Test; CIBIC-Plus=Clinician Interview-Based Impression of Change plus caregiver input; CMAI=Cohen Mansfield Agitation Inventory; COWAT= Controlled Oral Word Association Test; DEMQOL-Proxy=Quality of life for people with dementia;; Memantine-ER=memantine extended release; FAST=Functional Assessment Staging Tool; GDS=Global Deterioration Scale; GHQ-12=General Health Questionnaire-12; MENFIS=Mental Function Impairment Scale); MRI=magnetic resonance imaging; mg=milligrams; MMSE= Mini-Mental State Exam; NPI=Neuropsychiatric Inventory; NR=not reported; OT= Orientation test; SIT=Stroop Interference Test; SAEs=Serious Adverse Events; SIB= Severe Impairment Battery; SMMSE= Standardized MMSE; VAMC=Veterans Affairs Medical Centers; VFT= Verbal Fluency Test

*Howard 2012[184]: RCT had 4 arms but outcomes (article Table 2 and text) were reported for 2 groups only: 1) continuing vs. discontinuing donepezil (regardless of memantine assignment: active vs. placebo), and 2) adding active vs. placebo mematine (regardless of donepezil assignment: continue or discontinue donepezil). Interaction terms were provided in the text; outcomes for all 4 groups shown in article figures only. Harms through 52 weeks were reported by authors for 4 groups in a supplementary table; however no denominators were reported in the table

**"Non-memantine": Article was unclear whether the control group was randomized to placebo or nothing.

Appendix Table E.26. Outcomes assessed in low or medium risk of bias randomized trials of memantine versus placebo

Treatment	AD Severity	Global Brief Stand-Alone Tests	Global multidomain batteries	Domain level cognitive tests	Function	Quality of life	Global assessment of change	Serious adverse events	Other
Memantine vs. placebo monotherapy)	Mild to moderate AD		ADAS-Cog[170]		ADCS-ADL[170]		CIBIC-plus[170]	1 [170]	

Treatment	AD Severity	Global Brief Stand-Alone Tests	Global multidomain batteries	Domain level cognitive tests	Function	Quality of life	Global assessment of change	Serious adverse events	Other
Memantine vs. placebo (with AChEI)	Mild to moderate AD	MMSE[188]	ADAS-Cog[188]		ADCS-ADL[188]		CIBIC-plus[188]	1[188]	
Memantine vs. placebo (with AChEI)	Moderate to severe AD	MMSE[186]	SIB[181, 190]	Memory[186]: Story Recall, Rey-Osterrieth Complex Figure Recall Executive function[186]: Raven's Coloured Progressive Matrices, Digit Span, Spatial Span, Trail Making Test B Language: Token Test[186]; Verbal Fluency Test[181, 186] Attention[186]: Trail Making Test A, Spatial Span, Digit Span	ADCS-ADL [181, 190]		CIBIC-plus [181, 190]	2[181, 190]	Behavioral Rating Scale for Geriatric Patients [190]
Memantine-ER vs. placebo (concurrent donepezil in half of each group)	Moderate to severe AD	Standardized MMSE[184]			BADLS[184]			1[184]	
Total studies		3	4	2	5	0	4	5	1

Key: AChEI= acetylcholinesterase inhibitor; AD=Alzheimer's Disease; ADCS-ADL= Alzheimer Disease Cooperative Study–Activities of Daily Living**;** ADAS-Cog=Alzheimer Disease Assessment Scale–cognitive subscale score; BADLS=Bristol Activities of Daily Living Scale; CIBIC-Plus=Clinician Interview-Based Impression of Change plus caregiver input; ER=extended release; MMSE= Mini-Mental State Exam; SIB= Severe Impairment Battery

Appendix Table E.27. Risk of bias ratings: memantine versus placebo randomized controlled trials, with or without cholinesterase Inhibitor

Intervention	Study	Time	Selection Bias	Attrition Bias	Performance Bias	Detection Bias	Reporting Bias	Overall Rating* *Justification*
Memantine vs. Placebo monotherapy	Bakchine 2008 [194]	24 weeks	Medium	Medium	High	Low	Low	High
	Dyksen 2014[195]	2.1 years	Low	High	Low	Low	Low	High

Intervention	Study	Time	Selection Bias	Attrition Bias	Performance Bias	Detection Bias	Reporting Bias	Overall Rating* *Justification*
	Peskind 2006[170]	24 weeks	Low	Medium	Low	Low	Low	Medium
	Reisberg 2003[173]	28 weeks	Low	High	Low	Low	Low	High
	van Dyck 2007[176]	24 weeks	Medium	High	Low	Low	Low	High
	Wang 2013[177]	24 weeks	Medium	Medium	High	Low	Low	High
Memantine vs. Placebo, (added to ongoing cholinesterase inhibitor)	Araki 2014[178]	24 weeks	Low	High	High	Low	Low	High
	Ashford 2011[179]	52 weeks	Medium	High	High	Low	High	High
	Grossberg 2013[196]	24 weeks	Low	Medium	Low	Low	Low	Medium
	Herrmann 2013[183]	24 weeks	Medium	Medium	High	Low	Low	High
	Lorenzi 2011[186]	6 months	Medium	Low	Medium	High	Low	Medium
	Peters 2015[187]	52 weeks	Low	High	Low	Low	Low	High
	Porsteinsson 2008[188]	24 weeks	Low	Medium	Low	Low	Low	Medium
	Tariot 2004[190]	24 weeks	Low	High*	Low	Low	Low	Medium**
	Wilkinson 2012[193]	52 weeks	Low	High	Low	Low	High	High
	Howard 2012[184](2 arms)	30 weeks***	Low	Medium	Low	Low	Low	Medium for 30-week outcomes***

Abbreviations: AChEI= acetyl-cholinesterase inhibitor (donepezil, galantamine or rivastigmine)

*Justifications provided when overall risk of bias rating deviated from guidance provided in risk of bias assessment tool (Appendix B)

**Tariot 2004: Attrition bias was borderline Medium-High (20.3%) per EPC pre-determined criteria. Rated as Medium Overall Risk of Bias because one less participant lost would assign Attrition bias as Medium (< 20% attrition) and result in an Overall Risk of Bias of Medium.

***Howard 2012[184]: Risk of Bias rated for 30-week outcomes (16.6% attrition, overall Medium risk of bias); 52-week results were rated as High risk of bias (26.4% attrition).

Appendix Table E.28. Primary outcomes summary of medium risk of bias studies: memantine versus placebo, with and without concurrent cholinesterase Inhibitor

Drug Comparison	AD Severity	Study Characteristics: Author/Year, Followup, Risk of Bias	Cognitive	Function	Quality of Life	Global Change	Harms**
Memantine vs. placebo (monotherapy)	Mild to Moderate AD	Peskind 2006[170] 24 weeks Medium	ADAS-Cog: Mean change from baseline (SD) OC: I: 0.0 (7.8) C: 1.0 (7.9) p=0.13 MMRM: I: -0.9 (5.5) C: 0.4 (5.5) p=0.003 LOCF: I: -0.8 (7.9) C: 1.1 (7.9) p=0.003	ADCS-ADL: Mean change from baseline (SD) OC: I: -2.3 (10.7) C: -2.3 (10.9) p=0.98 MMRM: I: -2.1 (7.1) C: -1.8 (7.2) p=0.63 LOCF: I: -2.9 (10.8) C: -3.0 (10.9) p=0.89	NR	CIBIC-plus: Change from baseline (SD) OC: I: 4.2 (12.8) C: 4.5 (13.9) p=0.03 LOCF: I: 4.2 (1.0) C: 4.5 (1.1) chi2=8.2, p=0.004; SMD [95%CI]= -0.30 [-0.49, -0.10]	SAE: I: 10% C: 10% p=NR (NS*) Discontinued due to AE: I: 19 (10%) C: 10 (5%) p=0.09 (difference 4.5%= NS*) Somnolence I: 14/201 (7.0%) C: 2/202 (1.0%) p=0.002 (difference = 6.0%*) Confusion I: 10/201 (5.0%) C: 7/202 (3.5%) p=0.47 Fall I: 15/201 (7.4%) C: 15/202 (7.5%) p=1.00 Mortality I: 1/201 (0.5%) C:1/202 (0.5%) p=NR

Drug Comparison	AD Severity	Study Characteristics: Author/Year, Followup, Risk of Bias	Cognitive	Function	Quality of Life	Global Change	Harms**
Memantine vs. placebo (concurrent with any AChEI)	Mild to Moderate AD	Porsteinsson 2008[188] 24 weeks Medium	ADAS-Cog: Mean score (SD) LOCF: I: 28.5 (12.8) C: 28.0 (11.9) LSMD [95% CI] = -0.7 [-1.8. 0.4], p=0.184 OC: I: 28.2 (12.8) C: 27.6 (11.7) LSMD [95% CI] = -0.8 [-1.9. 0.4], p=0.186 MMSE: Mean score (SD) LOCF I: 16.5 (5.4) C: 16.4 (5.1) LSMD [95% CI]= 0.5 [-0.1. 1.1], p=0.123 OC I: 16.6 (5.4) C: 16.4 (5.1) LSMD [95% CI] = 0.4 [-0.2. 1.1], p=0.190	ADCS-ADL: Mean score (SD) OC: I: 51.8 (16.0) C: 53.6 (14.6) LSMD [95% CI]= -0.3 [-1.8. 1.3], p=0.741 LOCF: I: 51.8 (15.9) C: 52.0 (15.7) LSMD [95% CI]= -0.2 [-1.6. 1.3], p=0.816	NR	CIBIC-plus: Mean score (SD) LOCF: I: 4.4 (1.0) C: 4.4 (1.0) LSMD [95% CI]= 0.0 [-0.2, 0.2], p=0.843 OC: I: 4.4 (1.0) C: 4.4 (1.0) LSMD [95% CI]= 0.0 [-0.2, 0.2], p=0.650	SAE I: 27/217 (12.4%) C: 30/216 (13.9%) p=NR (difference1.5%= NS*) Confusion I: 12/217 (5.5%) C: 9/216 (4.2%) p=NR Fall I: 22/217 (10.1%) C: 15/216 (6.9%) p=NR (difference 3.2%= NS*) Mortality I: 3/217(1.45%) C: 2/216 (0.9%) p=NR Discontinued due to AE I: 13 (6.0%) C: 17 (7.9%) p=NR (difference 1.9%= NS*)

Memantine vs. placebo (concurrent with any stable AChEI)	Moderate to Severe AD	Grossberg 2013[181] 24 weeks Medium Memantine-ER 28 mg/day	SIB: Mean change from baseline (SD) LOCF: I: 2.7 (11.2) C: 0.3 (11.5) LSMD 2.6 [1.0, 4.2] p=0.001 Verbal Fluency Test: Mean change from baseline (SD): LOCF: I: 0.3 (2.8) C: -0.3 (2.5) LSMD 0.5 [0.2, 0.9] p=0.004	ADCS-ADL: Mean change from baseline (SD) LOCF: I: -0.7 (6.9) C: -1.3 (7.7) LSMD 0.7 [-0.3, 1.8] p=0.177	NR	CIBIC-plus: Mean change from baseline (SD) LOCF: I: 3.8 (1.2) C: 4.1 (1.2) p=0.008	SAE I: 28/341 (8.2%) C: 21/335 (6.3%) p=NR (difference 1.9%=NS*) Discontinued due to AE: I: 34/341 (9.9%) C: 21/335 (6.3%) p=NR (difference 3.6%=NS*) Somnolence I: 10/341 (2.9%) C: 4/335 (1.2%) p=NR (difference 1.7%=NS*) Confusion I: 6/341 (1.8%) C: 7/335 (2.1%) p=NR (difference 0.3%=NS*) Fall I: 19/341 (5.6%) C: 26/335 (7.8%) p= NR (difference 2.2%= NS*) Stroke I: 2/341 (0.6%) C: 0/335 (0) p=NR (difference 0.6%= NS*) Mortality: I: 4/341 (1.2%) C: 5/335 (1.5%) p=NR (difference 03%= NS*)
		Lorenzi 2011[186] 6 months Medium	Change from baseline:* MMSE*: I: -4.86	NR	NR	NR	NR

			C: 1.01 P=NR Raven's Coloured Progressive Matrices*: (Nonverbal reason) I: -0.86 C: -2.12 p=NR Rey-Osterrieth complex figure copy*: I: 7.15 C: -1.29 p=NR Trail Making Test (B-A)*: I: -2.93 C: 14.25 p=NR Verbal fluency, phonemic*: I: -4.06 C: -0.60 p=NR Verbal fluency, semantic*: I: -1.36 C: -3.10 p=NR Token Test*: I: -4.60 C: -2.80 p=NR Story recall: I: 0.94 C: 0.63 p=NR Rey-Osterrieth complex figure recall* I: -0.14				

Drug Comparison	AD Severity	Study Characteristics: Author/Year, Followup, Risk of Bias	Cognitive	Function	Quality of Life	Global Change	Harms**
			C: 0.13 p=NR Digit span* I: -2.27 C: -0.62 p=NR Spatial span*: I: -1.57 C: -0.74 p=NR				
		Tariot 2004[190] 24 weeks Medium	SIB: Least squares mean change from baseline (SE) OC: I: 1.0 (0.7) C: -2.4 (0.7) p< 0.001 LOCF: I: 0.9 (0.7) C: -2.5 (0.7) p< 0.001	ADCS-ADL: Least squares mean change from baseline (SE) OC: LSMD (SE) I: -1.7 (0.5) C: -3.3 (0.6) p=0.02 LOCF: I: -2.0 (0.5) C: -3.4 (0.5) p=0.03	NR	CIBIC-plus: Mean change from baseline (SD) OC: I: 4.4 (0.08) C: 4.6 (0.09) p=0.03 LOCF:I: 4.4 (0.07) C: 4.7 (0.08) p=0.03	Discontinued due to AE: I: 15/202 (7.4%) C: 25/201 (12.4%) p=NR (difference 5.0%= NS*) Confusion I: 16/202 (7.9%) C: 4/201 (2.0%) p=0.01 (difference 5.9%*) Fall I: 15/202 (7.4%) C: 14/201 (7.0%) p= NR

Memantine vs. placebo (concurrent with donepezil in 49% of memantine and 50% of placebo groups) **Moderate to Severe AD**		Howard 2012[184] 30 weeks± Medium	sMMSE: Mean difference [95% CI] between groups (MMRM analysis): 1.5 [0.5, 2.6], p=NR (sample determined MCID 1.4 points)	BADLS: Mean difference [95% CI] between groups (MMRM analysis): -1.9 [-4.3, 0.5], p=NR (sample determined MCID 3.5 points)	NR at 30 weeks	NR	SAE: 188 SAEs in 123 patients over 52 weeks. Study authors counted first event if > 1 SAE of same type in same person: Memantine/donepezil: 40/NR Memantine/placebo: 40/NR Placebo/donepezil: 46/NR Placebo/placebo: 46/NR p=NR Death: Memantine/donepezil: 7/NR Memantine/placebo: 10/NR Placebo/donepezil: 13/NR Placebo/placebo: 10/NR p=NR Stroke: Memantine/donepezil: 3/NR Memantine/placebo: 1/NR Placebo/donepezil: 5/NR Placebo/placebo: 3/NR p=NR Fall: Memantine/donepezil: 3/NR Memantine/placebo: 8/NR Placebo/donepezil:9/NR Placebo/placebo:

Drug Comparison	AD Severity	Study Characteristics: Author/Year, Followup, Risk of Bias	Cognitive	Function	Quality of Life	Global Change	Harms**
							12/NR p=NR

Abbreviations: AD=Alzheimer's Disease; RoB=Risk of Bias; SAE=Serious Adverse Event; LOCF=last observation carried forward; LSMD= least squares mean difference; MMRM=multilevel modeling repeated measures regression; sMMSE= standardized MMSE; MCID=minimum clinically important difference; NR=not reported; OC=observed case analysis at endpoint

*Calculated by EPC: 6-month follow-up value – baseline (per group)

**Number of patients with adverse event (not total number of events)

±Results beyond 30 weeks were high risk of bias due to attrition and therefore not reported here.

Harms: SAE, withdrawal due to AE, somnolence, confusion/delirium, fall, EPS, CVA, mortality

Appendix Table E.29. Summary of strength of evidence: memantine versus placebo

Outcome	CATD severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Cognition: Global Brief Stand-Alone Test	Mild to Moderate (with AChEI)	24 weeks	1 RCT (n=433)	No difference	Medium	Unknown	Direct	Precise	Insufficient
	Moderate to severe (with AChEI)	24-30 weeks	2 RCT (n=310)	1 favored memantine; 1 favored placebo	Medium	Inconsistent	Direct	Imprecise	Insufficient
Cognition: Global Brief Multidomain Battery	Mild to Moderate (without AChEI)	24 weeks	1 RCT (n=403)	No difference	Medium	Unknown	Direct	Precise	Insufficient
	Mild to Moderate (with AChEI)	24 weeks	1 RCT (n=433)	No difference	Medium	Unknown	Direct	Precise	Low
	Moderate to severe (with AChEI)	24 weeks	2 RCT (n=1,081)	Favored memantine	Medium	Consistent	Direct	Imprecise	Low
Language	Moderate to severe (with AChEI)	24-26 weeks	2 RCT (n=693)	1 favored memantine; 1 no difference	Medium	Inconsistent	Direct	Imprecise	Insufficient
Function	Mild to Moderate (without AChEI)	24 weeks	1 RCT (n=403)	No difference	Medium	Unknown	Direct	Precise	Low

Outcome	CATD severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
	Mild to Moderate (with AChEI)	24 weeks	1 RCT (n=433)	No difference	Medium	Unknown	Direct	Precise	Insufficient
	Moderate to severe (83% on AChEI)	24-30 weeks	3 RCT (n=1,376)	2 no difference, 1 favored memantine	Medium	Inconsistent	Direct	Imprecise	Low
Clinical Impression of Change	Mild to moderate (without AChEI	24 weeks	1 RCT (n=403)	No difference	Medium	Unknown	Direct*	Imprecise	Low
	Mild to Moderate (with AChEI)	24 weeks	1 RCT (n=433)	No difference	Medium	Unknown	Direct*	Precise	Low
	Moderate to severe (with AChEI)	24 weeks	2 RCT (n=1,081)	Both favored placebo	Medium	Consistent	Direct*	Precise	Low
Serious Adverse Events	Mild to moderate (without AChEI)	24 weeks	1 RCT (n=403)	No difference	Medium	Unknown	Direct	Imprecise	Insufficient
	Mild to Moderate (with AChEI)	24 weeks	1 RCT (n=433)	No difference	Medium	Unknown	Direct	Imprecise	Insufficient
	Moderate to severe (85% on AChEI)	24-30 weeks	2 RCT (n=972)	No difference	Medium	Unknown**	Direct	Imprecise	Insufficient
Quality of Life	NR	NR	NA	NA	NA	NA	NA	NA	Insufficient (no data)
Staging	NR	NR	NA	NA	NA	NA	NA	NA	Insufficient (no data)
Withdrawals Due to Adverse Events	Mild to moderate (without AChEI)	24 weeks	1 RCT (n=403)	No difference	Medium	Unknown	Direct	Imprecise	Insufficient
	Mild to moderate (with AChEI)	24 weeks	1 RCT (n=433)	No difference	Medium	Unknown	Direct	Imprecise	Insufficient
	Moderate to severe (with AChEI)	24 weeks	2 RCT (n=1,081)	No difference	Medium	Consistent	Direct	Imprecise	Insufficient

Key: AChEI: acetylcholinesterase inhibitor; AD=Alzheimer's Disease

*See Methods, Grading Strength of Evidence, for explanation why clinician and caregiver ratings were considered direct links between intervention and health outcomes in this report.
**Howard 2012[184] lacked denominators per group for serious adverse events.

Appendix F. Key Question 4: Efficacy and Harms of Supplements Versus Placebo for Cognition, Function, and Quality of Life

Appendix Table F.1. Outcome instruments used in low/medium risk of bias studies: supplements versus placebo

Supplement	Study Characteristics: Author/Year Risk of Bias	AD Severity	Cognition-Brief Stand-Alone Tests	Cognition-Brief Multidomain Batteries	Domain Level Tests Typically Part of a Larger Battery *	Function	Quality of Life	Global Staging	Clinical Impression of Change
Souvenaid	Schelten 2012[197] Olde Rikert 2015[198] Low	Mild	NR	NTB total composite z-score	NR	DAD	NR	NR	NR
	Shah 2013[199] Medium	Mild to Moderate	NR	ADAS-cog (11-item)	NR	ADCS-ADL	NR	CDR, Sum of Boxes	NR
Omega-3 Fatty Acids	Freund-Levi 2006[200] Eriksdotter 2015[201] Medium	Mild to Moderate	MMSE	ADAS-Cog	NR	NR	NR	CDR, Sum of Boxes	NR
	Shinto 2014[202] Medium	Mild to Moderate	MMSE	ADAS-cog	NR	ADL IADL	NR	NR	NR
Omega-3 Fatty Acid and Alpha Lipoic Acid	Shinto 2014[202] Medium	Mild to Moderate	MMSE	ADAS-cog	NR	ADL IADL		NR	NR
Antioxidants	Cornelli 2010[203] Medium	Moderate AD	MMSE	NR	NR	NR	NR	NR	NR
Choline Alfoscerate	De Jesus Moreno 2003[204] Medium	Mild to Moderate AD	MMSE	ADAS-Cog	NR	NR	NR	GDS	CGI
Prolonged Release Melatonin	Wade 2014[205] Medium	Mild to Moderate AD	MMSE	ADAS-Cog	NR	IADL	NR	NR	CGI
Sodium Selenate	Malpas 2016[206] Medium	Mild to Moderate AD	MMSE	ADAS-Cog	COWAT[c] Category Fluency Test	NR	NR	NR	NR
Soy Isolfavones	Gleason 2015[207] Medium	Not Specified	MMSE	NR	NR	NR	NR	NR	NR
Copper	Kessler 2008[208] Medium	Not Specified	MMSE	ADAS-Cog	NR	NR	NR	NR	NR

Supplement	Study Characteristics: Author/Year Risk of Bias	AD Severity	Cognition-Brief Stand-Alone Tests	Cognition-Brief Multidomain Batteries	Domain Level Tests Typically Part of a Larger Battery *	Function	Quality of Life	Global Staging	Clinical Impression of Change
Folic Acid and Vitamin B	Aisen 2008[209] Medium	Mild to Moderate AD	MMSE	ADAS-Cog	NR	ADCS-ADL	NR	CDR, Sum of Boxes	NR
	TOTAL		10	10	2	8	0	4	2

*Domain level tests typically part of a larger battery are tests of memory, executive function, language and/or attention: [a]Memory; [b]Executive Function; [c]Language; [d]Attention

AD=Alzheimer's Disease; ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS-ADL= Alzheimer's Disease Cooperative Study - Activities of Daily Living; ADL=Activities of Daily Living; CDR=Clinical Dementia Rating; CGI=Clinical Global Impression; COWAT=Controlled Oral Word Association Test; DAD= Disability Assessment for Dementia; GDS=Global Deterioration Scale; IADL=Instrumental Activities of Daily Living; MMSE=Mini-Mental State Examination; NTB= Neuropsychological Test Battery; NR=Not Reported

Souvenaid

Appendix Table F.2. Characteristics of eligible studies: souvenaid versus placebo

Study Characteristics: **Author/Year** **Design** **Country** **Risk of Bias**	**N=**	**Population:** **AD Severity** **Mean Age** **% Female** **% White** **Education (mean yrs.)** **Baseline Cognition**	**Intervention:** **Intervention** **Mode** **Components** **Frequency** **Duration**	**Comparison:** **Comparison** **Mode** **Components** **Frequency** **Duration**	**Outcome Timing**	**Outcome Domain [Instrument]**
Schelten 2010 [210] **RCT** **Multinational** **High** **Kamphius 2011**[211]	225	Mild AD Mean Age 73.7 50% Female Race NR Mean Years of Education Beyond Primary School 5.75 Baseline Cognition: MMSE 24	Souvenaid, 125 ml once a day at breakfast consumed within 1 hour	Nutritional control drink	24 weeks	Cognitive Tests Weschler Memory Scale-revised, Delayed Recall Weschler Memory Scale-revised, Immediate Recall 13-item ADAS-cog Function ADCS-ADL Quality of Life Quality of Life in Alzheimer's Disease Clinical Impression of Change CIBIC-plus Harms Withdrawal to AEs SAEs
Scheltens 2012[197] **RCT** **Multinational** **Low** **Olde Rikert 2015**[198]	259	Mild AD Mean Age 74 Race NR 34% Female Mean Years of Education Beyond Primary School 6.5 Baseline Cognition: MMSE 25	Souvenaid, 125 ml once a day	Nutritional control drink	24 weeks	Cognitive Tests NTB total composite z-score Function DAD Harms SAEs Withdrawal due to AEs

Study Characteristics: Author/Year Design Country Risk of Bias	N=	Population: AD Severity Mean Age % Female % White Education (mean yrs.) Baseline Cognition	Intervention: Intervention Mode Components Frequency Duration	Comparison: Comparison Mode Components Frequency Duration	Outcome Timing	Outcome Domain [Instrument]
Shah 2013[199] **RCT** **Multinational** **Medium**	527	Mild to Moderate AD Mean Age 77 Race NR 52% Female Mean Years of Education Beyond Primary School 6.6 Baseline Cognition: MMSE 19.5			24 weeks	Cognitive Tests 11-item ADAS-cog Function ADCS-ADL Global Staging CDR, Sum of Boxes Harms SAEs Withdrawal due to AEs Confusion Falls

Abbreviations: AD=Alzheimer's Disease; ADAS-Cog= Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS-ADL= Alzheimer's Disease Cooperative Study-Activities of Daily Living; AE=Adverse Event; CDR=Clinical Dementia Rating; CIBIC-plus: Clinician Interview-Based Impression of Change plus caregiver input; DAD= Disability Assessment for Dementia; MMSE=Mini-Mental State Examination; NTB= Neuropsychological Test Battery; NR=Not Reported; RoB=Risk of Bias; SAEs=Serious Adverse Events

Appendix Table F.3. Risk of bias ratings: souvenaid versus placebo

Study	Time	Selection Bias	Attrition Bias	Performance Bias	Detection Bias	Reporting Bias	Overall Rating
Scheltens 2010[210] **Kamphius 2011[211]**	24 weeks	Medium	High	Low	Low	Low	High
Schelten 2012[197] **Olde Rikert 2015[198]**	24 weeks	Low	Low	Low	Low	Low	Low
Shah 2013[199]	24 weeks	Low	Medium	Low	Low	Medium	Medium

Appendix Table F.4. Primary outcomes summary low and medium risk of bias studies: souvenaid versus placebo

Drug Comparison	AD Severity	Study Followup N RoB	Cognitive	Function	QoL	Global Staging	Clinical Impression of Change	Harms
Souvenaid vs. Placebo	Mild AD	Schelten 2012 [197] 24 weeks N=259 Low Olde Rikert 2015[198]	<u>NTB Total Composite, z-score</u> Mean Change from Baseline (SD) I: 0.12 (0.28) C: 0.04 (0.29) p=0.04 Standardized Mean Difference (95% CI) 0.30 (0.06, 0.54) 24 week trajectory p=0.053	<u>DAD</u> No difference between groups (p=0.36)	NR	NR	NR	<u>SAEs</u> I: 11 SAEs (10 patients. 7.7%) C: 7 SAEs (6 patients, 4.65%) <u>Withdrawal due to AEs</u> I: 3/130 (2.31%) C: 2/129 (1.55%)

Drug Comparison	AD Severity	Study Followup N RoB	Cognitive	Function	QoL	Global Staging	Clinical Impression of Change	Harms
Souvenaid vs. Placebo	Mild to Moderate AD	Shah 2013[199] 24 weeks N=527 Medium	11-item ADAS-cog Mean Change from Baseline (SD) I: 1.88 (6.44) C: 1.52 (5.63) p=0.55 Mean Difference Between Groups (SE) 0.37 (0.57) p=0.51	ADCS-ADL, Total Score Mean Change from Baseline (SD) I: -3.74 (9.76) C: -3.66 (8.03) p=0.926	NR	CDR, Sum of Boxes Mean Change from Baseline (SD) I: 0.77(1.96) C: 0.69 (1.90) p=0.68	NR	SAEs I: 34 SAEs (27 subjects, 10.2%) C: 36 SAEs (34 subjects, 13.1%) Withdrawal due to AEs I: 2 withdrawals due to SAEs (0.76%) C: 4 withdrawals due to SAEs (1.54%) Confusion I: 0/264 C: 1/260 (0.38%) Falls I: 1/264 (0.38%) 2: 1/260 (0.38%)

Abbreviations: AD=Alzheimer's Disease; ADAS-Cog= Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS-ADL= Alzheimer's Disease Cooperative Study-Activities of Daily Living; AE=Adverse Event; CDR=Clinical Dementia Rating; DAD= Disability Assessment for Dementia; NTB= Neuropsychological Test Battery; NR=Not Reported; RoB=Risk of Bias; SAEs=Serious Adverse Events

Appendix Table F.5. Summary of strength of evidence: souvenaid versus placebo

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Cognition - Brief Stand-Alone Tests	NA	NR	NR	NA	NA	NA	NA	NA	NA
Cognition-Brief Multidomain Batteries	Mild to Moderate CATD	24 weeks	2 RCTs [197-199] (N=786)	Studies reported inconsistent findings about the efficacy of Souvenaid compared with placebo on global cognition	Medium	Inconsistent	Direct	Imprecise	Insufficient

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
				measured by multidomain batteries.					
Cognition-Domain Level Tests Typically Part of a Larger Battery	NA	NR	NR	NA	NA	NA	NA	NA	NA
Function	Mild to Moderate CATD	24 weeks	2 RCTs[197-199] (N=786)	Both studies reported no difference between Souvenaid and placebo in measures of function. One study reported no difference on the DAD (p=0.36). The second study found no difference in mean change from baseline on the ADCS-ADL (p=0.93).	Medium	Consistent	Direct	Imprecise	Low (No Difference)
Quality of Life	NA	NR	NR	NA	NA	NA	NA	NA	NA
Global Staging	Mild to Moderate CATD	24 weeks	1 RCT[199] (N=527)	No difference in mean change from baseline on the CDR-SOB between Souvenaid (0.77, SD 1.96]) and placebo (0.69, SD 1.90) in function at 24 weeks (p=0.68).	Medium	Unknown	Direct	Imprecise	Insufficient
Clinical Impression of Change	NA	NR	NR	NA	NA	NA	NA	NA	NA

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Serious Adverse Events	Mild to Moderate CATD	24 weeks	2 RCTs[197-199] (N=786)	Studies reported similar rates of serious adverse events for Souvenaid compared with placebo.	Medium	Consistent	Direct	Imprecise	Low (No Difference)
Withdraws due to Adverse Events	Mild to Moderate CATD	24 weeks	2 RCTs[197-199] (N=786)	Studies reported similar rates of withdrawals due to serious adverse events for Souvenaid compared with placebo.	Medium	Consistent	Direct	Imprecise	Low (No Difference)

Abbreviations: ADCS-ADL: Alzheimer's Disease Cooperative Study -Activities of Daily Living; CATD=Clinical Alzheimer's-type Dementia; CDR-SOB=Clinical Dementia Rating, Sums of Boxes; DAD=Disability Assessment for Dementia; NA=Not Applicable; RCT=Randomized Controlled Trial; NR=Not Reported

Omega-3 Fatty Acids

Appendix Table F.6. Characteristics of eligible studies: omega-3 fatty acids versus placebo

Study Characteristics: Author/Year Design Country Risk of Bias	N=	Population: AD Severity Mean Age % Female % White Education (mean yrs.) Baseline Cognition	Intervention: Intervention Mode Components Frequency Duration	Comparison: Comparison Mode Components Frequency Duration	Outcome Timing	Outcome Domain [Instrument]
Freund-Levi 2006[200] **RCT** **Sweden** **Medium** **Eriksdotter 2015[201]**	204	Mild to Moderate AD Mean Age 73 54% Female Race NR Education NR Baseline Cognition: MMSE 23	Four capsules taken daily with 430 mg DHA and 150 mg EPA	Isocaloric Placebo Oil	6 months	<u>Cognitive Tests</u> MMSE ADAS-Cog <u>Global Staging</u> CDR, Sum of Boxes <u>Harms</u> Withdrawal due to AEs

Study Characteristics: **Author/Year** **Design** **Country** **Risk of Bias**	**N=**	**Population:** **AD Severity** **Mean Age** **% Female** **% White** **Education (mean yrs.)** **Baseline Cognition**	**Intervention:** **Intervention** **Mode** **Components** **Frequency** **Duration**	**Comparison:** **Comparison** **Mode** **Components** **Frequency** **Duration**	**Outcome Timing**	**Outcome Domain [Instrument]**
Shinto 2014[202] **RCT** **Medium** **US**	26	Mild to Moderate AD Mean Age 76 100% white 46% Female 46% College or Greater Baseline Cognition: MMSE 21	Fish oil concentrate with 675 mg and 975 EPA, 3 grams/day taken as 2 capsules	Placebo oil capsules (2 per day)	12 months	<u>Cognitive Tests</u> ADAS-cog MMSE <u>Function</u> ADL IADL <u>Harms</u> SAEs Mortality Falls
Quinn 2010[212] **RCT** **US** **High**	402	Mild to Moderate AD Mean Age 76 52% Female Race NR Mean Years Education 14 Baseline Cognition: MMSE 20.7	Algal DHA, 1 g twice a day	Placebo	18 months	<u>Cognitive Tests</u> ADAS-Cog MMSE <u>Function</u> ADCS-ADL <u>Quality of Life</u> Quality of Life Alzheimer's Disease Scale <u>Global Staging</u> CDR, Sums of Boxes <u>Harms</u> SAEs Withdrawal due to AEs Falls Mortality
Wolkowitz 2003[213] **RCT** **US** **High**	58	Mild to Moderate AD Mean Age 76 48% Female 83% White Education NR	DHEA, 50 mg twice a day	Placebo	6 months	<u>Cognitive Tests</u> ADAS-Cog MMSE <u>Clinical Impression of Change</u> CIBIC-Plus

Study Characteristics: Author/Year Design Country Risk of Bias	N=	Population: AD Severity Mean Age % Female % White Education (mean yrs.) Baseline Cognition	Intervention: Intervention Mode Components Frequency Duration	Comparison: Comparison Mode Components Frequency Duration	Outcome Timing	Outcome Domain [Instrument]
		Baseline Cognition: MMSE 22				<u>Harms</u> SAEs Withdrawal due to AEs

Abbreviations: AD=Alzheimer's Disease; ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADL=Activities of Daily Living; AE=Adverse Event; CIBIC-plus: Clinician Interview-Based Impression of Change plus caregiver input; IADL=Instrumental Activities of Daily Living; MMSE=Mini Mental State Exam; NR=Not Reported; RoB=Risk of Bias; SAEs=Serious Adverse Events

Appendix Table F.7. Risk of bias ratings: omega-3 fatty acids versus placebo

Study	Time	Selection Bias	Attrition Bias	Performance Bias	Detection Bias	Reporting Bias	Overall Rating
Freund-Levi 2006[200] **Eriksdotter 2015**[201]	6 months	Medium	Medium	Low	Low	Low	Medium
Shinto 2014[202]	12 months	Low	Medium	Low	Low	Low	Medium
Quinn 2010[212]	18 months	Low	High	Low	Low	Low	High
Wolkowitz 2003[213]	6 months	Low	High	Low	Low	Low	High

Appendix Table F.8. Primary outcomes summary low and medium risk of bias studies: omega-3 fatty acids versus placebo

Drug Comparison	AD Severity	Study Characteristics: Author/Year Followup N Risk of Bias	Cognitive	Function	QoL	Global Staging	Clinical Impression of Change	Harms
Omega-3 Fatty Acids	Mild to Moderate AD	Freund-Levi 2006[200] 6 months N=204 Medium Eriksdotter 2015[201]	<u>MMSE</u> Mean (95% CI) No difference between groups. I: 22.8 (21.9, 23.7) C: 22.4 (21.5, 23.4) <u>ADAS-Cog</u> Mean (95% CI) No difference between groups. I: 27.7 (25.4, 30.0) C: 28.3 (26.0, 30.6)	NR	NR	<u>CDR, Sum of Boxes</u> Mean (95% CI) No difference between groups. I: 6.2 (5.4, 6.9) C: 6.5 (5.7, 7.3)	NR	<u>Withdrawal due to AEs</u> 18 total withdrawals due to AE

Drug Comparison	AD Severity	Study Characteristics: Author/Year Followup N Risk of Bias	Cognitive	Function	QoL	Global Staging	Clinical Impression of Change	Harms
	Mild to Moderate AD	Shinto 2014[202] 12 months N=26 Medium	MMSE Mean Change (SE) I: -4.3 (1.3) C: -4.6 (1.4) p=0.80 ADAS-Cog Mean Change (SE) I: 4.4 (2.2) C: 3.2 (2.1) p=0.86	IADL Mean Change (SE) I: 0.7 (1.0) C: 4.2 (0.9) p=<0.01 Standardized Mean Difference for Mean Change from Baseline (95% CI) -0.99 (-1.77, -0.18) ADL Mean Change (SSE I: 2.5 (1.0) C: 2.9 (0.7) p=0.82	NR	NR	NR	SAEs 2 SAEs Mortality I: 0/13 (0%) C: 1/13 (7.69%) Falls I: 1/13 (7.69%) C: 2/13 (15.38%)

Abbreviations: AD=Alzheimer's Disease; ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADL=Activities of Daily Living; AE=Adverse Event; IADL=Instrumental Activities of Daily Living; MMSE=Mini Mental State Exam; NR=Not Reported; QoL=Quality of Life; RoB=Risk of Bias; SAEs=Serious Adverse Events

Appendix Table F.9. Summary of strength of evidence: omega-3 fatty acids versus placebo

Outcome AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Cognition - Brief Stand-Alone Tests **Mild to**	6-12 months	2 RCTs[200-202] (N=230)	No difference between groups on the MMSE. One study found no difference in the post treatment mean score between intervention (22.8 [95% CI 21.9, 23.7]) and placebo (22.4	Medium	Consistent	Direct	Imprecise	Low (No Difference)

Outcome AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Moderate CATD			[95% CI 21.5, 23.4]). The second study found no difference between groups in mean change from baseline (p=0.80)					
Cognition - Brief Multidomain Batteries **Mild to Moderate CATD**	6-12 months	2 RCTs[200-202] (N=230)	No difference between groups on the ADAS-Cog. One study found no difference in the post treatment mean score between intervention (27.7 [95% CI 25.4, 30]) and placebo (28.3 [95% CI 26.0, 30.6]). The second study found no difference between groups in mean change from baseline (p=0.86)	Medium	Consistent	Direct	Imprecise	Low (No Difference)
Cognition-Domain Level Tests Part of a Larger Battery	NR	NR	NA	NA	NA	NA	NA	NA
Function **Mild to Moderate CATD**	12 months	1 RCT[202] (N=26)	Inconsistent findings about the efficacy of omega-3 fatty acids on improving function. Improvements were seen in the omega-3 fatty group in IADLs compared with placebo (SMD -0.99 [95% CI -1.77, -0.18)], but not in ADLs.	Medium	Unknown	Direct	Imprecise	Insufficient
Quality of Life	NR	NR	NA	NA	NA	NA	NA	NA
Global Staging	6 months	1 RCT[202] (N=204)	No difference between the omega-3 fatty acid	Medium	Unknown	Direct	Imprecise	Insufficient

Outcome AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Mild to Moderate CATD			and placebo groups on the CDR-SOB.					
Clinical Impression of Change	NR	NR	NA	NA	NA	NA	NA	NA
Serious Adverse Events **Mild to Moderate CATD**	12 months	1 RCT[202] (N=26)	One study reported a total of 2 serious adverse events but did not separate results between the omega-3 fatty acid and placebo groups.	Medium	Unknown	Direct	Imprecise	Insufficient
Withdrawals due to Adverse Events **Mild to Moderate CATD**	6 months	1 RCT[200, 201] (N=204)	One study reported withdrawals due to adverse events but did not separate results between omega-3 fatty acid and placebo groups.	Medium	Unknown	Direct	Imprecise	Insufficient

Abbreviations: CATD=Clinical Alzheimer's-type Dementia; ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADL=Activities of Daily Living; IADL=Instrumental Activities of Daily Living; MMSE=Mini Mental State Exam; NR=Not Reported; NA=Not Applicable; RCT=Randomized Controlled Trial

Omega-3 Fatty Acid and Alpha Lipoic Acid

Appendix Table F.10. Characteristics of eligible studies: omega-3 fatty acid and alpha lipoic acid versus placebo

Study Characteristics: Author/Year Design Country Risk of Bias	N=	Population: AD Severity Mean Age % Female % White Education (mean yrs.) Baseline Cognition	Intervention: Intervention Mode Components Frequency Duration	Comparison: Comparison Mode Components Frequency Duration	Outcome Timing	Outcome Domain [Instrument]
Shinto 2014[202] **RCT** **Medium** **US**	26	Mild to Moderate AD Mean Age 76 100% White 46% Female 46% College or Greater Baseline MMSE 22	Fish oil concentrate with 675 mg and 975 EPA (3 grams/day taken as 2 capsules) and 600 mg/day of alpha lipoic acid (1 capsule)	Placebo oil capsules (2 per day)	12 months	Cognitive Tests ADAS-cog MMSE Function ADL IADL Harms SAEs Mortality Falls

Abbreviations: AD=Alzheimer's Disease; ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADL=Activities of Daily Living; IADL=Instrumental Activities of Daily Living; MMSE=Mini Mental State Exam; RoB=Risk of Bias; SAEs=Serious Adverse Events

Appendix Table F.11. Risk of bias ratings: omega-3 fatty acid and alpha lipoic acid versus placebo

Study	Time	Selection Bias	Attrition Bias	Performance Bias	Detection Bias	Reporting Bias	Overall Rating
Shinto 2014[202]	12 months	Low	Medium	Low	Low	Low	Medium

Appendix Table F.12. Primary outcomes summary low and medium risk of bias studies: omega-3 fatty acid and alpha lipoic acid versus placebo

Drug Comparison	AD Severity	Study Followup RoB	Cognitive	Function	QoL	Global Staging	Clinical Impression of Change	Harms
Omega-3 Fatty Acids and Alpha Lipoic Acid	Mild to Moderate AD	Shinto 2014[202] 12 months N=26 Medium	ADAS-Cog Mean Change (SD) I: -1.0 (0.7) C: -4.6 (1.4) p<0.01	IADL Mean Change (SD) I: 0.9 (1.1) C: 4.2 (0.0) p=0.01 ADL Mean Change (SD) I: 1.3 (0.8) C: 2.9 (0.7) p=0.15	NR	NR	NR	SAEs 2 SAEs Mortality I: 0/13 deaths C: 1/13 deaths Falls I: 0/13 falls C: 2/13 falls

Abbreviations: AD=Alzheimer's Disease; AD=Alzheimer's Disease; ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADL=Activities of Daily Living; IADL=Instrumental Activities of Daily Living; NR=Not Reported; QoL=Quality of Life; RoB=Risk of Bias; SAEs=Serious Adverse Events

Appendix Table F.13. Summary of strength of evidence: omega-3 fatty acid and alpha lipoic acid versus placebo

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
All Outcomes **Mild to Moderate CATD**		12 months	1 RCT[202] (n=26)	Unable to draw conclusions about efficacy of omega-3 fatty acids and alpha lipoic acid.	Medium	Unknown	Direct	Imprecise	Insufficient

Abbreviations: CATD=Clinical Alzheimer's-type Dementia; RCT=Randomized Controlled Trial

Antioxidant Supplementation

Appendix Table F.14. Characteristics of eligible studies: antioxidant supplementation versus placebo

Study Characteristics: **Author/Year** **Design** **Country** **Risk of Bias**	**N=**	**Population:** **AD Severity** **Mean Age** **% Female** **% White** **Education (mean yrs.)** **Baseline Cognition**	**Intervention:** **Intervention** **Mode** **Components** **Frequency** **Duration**	**Comparison:** **Comparison** **Mode** **Components** **Frequency** **Duration**	**Outcome Timing**	**Outcome Domain [Instrument]**
Cornelli 2010[203] **RCT** **US** **Medium**	52	Moderate AD Mean Age 75 Education NR Race NR Baseline Cognition: MMSE 24	Add-on antioxidant ampoule to stable donepezil (5 mg/day), 1 ampoule/day before breakfast	Add-on placebo ampoule to stable donepezil (5 mg/day), 1 ampoule/day before breakfast	6 months	Cognitive Tests MMSE

Abbreviations: AD=Alzheimer's Disease; MMSE=Mini Mental State Exam; NR=Not Reported; RoB=Risk of Bias

Appendix Table F.15. Risk of bias ratings: antioxidant supplementation versus placebo

Study	**Time**	**Selection Bias**	**Attrition Bias**	**Performance Bias**	**Detection Bias**	**Reporting Bias**	**Overall Rating**
Cornelli 2010[203]	6 months	Medium	Medium	Medium	Low	Medium	Medium

Appendix Table F.16. Primary outcomes summary low and medium risk of bias studies: antioxidant supplementation versus placebo

Drug Comparison	AD Severity	Study Followup N RoB	Cognitive	Function	QoL	Clinical Impression of Change	Global Staging	Harms
Add-on antioxidant ampoule vs. Placebo	Moderate AD	Cornelli 2010[203] 6 months N=52 Medium	MMSE Mean (SD) I: 24.3 (1.43) C: 24.2 (1.28) At least 1-point Increase on MMSE I: 12/23 C: 4/25 At least 1-point Decrease on MMSE I: 1/23 C: 2/25	NR	NR	NR	NR	NR

Abbreviations: AD=Alzheimer's Disease; MMSE=Mini Mental State Exam; RoB=Risk of Bias; NR=Not Reported; Quality of Life

Appendix Table F.17. Summary of strength of evidence: antioxidant supplementation versus placebo

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
MMSE	Moderate AD	6 months	1 RCT[203] (n=52)	Unable to draw conclusions about efficacy of add-on antioxidant supplementation.	Medium	Unknown	Direct	Imprecise	Insufficient

Abbreviations: AD=Alzheimer's Disease

Choline Alfoscerate

Appendix Table F.18. Characteristics of eligible studies: choline alfoscerate versus placebo

Study Characteristics: Author/Year Design Country Risk of Bias	N=	Population: AD Severity Mean Age % Female % White Education (mean yrs.) Baseline Cognition	Intervention: Intervention mode Components Frequency Duration	Comparison: Comparison mode Components Frequency Duration	Outcome Timing	Outcome Domain [Instrument]
De Jesus Moreno 2003[204] **RCT** **Mexico** **Medium**	261	Mild to Moderate AD Mean Age 72 76% Female 98% Hispanic Education NR Baseline Cognition: MMSE 18	Choline alfoscerate, 400 mg/pill, 3 pills a day	Placebo	180 days	Cognitive Tests ADAS-Cog MMSE Global Staging GDS Clinical Impression of Change CGI Harms Withdrawal due to AEs

Abbreviations: AD=Alzheimer's Disease; ADAS-Cog= Alzheimer's Disease Assessment Scale-Cognitive Subscale; AEs=Adverse Events; CGI=Clinical Global Impression; GDS=Global Deterioration Scale; MMSE=Mini Mental State Exam; NR=Not Reported; RoB=Risk of Bias

Appendix Table F.19. Risk of bias ratings: choline alfoscerate versus placebo

Study	Time	Selection Bias	Attrition Bias	Performance Bias	Detection Bias	Reporting Bias	Overall Rating
De Jesus Moreno 2003[204]	180 days	Low	Medium	Low	Low	Medium	Medium

Appendix Table F.20. Primary outcomes summary low and medium risk of bias studies: choline alfoscerate versus placebo

Drug Comparison	AD Severity	Study Characteristics: Author/Year Followup N Risk of Bias	Cognitive	Function	QoL	Global Staging	Clinical Impression of Change	Harms
Choline Alfoscerate vs. Placebo	Mild to Moderate AD	De Jesus Moreno 2003[204] 180 days N=261 Medium	<u>ADAS-Cog</u> Mean (SD) I: 32.32 (8.19) C: 39.64 (7.47) p<0.001 At least 2.20 point difference considered clinically relevant Responders (4-point Improvement) I: 61/132 (46.2%) C: 13/129 (10.1%) p<0.001 Complete Responders (7-point Improvement) I: 47/132 (35.6%) C: 5/129 (3.9%) p<0.001 Mean Change from	NR	NR	<u>GDS</u> Mean (SD) I: 2.78 (0.76) C: 3.91 (0.78) p<0.001 Mean Change from Baseline I: 0.95 C:0.19 p<0.001	<u>CGI</u> Mean (SD) I: 2.90 (0.66) C: 3.93 (0.69) p<0.001 Mean Change from Baseline I:1.02 C:0.16 p<0.001	<u>Withdrawal due to AEs</u> No withdrawals due to AEs

Drug Comparison	AD Severity	Study Characteristics: Author/Year Followup N Risk of Bias	Cognitive	Function	QoL	Global Staging	Clinical Impression of Change	Harms
			Baseline I: --3.20 C: 2.90 p<0.001 <u>MMSE</u> Mean (SD) I: 24.52 (3.82) C: 17.12 (4.04) p<0.001 Mean Change from Baseline I: 6.33 C: -0.50 P<0.001					

Abbreviations: AD=Alzheimer's Disease; RoB=Risk of Bias; SAEs=Serious Adverse Events AD=Alzheimer's Disease; ADAS-Cog= Alzheimer's Disease Assessment Scale-Cognitive Subscale; AEs=Adverse Events; CGI=Clinical Global Impression; GDS=Global Deterioration Scale; MMSE=Mini Mental State Exam; NR=Not Reported; QoL=Quality of Life; RoB=Risk of Bias

Appendix Table F.21. Summary of strength of evidence: choline alfoscerate versus placebo

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
All Outcomes	Mild to Moderate AD	108 days	1 RCT[204] (n=261)	Unable to draw conclusions about efficacy of choline alfoscerate.	Medium	Unknown	Direct	Imprecise	Insufficient

Abbreviations: AD=Alzheimer's Disease

Prolonged Release Melatonin

Appendix Table F.22. Characteristics of eligible studies: prolonged release melatonin versus placebo

Study Design Country RoB		N=	Population AD Severity Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome Timing	Outcome Domain [Instrument]
Wade 2014[205] **RCT** **Multinational** **Medium**		80	Mild to Moderate AD Mean Age 75 49% Female Race NR Education NR Baseline Cognition: 51% with MMSE >20	Add-on Prolonged release melatonin (stable on acetylcholinesterase inhibitor), 2 mg/day before bedtime	Placebo	24 weeks	Cognitive Tests ADAS-Cog MMSE Function IADL Clinical Impression of Change CGI Harms SAEs Withdrawal due to AEs Mortality

Abbreviations: AD=Alzheimer's Disease; ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; CGI=Clinical Global Impression; IADL=Instrumental Activities of Daily Living; MMSE=Mini Mental State Exam; RoB=Risk of Bias; SAEs=Serious Adverse Events; NR=Not Reported

Appendix Table F.23. Risk of bias ratings: prolonged release melatonin versus placebo

Study	Time	Selection Bias	Attrition Bias	Performance Bias	Detection Bias	Reporting Bias	Overall Rating
Wade 2014[205]	24 weeks	Low	Medium	Low	Low	High	Medium

Appendix Table F.24. Primary outcomes summary low and medium risk of bias studies: prolonged release melatonin versus placebo

Drug Comparison	AD Severity	Study Characteristics: Author/Year Followup Risk of Bias	Cognitive	Function	QoL	Global Staging	Clinical Impression of Change	Harms
Prolonged Release Melatonin vs. Placebo	Mild to Moderate AD	Wade 2014[205] 24 weeks N=80 Medium	ADAS-Cog Mean Change from Baseline (SD) I: 0.45 (5.0) C: 0.19 (6.28) p=0.45 MMSE Mean Change from Baseline (SD) I: -0.3 (2.8) C: -1.9 (3.5) P=0.04	IADL Mean Change from Baseline (SD) I: 0.77 (1.41) C: 1.62 (1.67) p=0.004	NR	NR	CGI No data reported	SAEs I: 3 SAEs (2 patients, 5.1%) C: 9 SAEs (5 patients, 14.7%) p=0.24 Withdrawal due to AEs I: 0 patients C: 2 patients (5.9%) Mortality No deaths during study period.

Abbreviations: AD=Alzheimer's Disease; ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; CGI=Clinical Global Impression; IADL=Instrumental Activities of Daily Living; MMSE=Mini Mental State Exam; NR=Not Reported; QoL=Quality of Life; RoB=Risk of Bias; SAEs=Serious Adverse Events;

Appendix Table F.25. Summary of strength of evidence: prolonged release melatonin versus placebo

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
All Outcomes	Mild to Moderate AD	24 weeks	1 RCT[205] (n=80)	Unable to draw conclusions about efficacy of prolonged release melatonin.	Medium	Unknown	Direct	Imprecise	Insufficient

Abbreviations: AD=Alzheimer's Disease

Sodium Selenate

Appendix Table F.26. Characteristics of eligible studies: sodium selenate versus placebo

Study Characteristics: Author/Year Design Country Risk of Bias	N=	Population: AD Severity Mean Age % Female % White Education (mean yrs.) Baseline Cognition	Intervention: Intervention mode Components Frequency Duration	Comparison: Comparison mode Components Frequency Duration	Outcome Timing	Outcome Domain [Instrument]
Malpas 2016[206] **RCT** **Australia** **Medium**	40	Mild to Moderate AD Mean Age 71 58% Female Race NR Education NR Baseline Cognition: MMSE 20	Sodium Selenate, 10 mg taken 3 times/day	Placebo or 320 µg of Sodium Selenate taken 3 times/day	28 weeks	Cognitive Tests ADAS-Cog MMSE COWAT Category Fluency Test Harms SAEs Withdrawal due to AEs

Abbreviations: AD=Alzheimer's Disease; ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; AE=Adverse Event; COWAT=Controlled Oral Word Association Test; MMSE=Mini Mental State Exam; RoB=Risk of Bias; SAEs=Serious Adverse Events

Appendix Table F.27. Risk of bias ratings: sodium selenate versus placebo

Study	Time	Selection Bias	Attrition Bias	Performance Bias	Detection Bias	Reporting Bias	Overall Rating
Malpas 2016[206]	28 weeks	Low	Low	Low	Low	High	Medium

Appendix Table F.28. Primary outcomes summary low and medium risk of bias studies: sodium selenate versus placebo

Drug Comparison	AD Severity	Study Followup N RoB	Cognitive	Function	QoL	Global Staging	Clinical Impression of Change	Harms
Sodium Selenate vs. Placebo	Mild to Moderate AD	Malpas 2016[206] 28 weeks N=40 Medium	ADAS-Cog Mean Change from Baseline (95% CI) I: 2.65 (0.12, 5.18)	NR	NR	NR	NR	SAEs I: 1/20 (5%) C: 0/20 Withdrawal due to AEs

Drug Comparison	AD Severity	Study Followup N RoB	Cognitive	Function	QoL	Global Staging	Clinical Impression of Change	Harms
			C: 0.14 (-3.04, 3.33) No difference between groups. <u>MMSE</u> Mean Change from Baseline (95% CI) I: -1 (-3, 1) C: -1 (-2, 0) No difference between groups <u>COWAT</u> Mean Change from Baseline (95% CI) I: –5 (–8, –2) C: –1 (–5, 4) No difference between groups <u>Category Fluency Test</u> Mean Change from Baseline (95% CI) I: 0 (–2, 0.2) C: 1 (–2, 4) No difference between groups					I: 2/20 (10%) C: 0/20

Abbreviations: AD=Alzheimer's Disease; ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; AE=Adverse Event; COWAT=Controlled Oral Word Association Test; MMSE=Mini Mental State Exam; NR=Not Reported; QoL=Quality of Life; RoB=Risk of Bias; SAEs=Serious Adverse Events

Appendix Table F.29. Summary of strength of evidence: sodium selenate versus placebo

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
All Outcomes	Mild to Moderate AD	28 weeks	1 RCT[206] (n=40)	Unable to draw conclusions about efficacy of sodium selenate.	Medium	Unknown	Direct	Imprecise	Insufficient

Abbreviations: AD=Alzheimer's Disease

Soy Isoflavones

Appendix Table F.30. Characteristics of eligible studies: soy isoflavones versus placebo

Study Characteristics: Author/Year Design Country Risk of Bias	N=	Population: AD Severity Mean Age % Female % White Education (mean yrs.) Baseline Cognition	Intervention: Intervention mode Components Frequency Duration	Comparison: Comparison mode Components Frequency Duration	Outcome Timing	Outcome Domain [Instrument]
Gleason 2015[207] **RCT** **US** **Medium**	65	Severity Not Specified Mean Age 76 52% Female Race NR Mean Years of Education 14.5 Baseline Cognition: MMSE 23	Soy Isoflavones, 50 mg/day	Placebo	6 months	Cognitive Tests MMSE Harms Mortality

Abbreviations: AD=Alzheimer's Disease; MMSE=Mini Mental State Exam; RoB=Risk of Bias;

Appendix Table F.31. Risk of bias ratings: soy isoflavones versus placebo

Study	Time	Selection Bias	Attrition Bias	Performance Bias	Detection Bias	Reporting Bias	Overall Rating
Gleason 2015[207]	6 months	Medium	Low	Low	Low	Low	Medium

Appendix Table F.32. Primary outcomes summary low and medium risk of bias studies: soy isoflavones versus placebo

Drug Comparison	AD Severity	Study Followup N RoB	Cognitive	Function	QoL	Global Staging	Clinical Impression of Change	Harms
Soy Isoflavones vs. Placebo	Severity Not Specified	Gleason 2015[207] 6 months N=65 Medium	MMSE Mean (SE) I: 23.4 (1.0) C: 21.3 (1.0) p=0.15	NR	NR	NR	NR	Mortality I: 2/33 (6%) C: 0/32

Abbreviations: AD=Alzheimer's Disease; MMSE=Mini Mental State Exam; NR=Not Reported; QoL=Quality of Life; RoB=Risk of Bias;

Appendix Table F.33. Summary of strength of evidence: soy isoflavones versus placebo

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
All Outcomes	Mild to Moderate AD	6 months	1 RCT[207] (n=65)	Unable to draw conclusions about efficacy of soy isoflavones.	Medium	Unknown	Direct	Imprecise	Insufficient

Abbreviations: AD=Alzheimer's Disease

Copper Add-On Treatment

Appendix Table F.34. Characteristics of eligible studies: copper add-on treatment versus placebo

Study Characteristics: Author/Year Design Country Risk of Bias	N=	Population: AD Severity Mean Age % Female % White Education (mean yrs.) Baseline Cognition	Intervention: Intervention mode Components Frequency Duration	Comparison: Comparison mode Components Frequency Duration	Outcome Timing	Outcome Domain [Instrument]
Kessler 2008[208] **RCT** **Germany** **Medium**	68	Severity Not Specified Mean Age 70 56% Female Race NR Mean Years Education 11 Baseline Cognition: Clock Drawing Test 2.8	Copper (verum) to stable donepezil, 8 mg/day	Placebo	12 months	Cognitive Tests ADAS-Cog MMSE Harms SAEs Withdrawal due to AEs

Abbreviations: AD=Alzheimer's Disease; ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale; AE=Adverse Event; MMSE=Mini Mental State Exam; NR=Not Reported; RoB=Risk of Bias; SAEs=Serious Adverse Events

Appendix Table F.35. Risk of bias ratings: copper add-on treatment versus placebo

Study	Time	Selection Bias	Attrition Bias	Performance Bias	Detection Bias	Reporting Bias	Overall Rating
Kessler 2008[208]	12 months	Medium	Medium	Medium	Low	Low	Medium

Appendix Table F.36. Primary outcomes summary low and medium risk of bias studies: copper add-on treatment versus placebo

Drug Comparison	AD Severity	Study Followup RoB	Cognitive	Function	QoL	Global Staging	Clinical Impression of Change	Harms
Copper Add-on vs. Placebo	Mild to Moderate	Kessler 2008[208] 12 months Medium	ADAS-Cog Percent Increase in Scores I: 8.8% C: 15.5% p=0.78 MMSE Percent Decrease in Scores I: -10.5% C: -9.5% p=0.88	NR	NR		NR	SAEs I: 3/35 (8.5%) C: 0 Withdrawal due to AEs I: 3/35 (8.5%) C: 0/33

Abbreviations: AD=Alzheimer's Disease; ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale; AE=Adverse Event; MMSE=Mini Mental State Exam; NR=Not Reported; Qol=Quality of Life; RoB=Risk of Bias; SAEs=Serious Adverse Events

Appendix Table F.37. Summary of strength of evidence: copper add-on treatment versus placebo

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
All Outcomes	All CATD	12 months	1 RCT[208] (n=68)	Unable to draw conclusions about efficacy of copper add-on treatment.	Medium	Unknown	Direct	Imprecise	Insufficient

Abbreviations: AD=Alzheimer's Disease

Folic Acid and Vitamin B

Appendix Table F.38. Characteristics of eligible studies: folic acid and vitamin B versus placebo

Study Characteristics: Author/Year Design Country Risk of Bias	N=	Population: AD Severity Mean Age % Female % White Education (mean yrs.) Baseline Cognition	Intervention: Intervention mode Components Frequency Duration	Comparison: Comparison mode Components Frequency Duration	Outcome Timing	Outcome Domain [Instrument]
Aisen 2008[209]] **RCT** **US** **Medium**	409	Mild to Moderate AD Mean Age 76 56% Female Race NR Mean Years Education 13.9 Baseline Cognition: MMSE 20.95	Folic acid and vitamin B supplement consisting of 5 mg/d of folic acid, 1 mg/d of vitamin B12 and 25 mg/d of vitamin B6	Placebo	18 months	Cognitive Tests ADAS-Cog MMSE Function ADCS-ADL Global Staging CDR-Sum of Boxes Harms SAEs Withdrawal due to AEs Mortality

Abbreviations: AD=Alzheimer's Disease; ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS-ADL= Alzheimer Disease Cooperative Study Activities of Daily Living; AE=Adverse Event; CDR=Clinical Dementia Rating; MMSE=Mini Mental State Exam; NR=Not Reported; RoB=Risk of Bias; SAEs=Serious Adverse Events

Appendix Table F.39. Risk of bias ratings: folic acid and vitamin B versus placebo

Study	Time	Selection Bias	Attrition Bias	Performance Bias	Detection Bias	Reporting Bias	Overall Rating
Aisen 2008[209]	18 months	Low	Medium	Low	Low	Medium	Medium

Appendix Table F.40. Primary outcomes summary low and medium risk of bias studies: folic acid and vitamin B versus placebo

Drug Comparison	AD Severity	Study Followup RoB	Cognitive	Function	QoL	Global Staging	Clinical Impression of Change	Harms
Vitamin B vs. Placebo	Mild to Moderate AD	Aisen 2008[209] 18 months Medium	<u>ADAS-Cog</u> Mean Change from Baseline (SD) I: 7.38 (9.72) C: 6.54 (8.17) p=0.52 (over 18 months) Rate of Change I: 0.40 points/month C: 0.37 points/month p=0.52 95% CI of rate difference [-0.06, 0.12] <u>MMSE</u> Mean Change from Baseline, I: −2.65 (4.56) C: −3.08 (4.46) p=0.69 (over 18 months)	<u>ADCS-ADL</u> Mean Change from Baseline (SD) I: −10.96 (12.36) C: −10.00 (11.09) p=0.42 (over 18 months)	NR	<u>CDR, Sum of Boxes</u> Mean Change from Baseline (SD) I: 2.58 (2.45) C: 2.51 (2.57) p=0.57 (over 18 months)	NR	<u>SAEs</u> I: 123/240 (51.3%) C: 95/169 (56.2%) p=0.37 <u>Withdrawal due to AEs</u> I: 3/240 (1.3%) C: 2/169 (1.2%) <u>Mortality</u> I: 3/240 (1.3%) C: 4/169 (2.4%) p=0.39

Abbreviations: AD=Alzheimer's Disease; ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS-ADL= Alzheimer Disease Cooperative Study Activities of Daily Living; AE=Adverse Event; CDR=Clinical Dementia Rating; MMSE=Mini Mental State Exam; NR=Not Reported; Qol=Quality of Life; RoB=Risk of Bias; SAEs=Serious Adverse Events

Appendix Table F.41. Summary of strength of evidence: folic acid and vitamin B versus placebo

Outcome AD Severity	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
All Outcomes	**Mild to Moderate CT**	18 months	1 RCT[209][(n=409)	Unable to draw conclusions about efficacy of folic acid and vitamin B supplementation.	Medium	Unknown	Direct	Imprecise	Insufficient

Abbreviations: AD=Alzheimer's Disease

Appendix Table F.42. Characteristics of eligible studies: supplements versus placebo, high risk of bias studies

Supplement	Study Design Country RoB	N=	Population AD Severity Age (mean) Sex (% female) Race (% White) Education (mean years) Baseline Cognition	Intervention Mode Components Frequency Duration	Comparison Mode Components Frequency Duration	Outcome Timing	Outcome Domain [Instrument]
Ginseng	Lee 2008[214] RCT Korea High	97	Severity Not Specified Mean Age 66 64% Female Race NR Education NR Baseline Cognition: MMSE 22	Panax ginseng powder. 4.5 g/day	Control (Not described)	24 weeks	Cognitive Tests MMSE ADAS-Cog Harms Mortality
	Heo 2012[215] RCT South Korea High	40	Moderate AD Mean Age 73 75% Female Race NR Education NR Baseline Cognition: MMSE 13.7	Heat processed ginseng, 1.5, 3, or 4.5 g/day	Control (Not described)	24 weeks	Cognitive Tests ADAS-Cog MMSE Global Staging CDR Harms Withdrawal due to AEs
	Heo 2011[216] South Korea	61	Severity Not Specified Mean Age 67 61% Female Race NR Education NR Baseline Cognition MMSE 21.6	Korean Red Ginseng, 4.5 or 9 g/day	Control (Not described)	24 weeks	Cognitive Tests ADAS-Cog MMSE (Korean Version) Global Staging CDR Harms Withdrawal due to AEs
Ginkgo Biloba	Le Bars 1997[217] RCT US High Le Bars 2000[218] Le Bars 2002[219]	236	All CATD Mean Age 86 58% Female Race NR Median Years Education 14 Baseline Cognition: MMSE 21.2	Ginkgo Biloba (EGb 761), 120 mg/day	Placebo	52 weeks	Cognitive Tests ADAS-Cog Function Geriatric Evaluation by Relative's Rating Instrument

							Clinical Impression of Change CGI-C Harms SAEs Withdrawal due to AEs Mortality
	Kanowski 1996[220] RCT Germany High Kanowski 2003[221]	222	Mild to Moderate AD Mean Age 70 67% Female Race NR Education NR Baseline Cognition NR	Ginkgo Biloba (EGb 761), 240 mg/day	Placebo	24 weeks	Cognitive Tests Syndrom-Kurztest Harms Withdrawals due to AEs SAEs
	Ihl 2012[222] RCT Ukraine High	333	Mild to Moderate AD Mean Age 64 66% Female Race NR Education NR Baseline Cognition: SKT 16.7	Ginkgo Biloba (EGb 761), 240 mg/day	Placebo	24 weeks	Cognitive Tests SKT Verbal Fluency Test (Animal Fluency) Function ADL (International Scale) Quality of Life DEMQOL-proxy Quality of Life Scale Clinical Impression of Change ADCS-CGIC Harms SAEs
	McCarney 2008[223] RCT England High	176	Mild to Moderate AD Mean Age 80 61% Female 95% White Median Years Education 10 Baseline Cognition: Median MMSE 22	Ginkgo Biloba (EGb 761), 120 mg/day	Placebo	6 months	Cognitive Tests ADAS-Cog Function Geriatric Evaluation by Relative's Rating Instrument Quality of Life QoL-AD

							Harms SAEs Withdrawal due to AEs
	Schneider 2005[224] RCT US High	513	Mild to Moderate AD Mean Age 78 52% Female 87% White Education NR Baseline Cognition: MMSE 18	Ginkgo Biloba (EGb 761), 120 or 240 mg/day	Placebo	26 weeks	Cognitive Tests ADAS-Cog Function Geriatric Evaluation by Relative's Rating Instrument Clinical Impression of Change ADCS-CGIC Harms Withdrawal due to AEs SAEs
	Mazza 2006[135] RCT Italy High	51	Mild to Moderate AD Mean Age 68 57% Female Race NR Education NR Baseline Cognition: MMSE 18.8	Ginkgo Biloba, 160 mg/day	Placebo	24 weeks	Cognitive Tests MMSE SKT Harms Withdrawal due to AEs
Acetyl-L-carnitine	Livingston 1991[225] RCT UK High	71	All CATD Age 65+ 82% Female Race NR Education NR Baseline Cognition: MMSE 16	Acetyl-L-carnitine (dose not specified)	Placebo	24 weeks	Cognitive Tests MMSE Kenwood Object Learning Test Word Fluency Drawing Recognition Memory for Words Recognition Memory for Pictures Modified Name Learning Test Function Performance ADL Clinical Impression of Change

							CGI <u>Harms</u> Mortality
	Rai 1990[226] RCT UK High	36	Mild to Moderate AD Mean Age 79 72% Female Race NR Education NR Baseline Cognition: Reisberg Global Deterioration Score 3.0	Acetyl-L-carnitine, 1 gram twice daily	Placebo	24 weeks	<u>Cognitive Tests</u> Kendrick Battery Tests (Object Learning, Digit Copying) Word Fluency Test Automated Classification and Digit Recall Tests <u>Function</u> ADL <u>Harms</u> Withdrawals due to AE
	Sano 1992[227] RCT US High	30	Mild to Moderate AD Mean Age 69 Sex NR Race NR Mean Years Education 14.7 Baseline Cognition: MMSE 19	Acetyl Levocarnitine Hydrochloride, 2.5 g/day for 3 months followed by 3 g/day for 3 months	Placebo	6 months	<u>Cognitive Tests</u> Selective Reminding Test Total Recall Weschler Memory Scale Benton Visual Retention Test MMSE Cancellations Verbal Fluency (Category and Letter) Digit Span Test <u>Clinical Impression of Change</u> CGI <u>Harms</u> Mortality
	Spagnoli 1991[228] RCT Italy High	130	All AD Mean Age 75 71% Female Race NR 7.7% with a Higher Degree	Acetyl-L-carnitine, 2 g/day	Placebo	1 year	<u>Cognitive Tests</u> Blessed Information Memory Concentration Test Verbal Judgement and Mental Calculation Test

			Baseline Cognition NR				Visual Search on Matrices of Digits Prose Memory Test Supra-span Verbal Learning Block-tapping Task Token Test Word Association Test <u>Function</u> Blessed Dementia Scale <u>Harms</u> SAEs
	Thal 1996[229] RCT US High	431	Mild to Moderate AD Mean Age 72 56% Female 94% White 32% College Graduate or Postgraduate Baseline Cognition: MMSE 20	Acetyl-L-Carnitine Hydrochloride, 3 g/day	Placebo	12 months	<u>Cognitive Tests</u> MMSE ADAS-Cog <u>Function</u> ADL IADL <u>Clinical Impression of Change</u> CGI-C <u>Global Staging</u> CDR <u>Harms</u> Withdrawal due to AE Mortality
Vitamin E	Dyksen 2014[180] RCT US High	304	Mild to Moderate AD Mean Age 79 3% Female 86% White 24% With College or Advanced Degree Baseline Cognition: MMSE 21.1	Vitamin E (alpha tocopherol, 1000 IU, twice a day)	Placebo	2.5 years	<u>Cognitive Tests</u> MMSE ADAS-Cog <u>Function</u> ADCS-ADL <u>Harms</u> SAEs Mortality

	Sano 1997[230] RCT US High	169	Moderate AD Mean Age 74 63% Female Race NR Mean Years Education 12.5 Baseline Cognition: MMSE 13.1	Vitamin E (alpha tocopherol, 1000 IU, twice a day	Placebo	2 years	<u>Cognitive Tests</u> MMSE ADAS-Cog <u>Function</u> Blessed Dementia Scale Dependence Scale <u>Harms</u> Mortality
Curcumin	Baum 2008[231] RCT China High	34	Severity Not Specified Mean Age 73 Race NR Education NR Baseline Cognition: MMSE 15.5	Curcumin, 1 or 4 g/day	Placebo	6 months	<u>Cognitive Tests</u> MMSE
	Ringman 2012[232] RCT US High	36	Mean Age 74 63% Female Race NR Mean Years of Education 15.2 Baseline Cognition: MMSE 22.5	Curcumin C3 Complex®, 2 or 4 g/day	Placebo	24 weeks	<u>Cognitive Tests</u> MMSE ADAS-Cog <u>Function</u> ADCS-ADL <u>Harms</u> Withdrawal due to AEs
Lecithin	Little 1993[233] RCT UK High	63	Mild to Moderate AD Mean Age 76 % Female NR Race NR Education NR Baseline Cognition NR	Purified soya lecithin, 20-25 g/day	Placebo	6 months	<u>Cognitive Tests</u> Paired-Associate Learning Test Immediate and Delayed) Verbal Fluency Orientation Questionnaire <u>Function</u> IADL
	Heyman 1987[234] US	37	Mild to Moderate AD Mean Age 63 % Female NR Race NR Education NR	Dehydrated soup with high purity lecithin, 2 daily servings	Placebo soup mixture	6 months	Patients who remained stable Patients who worsened

			Baseline Cognition: CDR 1.6				
Thiamine	Nolan 1991[235] RCT US High	15	All CATD Mean Age 76 67% Female Race NR Education NR Baseline Cognition: MMSE 16.4	Thiamine Hydrochloride, 3 g/day	Lactose placebo	12 months	Cognitive Tests MMSE
Coconut Oil	Chan 2017[236] RCT Malaysia High	40	Mild to Moderate AD 58% between age 70 and 79 65% Female 85% Chinese 43% Primary School Education Baseline Cognition NR	Cold Pressed Coconut Oil, 60 ml daily divided into two doses	Placebo (Water and Coconut Essence)	6 months	Cognitive Tests MMSE Clock Drawing Test Harms Withdrawal due to Adverse Event
Folic Acid Supplementation	Connelly 2008[237] RCT UK High	57	All CATD Mean Age 77 51% Female Race NR Education NR Baseline Cogntion: MMSE 23.5	Folic Acid Supplementation, 1 mg/day	Placebo	6 months	Cognitive Tests MMSE Digit Symbol Substitution Test Function IADL Harms SAEs
Colostrinin®	Leszek 1999[238] RCT Poland High		All CATD Mean Age 69 71% Female Race NR 9.6% with College Education Baseline Cognition NR	Colostrinin®,100 µg per tablet, every second day	Placebo	12 months	Cognitive Tests MMSE Harms Mortality
Selenium	Leszek 1999[238] RCT Poland High	31	All CATD Mean Age 69 71% Female Race NR 9.6% with College Education Baseline Cognition NR	Selenium, 100 µg per tablet, every second day	Placebo	12 months	Cognitive Tests MMSE Harms Mortality

Multivitamin	Sun 2007[239] RCT Taiwan High	89	Mild to Moderate AD Mean Age 75 49% Female Race NR Education NR Baseline Cognition: MMSE 18.7	Multivitamin Supplement with Mecobalamin (0.5 mg) add-on to Donepezil	Placebo (Add-on to Donepezil)	26 weeks	Cognitive Tests 11-item ADAS-Cog (Chinese Version) MMSE Function IADL ADL Harms SAEs Withdrawal due to AEs Delirium
Oral Nicotinamide Adenine Dinucleotide	Demarin 2004[240] RCT Croatia High	26	Severity Not Specified Median Age 68.5 % Female NR Race NR Education NR Baseline Cognition: Median MMSE 19.2	Stable Oral Nicotinamide Adenine Dinucleotide, 10 mg/day	Placebo	6 months	Cognitive Tests Mattis Dementia Rating Scale Hopkins Verbal Learning Test Verbal Fluency Test Global Staging CDR Harms SAEs
Ninjin'yoeito	Kudoh 2016[241] CCT Japan High	23	Mild to Moderate AD Mean Age 76 27% Female Race NR Education NR Baseline Cognition: MMSE 20.4	Ninjin'yoeito (7.5 g/day) added-on to Donepezil (5 mg/day)	Continue Donepezil, 5 mg/day	24 months	Cognitive Tests MMSE ADAS-Cog (Japanese Version) Harms Withdrawal due to AEs
Resveratrol	Turner 2015[242] RCT US High	119	Mild to Moderate AD Mean Age 71 57% Female Race NR Mean Years Education 15.1 Baseline Cognition: MMSE 20.4	Resveratrol, 500 mg/day	Placebo	52 weeks	Cognitive Tests MMSE ADAS-Cog Function ADCD-ADL Global Staging CDR, Sums of Boxes Harms

							SAEs Withdrawal due to AEs

Abbreviations: AD=Alzheimer's Disease; ADAS-Cog= Alzheimer's Disease Assessment Cognitive Subscale; ADCS-ADL=Alzheimer's Disease Cooperative Study-Activities of Daily Living; ADCS-CGIC= Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change; AEs=Adverse Events; CDR=Clinical Dementia Rating; CGI=Clinical Global Impression; DEMQOL-proxy=Dementia Quality of Life Measure; IADL=Instrumental Activities of Daily Living; MMSE=Mini-Mental State Examination; NR=Not Reported; QoL=Quality of Life; RCT=Randomized Controlled Trial; RoB=Risk of Bias; SAEs=Serious Adverse Events; SKT=Short Cognitive Performance Test

Appendix Table F.43. Risk of bias ratings: supplements versus placebo, high risk of bias studies

Supplement	Study	Time	Selection Bias	Attrition Bias	Performance Bias	Detection Bias	Reporting Bias	Overall Rating*
Ginseng	Lee 2008[214]	24 weeks	Medium	High	Low	Low	Low	High
	Heo 2012[215]	24 weeks	Low	High	Medium	Low	Medium	High
	Heo 2011[216]	24 weeks	Low	High	Low	Low	Medium	High
Ginkgo Biloba	Le Bars 1997[217] Le Bars 2000[218] Le Bars 2002[219]	52 weeks	Low	High	Low	Low	Medium	High
	Kanowski 1996[220] Kanowski 2003[221]	24 weeks	Low	High	Low	Low	Low	High
	Ihl 2012[222]	24 weeks	Low	High	Low	Low	Low	High
	McCarney 2008[223]	6 months	Low	High	Low	Low	Medium	High
	Schneider 2005[224]	26 weeks	Low	High	Low	Low	Medium	High
	Mazza 2006[135]	24 weeks	Low	High	Low	Low	Low	High
Acetyl-L-carnitine	Livingston 1991[225]	24 weeks	Low	High	Low	Low	Low	High
	Rai 1990[226]	24 weeks	Low	High	Low	Low	Medium	High
	Sano 1992[227]	6 months	Medium	Medium	Low	Low	High	High

Supplement	Study	Time	Selection Bias	Attrition Bias	Performance Bias	Detection Bias	Reporting Bias	Overall Rating*
	Spagnoli 1991[228]	1 year	Low	High	Low	Low	Low	High
	Thal 1996[229]	1 year	Low	High	Low	Low	Medium	High
Vitamin E	Dyksen 2014[180]	2.5 years	Low	High	Low	Low	Low	High
	Sano 1997[230]	2 years	Low	Low	Low	High	High	High
Curcumin	Baum 2008[231]	6 months	Medium	High	Medium	Low	Low	High
	Ringman 2012[232]	24 weeks	Low	High	Medium	Low	Low	High
Lecithin	Little 1993[233]	12 months	Medium	High	Medium	Medium	Medium	High
	Heyman 1987[234]	6 months	Medium	Low	Medium	High	High	High
Thiamine	Nolan 1991[235]	12 months	Low	High	Medium	Low	Medium	High
Coconut Oil	Chan 2017[236]	6 months	Low	High	Medium	Low	Medium	High
Folic Acid Supplementation	Connelly 2008[237]	6 months	Low	High	Low	Low	High	High
Colostrinin®	Leszek 1999[238]	12 months	Low	High	Medium	Low	High	High
Selenium	Leszek 1999[238]	12 months	Low	High	Medium	Low	High	High
Multivitamin	Sun 2007[239]	26 weeks	Low	High	Low	Low	Low	High
Oral Nicotinamide Adenine Dinucleotide	Demarin 2004[240]	6 months	High	Low	Medium	Low	Low	High
Ninjin'yoeito	Kudoh 2016[241]	6 months, 24 months	High	Low	Medium	Low	Medium	High
Resveratrol	Turner 2015[242]	52 weeks	Low	High	Low	Low	Low	High

Appendix G. Key Question 5: Comparative Effectiveness and Harms of Prescription Drug Treatment Versus Other Active Treatments for Cognition, Function, and Quality of Life

Galantamine Versus Donepezil

Appendix Table G.1. Characteristics of eligible studies: galantamine versus donepezil

Study Characteristics: **Author/Year** **Design** **Country** **Risk of Bias**	**N=**	**Population:** **AD Severity** **Mean Age** **% Female** **% White** **Education (mean yrs.)** **Baseline Cognition**	**Intervention:** **Intervention mode** **Components** **Frequency** **Duration**	**Comparison:** **Comparison mode** **Components** **Frequency** **Duration**	**Outcome Timing**	**Outcom** **Domain [Instrument]**
Wilcock 2003 [243] **RCT** **UK** **Medium**	188	AD not defined (most had MMSE scores <18, mean 15) Mean Age 73 62% Female Race: White 99% Education NR Baseline Cognition: MMSE 15	Galantamine, up to 24 mg/day	Donepezil, up to 10 mg/day based on subject tolerance	52 weeks	Cognitive Tests MMSE ADAS-cog/11 Function Bristol Activities of Daily Living Scale Harms SAEs Withdrawal due to AE All-cause mortality
Shimizu 2015[244] **RCT** **Japan** **High**		Mild to Moderate AD Mean Age 77 55% Female Race: NR Education: mean 7 years Baseline Cognition: MMSE 21	Galantamine, 24 mg/day			Cognitive Tests MMSE ADAS-cog Function Functional Activities Questionnaire Harms Withdrawal due to AE

Study Characteristics: Author/Year Design Country Risk of Bias	N=	Population: AD Severity Mean Age % Female % White Education (mean yrs.) Baseline Cognition	Intervention: Intervention mode Components Frequency Duration	Comparison: Comparison mode Components Frequency Duration	Outcome Timing	Outcom Domain [Instrument]
Aguglia 2004 [245] **CCT** **Italy** **High**	121	Mild to Moderate AD Mean Age 78 66% Female Race: NR Education: mean 7 years Baseline Cognition: MMSE 21	Galantamine, 16 mg/day	Donepezil, up to 10 mg/day	26 weeks	Cognitive Tests MMSE ADAS-cog Function ADL IADL Harms All-cause mortality

Abbreviations: AD=Alzheimer's Disease; ADAS-Cog= Alzheimer's Disease Assessment Scale-Cog; ADCS-ADL=Alzheimer's Disease Cooperative Study-Activities of Daily Living; AEs=Adverse Events; CIBIC-plus= Clinician's Interview-Based Impression of Change-Plus Caregiver Input; DAD= Disability Assessment for Dementia; ER=Extended Release; GDS=Global Deterioration Scale; MDS ADL=Minimum Data Set Activities of Daily Living; MMSE=Mini-Mental State Examination; RCT=Randomized Controlled Trial; RoB=Risk of Bias; SAEs=Serious Adverse Events; SIB=Severe Impairment Battery

Appendix Table G.2. Risk of bias ratings: galantamine versus donepezil

Study	Time	Selection Bias	Attrition Bias	Performance Bias	Detection Bias	Reporting Bias	Overall Rating
Wilcock 2003 [243]	52 weeks	Low	Medium	Medium	Low	Low	Medium
Shimizu 2015 [244]	52 weeks	Medium	High	High	Low	Low	High
Aguglia 2004 [245]	26 weeks	Medium	High	High	High	Medium (withdrawals)	High

Appendix Table G.3. Primary outcomes summary low and medium risk of bias studies: galantamine versus donepezil

Drug Comparison	AD Severity	Study Followup N RoB	Cognitive	Function	QoL	Global Change	Harms
Galantamine (G) vs. Donepezil (D)	Mild to Moderate AD	Wilcock 2003[243] 52 weeks N=182 Medium	MMSE Mean Change from Baseline (SD) G: -0.52 (SE 0.39) D: -1.58 (SE 0.42) P NS between groups ADAS-Cog/11 Mean Change from Baseline (SD) G: -2.22 (SE 0.77) D: -3.43 (SE 0.80) P NS between groups	Bristol Activities of Daily Living Scale (increase denotes decline) Mean Change from Baseline (SD) G: 2.46 (SE 0.71) D: 2.67 (SE 0.74) P NS between groups	NR	NR	SAEs G: 18.6% (18/97) D: 19.8% (18/91) Withdrawal due to AE G: 13.4% (13/97) D: 13.2% (12/91) Falls G: 16.5% (16/97) D: 8.8%% (8/91) All-cause mortality G: 2.1% (2/97) D: 3.3% (3/91)

Abbreviations: AD=Alzheimer's Disease; ADAS-Cog=Alzheimer's Disease Assessment Scale-Cog; AEs=Adverse Events; CI=Confidence Interval; CIBIC-plus= Clinician's Interview-Based Impression of Change-Plus Caregiver Input; DAD= Disability Assessment for Dementia; LS=Least Squares; MDS ADL=Minimum Data Set Activities of Daily Living; MMSE=Mini-Mental State Examination; NR=Not Reported; RoB=Risk of Bias; SAEs=Serious Adverse Events; SD=Standard Deviation; SIB=Severe Impairment Battery

Appendix Table G.4. Summary of strength of evidence: galantamine versus donepezil

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Cognition (Global Brief Stand-Alone Tests-MMSE)	Moderate to severe AD	52 weeks	1 RCT (n=182)	Improvement in MMSE was similar with galantamine compared with donepezil, SMD 0.28 [95%CI -0.02 to 0.57].	Medium	Unknown	Direct	Imprecise	Insufficient (medium ROB, large imprecision, and unknown consistency)

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Cognition (Multiple Measures – ADAS-cog)	Moderate to severe AD	52 weeks	1 RCT (n=182)	Improvement in ADAS-cog was similar with memantine compared with donepezil, SMD -0.16 [95%CI -0.45 to 0.13]	Medium	Unknown	Direct	Imprecise	Insufficient (medium ROB, imprecision, and unknown consistency)
Serious Adverse Events	Moderate to severe AD	52 weeks	1 RCT (n=188)	Participants treated with galantamine were not more likely to experience a serious adverse event than those treated with donepezil, 18.6% vs. 19.8%; ARD -1.2% [95% CI -12.5 to 10.0]; RR 0.94 [95% CI 0.52 to 1.69]	Medium	Unknown	Direct	Imprecise	Insufficient (medium RoB, imprecision, and unknown consistency)
Withdrawals due to Adverse Events	Moderate to severe AD	52 weeks	1 RCT (n=188)	Participants treated with galantamine were not more likely to experience a serious adverse event than those treated with donepezil, 13.4% vs. 13.2%; ARD 0.2% [95% CI -9.5 to 9.9]; RR 1.02 [95% CI 0.49, 2.11]	Medium	Unknown	Direct	Imprecise (large)	Insufficient (medium RoB, large imprecision, and unknown consistency)

Abbreviations: AD=Alzheimer's Disease; ADAS-Cog=Alzheimer's Disease Assessment Scale-Cog; RCT=Randomized Controlled Trial; SIB=Severe Impairment Battery

Memantine Versus Donepezil

Appendix Table G.5. Characteristics of eligible studies: memantine versus donepezil

Study Characteristics: Author/Year Design Country Risk of Bias	N=	Population: AD Severity Mean Age % Female % White Education (mean yrs.) Baseline Cognition	Intervention: Intervention mode Components Frequency Duration	Comparison: Comparison mode Components Frequency Duration	Outcome Timing	Outcome Domain [Instrument]
Modrego 2010[246] **RCT** **Spain** **Medium**	67	Mild to Moderate AD Mean Age 77 70% Female Race NR Education NR Baseline Cognition: MMSE 23	Memantine, 20 mg/day	Donepezil, 10 mg/day	24 weeks	Cognitive Tests ADAS-cog Function DAD Harms Harm outcomes of interest NR

Abbreviations: AD=Alzheimer's Disease; ADAS-Cog= Alzheimer's Disease Assessment Scale-Cog; ADCS-ADL=Alzheimer's Disease Cooperative Study-Activities of Daily Living; AEs=Adverse Events; CIBIC-plus= Clinician's Interview-Based Impression of Change-Plus Caregiver Input; DAD= Disability Assessment for Dementia; ER=Extended Release; GDS=Global Deterioration Scale; MDS ADL=Minimum Data Set Activities of Daily Living; MMSE=Mini-Mental State Examination; RCT=Randomized Controlled Trial; RoB=Risk of Bias; SAEs=Serious Adverse Events; SIB=Severe Impairment Battery

Appendix Table G.6. Risk of bias ratings: memantine versus donepezil

Study	Time	Selection Bias	Attrition Bias	Performance Bias	Detection Bias	Reporting Bias	Overall Rating
Modrego 2010 [246]	24 weeks	Low	Low	Medium	Low	Low	Low

Appendix Table G.7. Primary outcomes summary low and medium risk of bias studies: memantine versus donepezil

Drug Comparison	AD Severity	Study Followup N RoB	Cognitive	Function	QoL	Global Change	Harms
Memantine vs. Donepezil	Mild to Moderate AD	Modrego 2010[246] 24 weeks N=67 Medium	ADAS-Cog Mean Change from Baseline (SD) M: -1.37 (NR) D: -0.12 (NR) Between-group difference (95% CI) -1.25 (NR); PNS	DAD Mean Change from Baseline (SD) M: 4.5 (NR) D: 6.7 (NR) Between-group difference (95% CI) -2.2 (NR); P NS	NR	NR	NR Three patients on memantine were changed to donepezil because of headache and irritability, and one on donepezil to memantine because of gastric disturbances

Abbreviations: AD=Alzheimer's Disease; ADAS-Cog=Alzheimer's Disease Assessment Scale-Cog; AEs=Adverse Events; CI=Confidence Interval; CIBIC-plus= Clinician's Interview-Based Impression of Change-Plus Caregiver Input; DAD= Disability Assessment for Dementia; LS=Least Squares; MDS ADL=Minimum Data Set Activities of Daily Living; MMSE=Mini-Mental State Examination; NR=Not Reported; RoB=Risk of Bias; SAEs=Serious Adverse Events; SD=Standard Deviation; SIB=Severe Impairment Battery

Appendix Table G.8. Summary of strength of evidence: memantine versus donepezil

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Cognition (Multiple Measures)	Mild to Moderate AD	24 weeks	1 RCTs (n=67)	Improvement in global cognitive function as measured by brief multidomain batteries (ADAS-cog) was similar with memantine compared with donepezil, SMD -0.14 [95%CI -0.65 to 0.35]	Medium	Unknown	Direct	Imprecise (large)	Insufficient (large imprecision, and unknown consistency)

Abbreviations: AD=Alzheimer's Disease; ADAS-Cog=Alzheimer's Disease Assessment Scale-Cog; RCT=Randomized Controlled Trial; SIB=Severe Impairment Battery

Memantine Versus Antipsychotics

Appendix Table G.9. Characteristics of eligible studies: memantine versus antipsychotic

Study Characteristics: Author/Year Design Country Risk of Bias	**N=**	**Population: AD Severity Mean Age % Female % White Education (mean yrs.) Baseline Cognition**	**Intervention: Intervention mode Components Frequency Duration**	**Comparison: Comparison mode Components Frequency Duration**	**Outcome Timing**	**Outcome Domain [Instrument]**
Ballard 2015[247] **UK, Norway** **Medium**	199	NR (Severe by MMSE) 83 yrs. 69% female % white NR Education: NR MMSE: 8 (based on 130 of 199 patients at baseline) All residing in care homes, and all taking antipsychotic for ≥ 3 months at baseline	(Memantine + placebo antipsychotic) [=discontinue antipsychotic], with or without AChEI n=99 20 mg/day (= 10 mg twice/day) 24 weeks Concurrent neuroleptic: 26%	(Placebo memantine + continue antipsychotic: [haloperidol, risperidone, olanzapine, or quetiapine]), with or without AChEI n=100 1 to 2 times/day 24 weeks Concurrent neuroleptic: 27%	24 weeks	Cognitive: MMSE Function: BADLS Staging: FAST (baseline only) Global Change: CGIC Harms: AE, SAE, CVA, mortality Other: CMAI, NPI

Abbreviations: AChEI= acetylcholinesterase inhibitor; AE=Adverse Events; BADLS= Bristol Activities of Daily Living Scale; CGIC=Clinical Global Impression of Change; CMAI=Cohen-Mansfield Agitation Inventory; CVA=cerebrovascular accident; FAST=Functional Assessment Staging Tool; mg=milligrams; MMSE=Mini-Mental State Examination; n=number; NPI=Neuropsychiatric Inventory; NR=not reported; SAE=Serious Adverse Events; UK=United Kingdom

Appendix Table G.10. Primary outcomes summary of low and medium risk of bias studies: memantine versus antipsychotic

Drug Comparison	AD Severity	Study Characteristics: Author/Year Followup Risk of Bias	Cognitive	Function	Quality of Life	Global Change	Harms**
Memantine vs. continued antipsychotic	NR (Table 1 shows Severe AD by MMSE)	Ballard 2015[247] 24 weeks Medium	NR*	BADLS: Mean score (SD) at 24 weeks [out of 199 randomized]: I: 34.9 (10.8); n=81 C: 32.3 (10.3); n=83 Difference* [95% CI] = 0.23 [-1.8, 2.3], p=0.8204 SMD 0.03 [-0.27 to 0.34] *adjusted for baseline score	NR	NR*	SAE: I: 18/NR (% NR) C: 25/NR (% NR) p=NR CVA: I: 0/NR C: "> 1"/NR (% NR) p=NR Mortality I: 9/NR (% NR) C:4/NR (% NR) p=NR

Abbreviations: AD=Alzheimer's Disease; BADLS= Bristol Activities of Daily Living Scale; C=Control group; CVA=cerebrovascular accident; I=Intervention group; n=number; NR=not reported; SAE=Serious Adverse Events; SD=Standard Deviation; SMD=standardized mean difference
*****High risk of bias outcomes were not extracted

Appendix Table G.11. Risk of bias ratings: memantine versus antipsychotic

Study	Time	Selection Bias	Attrition Bias	Performance Bias	Detection Bias	Reporting Bias	Overall Risk of Bias Rating
Ballard 2015[247] UK, Norway	24 weeks	Low	Medium 16.6% MMSE: 43.2% BADLS: 17.6% CGIC: 25.6%	Low	Low	Low	**MEDIUM** for BADLS **HIGH** for MMSE **HIGH** for CGIC

Abbreviations: BADLS= Bristol Activities of Daily Living Scale; CGIC=Clinical Global Impression of Change; MMSE=Mini-Mental State Examination; UK=United Kingdom

Appendix Table G.12. Summary of strength of evidence: memantine versus antipsychotic

Drug Comparison	Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Memantine vs. continued antipsychotic with or without AChEI	BADLS	Severe AD	24 weeks	1 RCT (n=164*)	No difference	Medium	Unknown	Direct	Imprecise	Insufficient

Abbreviations: AChEI= acetylcholinesterase inhibitor; AD=Alzheimer's Disease; BADLS= Bristol Activities of Daily Living Scale; n=number; RCT=Randomized Controlled Trial

*Outcomes reported for 164 of 199 randomized

Supplements Versus Drugs

Appendix Table G.13. Characteristics of eligible studies: supplement versus drug

Supplement Drug	Study Characteristics: Author/Year Design Country Risk of Bias	N=	Population: AD Severity Mean Age % Female % White Education (mean yrs.) Baseline Cognition	Intervention: Intervention mode Components Frequency Duration	Comparison: Comparison mode Components Frequency Duration	Outcome Timing	Outcome Domain [Instrument]
Ginkgo Biloba Rivastigmine	Nasab 2012[248] RCT Iran High	56	Mild to Moderate AD Mean Age 66 55% Female Baseline Cognition: MMSE 16.6	Ginkgo Biloba, 120 mg/day	Rivastigmine, 4.5 mg/day	24 weeks	Cognitive Tests MMSE 7MS
Ginkgo Biloba Donepezil	Mazza 2006[135] RCT Italy Medium	50	Mild to Moderate AD Mean Age 68.5 54% Female Baseline Cognition: MMSE 18.7	Ginkgo Biloba, 160 mg/day	Donepezil, 5 mg/day	24 weeks	Cognitive Tests MMSE SKT Global Change CGI item 2 Harms Withdrawal due to AEs

Supplement Drug	Study Characteristics: Author/Year Design Country Risk of Bias	N=	Population: AD Severity Mean Age % Female % White Education (mean yrs.) Baseline Cognition	Intervention: Intervention mode Components Frequency Duration	Comparison: Comparison mode Components Frequency Duration	Outcome Timing	Outcome Domain [Instrument]
Saffron Extract Memantine	Farokhnia 2014[249] RCT Iran Medium	68	Moderate to Severe AD Mean Age 77.6 43% Female Baseline Cognition: MMSE 11.2	Saffron Extract, 30 mg/day	Memantine, 20 mg/day	12 months	Cognitive Tests MMSE SCIRS Global Change FAST Harms CVD mortality Sedation Confusion
Vitamin E Donepezil	Onofrj 2002 [250] RCT Italy High	67	Mild to Severe AD Mean Age 66 55% Female Mean Years Education 6.5 Baseline Cognition: MMSE 16.6	Vitamin E, 2000 IU/day, postprandial	Donepezil, 10 mg/day, postprandial	6 months	Cognitive Tests MMSE ADAS-Cog Verbal and Performance WAIS subscales Harms Withdrawal due to AEs
Vitamin E Donepezil	Thomas 2001[251] RCT Italy Medium	40	Mild to Severe AD Mean Age 66.0 53% Female Baseline Cognition: MMSE 16	Vitamin E, 2000 IU/day, postprandial	Donepezil, 10 mg/day, postprandial	26 weeks	Cognitive Tests MMSE ADAS-Cog WAIS, Verbal and Performance subscales Harms Withdrawal due to AEs
Vitamin E Rivastigmine	Thomas 2001[251] RCT Italy Medium	40	Mild to Severe AD Mean Age 65.3 53% Female Baseline Cognition: MMSE 16x	Vitamin E, 2000 IU/day, postprandial	Rivastigmine, 6 mg twice a day, postprandial	26 weeks	Cognitive Tests MMSE ADAS-Cog WAIS, Verbal and Performance Subscales

Supplement Drug	Study Characteristics: Author/Year Design Country Risk of Bias	N=	Population: AD Severity Mean Age % Female % White Education (mean yrs.) Baseline Cognition	Intervention: Intervention mode Components Frequency Duration	Comparison: Comparison mode Components Frequency Duration	Outcome Timing	Outcome Domain [Instrument]
							Harms Withdrawal due to AEs
Vitamin E Memantine	Dysken 2014[195] RCT United States High	307	Mild to Moderate AD Mean Age 78.8 3% Female 86% White 78% high school graduate or higher Baseline Cognition: MMSE 21	Vitamin E, 1000 IU twice a day	Memantine, 10 mg twice a day	Mean follow-up 2.27 years	Cognitive Tests MMSE ADAS-Cog Function ADCS-ADL CAS Dependence Scale Behavior NPI Harms SAEs Withdrawal due to AEs Falls All-cause mortality CVD mortality Non-CVD mortality
Yishen Huazhuo decoction (YHD) Donepezil	Zhang 2015[252, 253] RCT China High	144	Mild AD Mean Age 72.9 62% Female 11% College-educated Baseline cognition: MMSE 20.2	YDH 100 mL daily 30 min before breakfast	Donepezil, 5mg nightly	24 weeks	Cognitive Tests MMSE ADAS-Cog Function ADL scale Behavior NPI Harms SAEs

Supplement Drug	Study Characteristics: Author/Year Design Country Risk of Bias	N=	Population: AD Severity Mean Age % Female % White Education (mean yrs.) Baseline Cognition	Intervention: Intervention mode Components Frequency Duration	Comparison: Comparison mode Components Frequency Duration	Outcome Timing	Outcome Domain [Instrument]
							Withdrawal due to AEs Stroke
Huannao Yicong Formula (HYF) Donepezil	Yang 2018[254] RCT China Medium	60	Mild to Moderate AD Mean Age 62.3 75% Female Mean Years Education 5.5 Baseline Cognition: MMSE 21.8	HYF 5 gm twice a day and placebo daily	Donepezil 5mg once daily and placebo twice a day	6 months	Cognitive Tests ADAS-Cog MMSE MoCA Harms SAEs Mortality

Abbreviations: ADL=Activities of Daily Living; AEs=Adverse Events; AD=Alzheimer's Disease; ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognition; ADCS-ADL=Alzheimer's Disease Cooperative Study/Activities of Daily Living; CVD=Cardiovascular; CAS=Caregiver Activity Survey; CGI=Clinical Global Impression; FAST=Functional Assessment Staging Tool; GBS-scale=Geriatric Behavioral Syndrome scale; GDS=Global Deterioration Scale; MMSE=Mini-Mental State Examination; MoCA=Montreal Cognitive Assessment; NPI=Neuropsychiatric Inventory; RoB=Risk of Bias; 7MS=Seven Minute Test; SKT=Syndrom Kurz Test; SCIRS=Severe Cognitive Impairment Rating Scale; WAIS=Wechsler Adult Intelligence Scale; YHD=Yishen Huazhuo Decoction (Composed of Yinyanghuo [Epimedium], Nvzhenzi [Fructus Ligustri Lucidi], Buguzhi [Psoralea fruit], Heshouwu [Radix Polygoni Multiflori], Huangqi [Radix Astragali], Chuanxiong [Ligusticum wallichi Franchat], Shichangpu [Acorus gramineus])

Appendix Table G.14. Risk of bias ratings: supplement versus drug

Supplement Drug	Study	Time	Selection Bias	Attrition Bias	Performance Bias	Detection Bias	Reporting Bias	Overall Rating
Gingko Biloba Rivastigmine	Nasab 2012[248]	24 weeks	Medium	Low	High	Low	High	High
Ginkgo Biloba Donepezil	Mazza 2006[135]	24 weeks	Low	Medium	Low	Low	Low	Medium
Saffron Extract Memantine	Farokhnia 2014[249]	12 months	Low	Medium	Low	Low	Low	Medium
Vitamin E Donepezil	Onofrj 2002[250]	6 months	Medium	Medium	High	Low	High	High
Vitamin E Donepezil Rivastigmine	Thomas 2001[251]	26 weeks	Low	Medium	Medium	Low	High	Medium

Supplement Drug	Study	Time	Selection Bias	Attrition Bias	Performance Bias	Detection Bias	Reporting Bias	Overall Rating
Vitamin E Memantine Placebo	Dysken 2014[195]	Mean follow-up 2.27 years	Low	High	Low	Low	Low	High
YHD Donepezil	Zhang 2015[252, 253][	24 weeks	Low	High	Low	Low	Low	High
HYF Donepezil	Yang 2018[254][	6 months	Low	Medium	High	Low	Low	Medium

Abbreviations: YHD=Yishen Huazhuo Decoction (Composed of Yinyanghuo [Epimedium], Nvzhenzi [Fructus Ligustri Lucidi], Buguzhi [Psoralea fruit], Heshouwu [Radix Polygoni Multiflori], Huangqi [Radix Astragali], Chuanxiong [Ligusticum wallichi Franchat], Shichangpu [Acorus gramineus])

Appendix Table G.15. Outcome instruments used in low/medium risk of bias studies: supplement versus drug

Supplement Drug	Study	RoB	AD Severity	Global Brief Stand-Alone Tests	Global Multidomain Tests	Domain Level Tests Typically Part of a Larger Battery*	Function	Quality of Life	Clinical Impression of Change
Ginkgo Biloba Donepezil	Mazza 2006[135]	Medium	Mild to Moderate AD	MMSE SKT	NR	NR	NR	NR	CGI item 2
Saffron Extract Memantine	Farokhnia 2014[249]	Medium	Moderate to Severe AD	MMSE SCIRS	NR	NR	NR	NR	FAST
Vitamin E Rivastigmine	Thomas 2001{Thomas, 2001 #201]	Medium	Mild to Severe AD	MMSE	WAIS, Verbal and Performance subscales ADAS-Cog	NR	NR	NR	NR
Vitamin E Rivastigmine	Thomas 2001[251]	Medium	Mild to Severe AD	MMSE	WAIS, Verbal and Performance subscales ADAS-Cog	NR	NR	NR	NR
HYF Donepezil	Yang2018[254]	Medium	Mild to Moderate AD	MMSE MoCA	ADAS-Cog	NR	NR	NR	NR
	TOTAL			8	5	0	0	0	1

*Domain level tests typically part of a larger battery are tests of memory, executive function, language and/or attention: [a]Memory; [b]Executive Function; [c]Language; [d]Attention

Abbreviations: AD=Alzheimer's Disease; CGI=Clinical Global Impression; FAST=Functional Assessment Staging Tool; MMSE=Mini-Mental State Examination; NR=Not Rated; RoB=Risk of Bias; SCIRS=Severe Cognitive Impairment Rating Scale; SKT=Syndrom Kurz Test

Appendix Table G.16. Primary outcomes summary low and medium risk of bias studies: supplement versus drug

Supplement Drug	AD Severity	Study Characteristics: Author/Year Followup Risk of Bias	Cognitive	Function	QoL	Clinical Impression of Change	Harms
Ginkgo Biloba Donepezil	Mild to Moderate AD	Mazza 2006[135]* 24 weeks Medium	MMSE Mean Change from Baseline (95% CI) Ginkgo Biloba: 0.6 (-1.8 to 3) Donepezil: 1.2 (-1.2 to 3.6) No difference between groups SMD -0.18 (95% CI -0.80, 0.43) SKT Mean Change from Baseline (95% CI) Ginkgo Biloba: -3.3 (-2.3 to -4.27) Donepezil: -3.3 (-2.3 to -4.29) No difference between groups SMD, 0.0 (95% CI -0.61, 0.61)	NR	NR	CGI item 2 Mean Change from Baseline (95% CI) Ginkgo Biloba: -0.9 (-0.5 to -1.2) Donepezil: -0.9 (-0.5 to -1.2) No difference between groups SMD, 0.0 (95% CI -0.61, 0.61)	Withdrawal due to AEs Gingko Biloba: 0/25 (0%) Donepezil: 4/25 (16%) RR, 0.11 (95% CI 0.01, 2.0)
Saffron Extract Memantine	Moderate to Severe AD	Farokhnia 2014[249] 12 months Medium	MMSE Mean Change from Baseline (SD) Saffron Extract: -1.29 (1.36) Memantine: -1.67 (1.57) p=0.28 SMD 0.28 (95% CI -0.79, 0.23) SCIRS Mean Change from Baseline (SD) Saffron Extract: -1.88 (1.14) Memantine: -1.61 (1.34) p=0.38 SMD 0.22 (95% CI -0.29, 0.73)	NR	NR	FAST Mean Change from Baseline (SD) Saffron Extract: -0.94 (0.73) Memantine: -0.97 (0.83) p=0.87 SMD -0.03 (95% CI -0.53 to 0.48)	CVD mortality Saffron Extract: 1/34 (2.9%) Memantine: 1/34 (2.9%) RR, 1.0 (95% CI 0.7, 15.3) Sedation Saffron Extract: 1/34 (2.9%) Memantine: 3/34 (8.8%) RR, 0.33 (95% CI 0.04, 3.0) Confusion Saffron Extract: 1/34 (2.9%) Memantine: 1/34 (2.9%) RR, 1.0 (95% CI 0.7, 15.3)

Supplement Drug	AD Severity	Study Characteristics: Author/Year Followup Risk of Bias	Cognitive	Function	QoL	Clinical Impression of Change	Harms
Vitamin E Donepezil	Mild to Severe AD	Thomas[251] 2001 26 weeks Medium	<u>MMSE</u> Vitamin E Baseline (SE): 16 (0.5) 26 weeks (SE): 15 (0.6) p=0.07 Donepezil Baseline (SE): 16 (0.5) 26 weeks (SE): 16 (0.5) p=0.06 Post-treatment SMD -0.42 (95% -1.06, 0.23) <u>WAIS, Verbal and Performance subscales</u> Vitamin E Baseline (SE): 72 (2.0) 26 weeks (SE): 71 (2.1) p=0.43 Donepezil Baseline (SE): 72 (2.0) 26 weeks (SE): 75 (2.0) p=0.15 Post-treatment SMD -0.45 (95% CI -1.09, 0.20) <u>ADAS-Cog</u> Vitamin E Baseline (SE): 33.45 (2.6) 26 weeks (SE): 39.07 (2.7) p<0.01 Donepezil Baseline (SE): 33.34 (2.7) 26 weeks (SE): 31.84 (2.7) p<0.001Post-treatment SMD -0.61 (95% CI -1.26, 0.04)	NR	NR	NR	<u>Withdrawal due to AEs:</u> Vitamin E: 0/20 (0%) Donepezil: 0/20 (0%)
Vitamin E Rivastigmine	Mild to Severe AD	Thomas[251] 2001 26 weeks Medium	<u>MMSE</u> Vitamin E Baseline (SE): 16 (0.5) 26 weeks (SE): 15 (0.6)	NR	NR	NR	<u>Withdrawal due to AEs:</u> Vitamin E: 0/20 (0%) Rivastigmine: 3/20 (15%)

Supplement Drug	AD Severity	Study Characteristics: Author/Year Followup Risk of Bias	Cognitive	Function	QoL	Clinical Impression of Change	Harms
			p=0.07 Rivastigmine Baseline (SE): 16 (0.5) 26 weeks (SE): 16 (0.5) p=0.06 Post-treatment SMD -0.42 (95% CI -1.09, 0.27) <u>WAIS, Verbal and Performance Subscales</u> Vitamin E Baseline (SE): 72 (2.0) 26 weeks (SE): 71 (2.1) p=0.43 Rivastigmine Baseline (SE): 71 (1.9) 26 weeks (SE): 74 (2.0) P<0.05 Post-treatment SMD -0.34 (95% CI -1.01, 0.34) <u>ADAS-Cog</u> Vitamin E Baseline (SE): 33.45 (2.6) 26 weeks (SE): 39.07 (2.7) p<0.01 Rivastigmine Baseline (SE): 33.39 (2.7) 26 weeks (SE): 31.02 (2.5) p<0.01 Post-treatment SMD -0.71 (-1.40, -0.01)				
HYF Donepezil	Mild to Moderate AD	Yang{Yang, 2018 #468 2018 6 months Medium	<u>MMSE</u> HYF Increase in score, p<0.01 Donepezil Increase in score, p<0.01 No post-treatment difference between groups, p>0.05	NR	NR	NR	<u>Dreaminess/Confusion</u> HYF: 0/28 (0%) Donepezil: 1/24 (4.2%) RR 0.29 (95% CI 0.01, 6) <u>SAEs</u> No SAEs reported

Supplement Drug	AD Severity	Study Characteristics: Author/Year Followup Risk of Bias	Cognitive	Function	QoL	Clinical Impression of Change	Harms
			MoCA HYF Increase in score, p<0.01 Donepezil Increase in score, p<0.01 Post-treatment difference between groups NR ADAS-Cog HYF Decrease in score, p<0.01 Donepezil Decrease in score, p<0.01 No post-treatment difference between groups, p>0.05				during study period. Mortality No deaths during study period

Abbreviations: AEs=Adverse Events; AD=Alzheimer's Disease; CVD=Cardiovascular; CGI=Clinical Global Impression; CI=Confidence Interval; FAST=Functional Assessment Staging Tool; MMSE=Mini-Mental State Examination; NR=Not Reported; RR=Relative Risk; RoB=Risk of Bias; SD=Standard Deviation; SCIRS=Severe Cognitive Impairment Rating Scale; SMD=Standardized Mean Difference; SKT=Syndrom Kurz Test

*Authors reported 95% confidence intervals that appeared consistently incorrect for the MMSE, SKT, and CGI item 2, with the point estimates either far from centered between the upper and lower bounds or outside the confidence intervals. It appeared that authors placed incorrect signs on all the upper and lower confidence interval bounds. The Evidence-based Practice Center has modified the confidence intervals while waiting for clarification from study authors.

Appendix Table G.17. Summary of strength of evidence: supplement versus drug

Supplement Drug	Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Ginkgo Biloba Donepezil	All outcomes	Mild to Moderate AD	24 weeks	1 RCT (n=50)	No preference	Medium	Unknown	Direct	Imprecise	Insufficient
Saffron Extract Memantine	All outcomes	Moderate to Severe AD	12 months	1 RCT (n=68)	No preference	Medium	Unknown	Direct	Imprecise	Insufficient
Vitamin E Donepezil	All outcomes	Mild to Severe AD	26 weeks	1 RCT (n=40)	No preference	Medium	Unknown	Direct	Imprecise	Insufficient
Vitamin E Rivastigmine	All outcomes	Mild to Severe AD	26 weeks	1 RCT (n=40)	No preference	Medium	Unknown	Direct	Imprecise	Insufficient

Supplement Drug	Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
HYF Donepezil	All outcomes	Mild to Moderate AD	6 months	1 RCT (n=60)	No preference	Medium	Unknown	Direct	Imprecise	Insufficient

Abbreviations: AD=Alzheimer's Disease; RCT=Randomized Controlled Trial

Additional Drug Versus Drug Comparisons

Appendix Table G.18. Characteristics of eligible studies: rivastigmine versus donepezil

Study Characteristics: Author/Year Design Country Risk of Bias	N=	Population: AD Severity Mean Age % Female % White Education (mean yrs.) Baseline Cognition	Intervention: Intervention mode Components Frequency Duration	Comparison: Comparison mode Components Frequency Duration	Outcome Timing	Outcome Domain [Instrument]
Thomas 2001[251] **RCT** **Italy** **High**	40	Mild to Moderate CATD Mean Age: 65.8 % Female: 55.0 % White: NR Mean Education: NR Baseline Cognition: MMSE 16	Rivastigmine, 12 mg/day oral	Donepezil, 10 mg/day	26 weeks	Cognition MMSE ADAS-Cog WAIS (subscale composed of verbal and performance scales) Harms Withdrawals due to adverse events Somnolence
Aguglia 2004[245] **CCT** **Italy** **High**	191	Mild to Moderate CATD Mean Age: 77.6 % Female: 65.3 % White: NR Mean Education: 8.0 Baseline Cognition: MMSE 20.4	Rivastigmine, 6-12 mg/day oral	Donepezil, 10 mg/day	6 months	Cognition MMSE ADAS-Cog Function ADL IADL Harms Mortality

Study Characteristics: Author/Year Design Country Risk of Bias	N=	Population: AD Severity Mean Age % Female % White Education (mean yrs.) Baseline Cognition	Intervention: Intervention mode Components Frequency Duration	Comparison: Comparison mode Components Frequency Duration	Outcome Timing	Outcome Domain [Instrument]
Bullock 2005[255] **RCT** **Australia, Canada, France, Germany, Italy, Spain, UK** **High**	998	Moderate CATD Mean Age: 75.9 % Female: 68.7 % White: 98.8 Mean Education: NR Baseline Cognition: MMSE 15.1	Rivastigmine, 12 mg/day oral	Donepezil, 10 mg/day	104 weeks	Cognition SIB MMSE Function ADCS-ADL Global Change GDS Harms Serious adverse events Withdrawals due to adverse events Mortality
Shimizu 2015[244] **RCT** **Japan** **High**	50	Mild to Moderate CATD Mean Age: 77.8 % Female: 55.3 % White: NR Mean Education: 12.7 Baseline Cognition: MMSE 21.0	Rivastigmine, 18 mg/day patch	Donepezil, 5 mg/day	48 weeks	Cognition MMSE ADAS-Cog Cognition (memory) ADAS-Cog memory Cognition (language) ADAS-Cog language Cognition (attention) TMT-A Function FAQ Harms Withdrawals due to adverse events
Abolfazli 2008[256] **CCT**	70	Mild to Moderate CATD Mean Age: NR % Female: 51.4	Rivastigmine, 6-12 mg/day oral	Donepezil, 5-10 mg/day	6 months	Cognition MMSE Clock drawing test

Study Characteristics: Author/Year Design Country Risk of Bias	N=	Population: AD Severity Mean Age % Female % White Education (mean yrs.) Baseline Cognition	Intervention: Intervention mode Components Frequency Duration	Comparison: Comparison mode Components Frequency Duration	Outcome Timing	Outcome Domain [Instrument]
Iran **High**		% White: NR Mean Education: NR Baseline Cognition: MMSE 20.3				Cognition (visuospatial and executive) Visual Motor Gestalt test

Abbreviations: ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive subscale; ADCS-ADL=Alzheimer's Disease Cooperative Study—Activities of Daily Living; ADL=Activities of Daily Living; CATD=clinical Alzheimer-type dementia; CCT=controlled clinical trial; FAQ=Functional Activities Questionnaire; GDS=Global Deterioration Scale; IADL=Instrumental Activities of Daily Living; MMSE=Mini-Mental State Examination; NR=Not Reported; RCT=randomized controlled trial; RoB=Risk of Bias; SIB=Severe Impairment Battery; TMT-A=Trail Making Test Part A; WAIS=Wechsler Adult Intelligence Scale

Appendix Table G.19. Risk of bias ratings: rivastigmine versus donepezil

Study	Time	Selection Bias	Attrition Bias	Performance Bias	Detection Bias	Reporting Bias	Overall Rating
Thomas 2001[251]	26 weeks	Low	Medium	High	Low	High	High
Aguglia 2004[245]	6 months	Medium	High	High	High	Medium	High
Bullock 2005[255]	104 weeks	Low	High	Low	Low	Low	High
Shimizu 2015[244]	48 weeks	Medium	High	High	Low	Low	High
Abolfazli 2008[256]	6 months	High	High	High	Low	Low	High

Appendix H. Key Question 6: Efficacy and Harms of Prescription Drug Treatment Versus Placebo for Behavioral and Psychological Symptoms of Dementia

Antipsychotics Versus Placebo

Appendix Table H.1. Characteristics of eligible studies: antipsychotics versus placebo

Study Characteristics: Author/Year Design Country Risk of Bias	**N=**	**Population: AD Severity Mean Age % Female % White Education (mean yrs.) Baseline Cognition**	**Intervention: Intervention mode Components Frequency Duration**	**Comparison: Comparison mode Components Frequency Duration**	**Outcome Timing**	**Outcome Domain [Instrument]**
Ballard 2018[257] **Ballard 2019**[258] **RCT UK Medium**	181	Severity NR Severe Psychosis (Subgroup analysis NPI-NH≥12) Mean Age 86 72% Female 85% White Education NR MMSE 10	Pimavanserin 34mg/day	Placebo	6, 12 weeks	Agitation CMAI-SF + subscales NPI-NH Psychosis NPI-NH psychosis subscale Harms SAEs Withdrawal due to AEs Mortality Falls
Ballard 2009[259] **RCT UK High**	165	Severity NR Mean age 85 77% Female Race NR Education NR Standardized MMSE 11 Severe Impairment Battery 72	Antipsychotics (thioridazine, chlorpromazine, haloperidol, trifluoperazine,or risperidone, doses NR)	Placebo	12 months, up to 54 months	Harms Mortality
Mintzer 2007[260] **RCT Multinational High**	487	Severity NR Mean Age 82% Female 88% White Education NR MMSE 12	Aripiprazole, 2, 5, 10mg/day	Placebo	6 weeks	Psychosis NPI-NH Psychosis BPRS CMAI

Study Characteristics: Author/Year Design Country Risk of Bias	N=	Population: AD Severity Mean Age % Female % White Education (mean yrs.) Baseline Cognition	Intervention: Intervention mode Components Frequency Duration	Comparison: Comparison mode Components Frequency Duration	Outcome Timing	Outcome Domain [Instrument]
						Harms SAEs
Zhong 2007 [261] **RCT** **US** **High**	333	Severity NR Mean Age 83 74% Female 84% White Education NR MMSE 5	Quetiapine, 100, 200mg/day	Placebo	10 weeks	Agitation CMAI NPI-NH PANSS-EC Harms SAEs
Mintzer 2006 [262 267 267 267 267] **RCT** **Location NR** **High**	473	Severity NR Mean Age 83 77% Female 80% White Education NR MMSE 13	Risperidone, 1.0-1.5mg/day	Placebo	8 weeks	Agitation BEHAVE-AD Harms SAEs
CATIE Trial **Schneider 2006**[263] **Sultzer 2008**[264] **Zheng 2009**[265] **Ozawa 2017**[266] **Nagata 2018**[267] **RCT** **US** **High**	416	Severity NR Mean Age 78 56% Female 79% White 24% No School Diploma 34% School Diploma 21% <4yrs college 17% >4yrs college MMSE 15	Olanzapine (2.5, 5mg), Quetiapine (25, 50mg), Risperidone (0.5, 1mg)	Placebo	12 weeks for efficacy, 36 weeks for harms	Agitation NPI (agitation, hallucination, delusions subscales) BPRS Harms SAEs
Tariot 2006[268] **RCT** **US** **High**	179	Severity NR Mean Age 83 73% Female 91% White Education NR MMSE 13	Quetiapine, 25mg/day	Placebo Additional active comparator arm	10 weeks	Agitation BPRS + subscales NPI-NH14 + subscales Harms SAEs
Ballard 2005[269] **RCT** **UK** **Medium**	62	Severe AD Mean Age 84 82% Female Race NR Education NR	Quetiapine, 25-50mg/twice daily for 12 weeks, 50mg/twice	Placebo Additional active comparator arm	6, 26 weeks	Agitation CMAI Harms

Study Characteristics: Author/Year Design Country Risk of Bias	N=	Population: AD Severity Mean Age % Female % White Education (mean yrs.) Baseline Cognition	Intervention: Intervention mode Components Frequency Duration	Comparison: Comparison mode Components Frequency Duration	Outcome Timing	Outcome Domain [Instrument]
		Severe Impairment Battery 64	daily after No concomitant psychosocial intervention reported			SAEs Mortality
Deberdt 2005[270] **RCT** **Multinational** **High**	494	Severity NR Mean Age 78 64% Female 84% White Education NR MMSE 14	Olanzapine (2.5-10mg/day), Risperidone (0.5-2mg/day)	Placebo Additional active comparator arm	10 weeks	Agitation BPRS CMAI NPI Total NPI-Psychosis Harms SAEs
De Deyn 2005[271] **RCT** **Multinational** **Medium**	208	Severity NR Mean Age 82 72% Female 98% White Education NR MMSE 14	Aripiprazole, 2-15mg/day No concomitant psychosocial intervention reported	Placebo	10 weeks	Agitation BPRS NPI Total NPI-Psychosis Harms SAEs
De Deyn 2004[272] **RCT** **Multinational** **High**	649	Severity NR Mean Age 77 75% Female 99% White Education NR MMSE 14	Olanzapine, 1, 2.5, 5, 7.5mg/day	Placebo	10 weeks	Agitation BPRS NPI-NH Harms SAEs
Street 2000[273] **Kennedy 2001**[274] **Mintzer 2001**[275] **RCT** **US** **High**	206	Severity NR Mean Age 83 62% Female Race NR Education NR MMSE 7	Olanzapine, 5, 10, 15mg/day	Placebo	6 weeks	Agitation BPRS NPI-NH + subscales Harms SAEs
Teri 2000[276] **RCT** **US** **High**	70	Severity NR Mean Age 75 73% Female 86% White	Haloperidol, 0.5mg/day	Placebo Additional active comparator and	16 weeks	Agitation ABID CMAI RMBPC

Study Characteristics: Author/Year Design Country Risk of Bias	N=	Population: AD Severity Mean Age % Female % White Education (mean yrs.) Baseline Cognition	Intervention: Intervention mode Components Frequency Duration	Comparison: Comparison mode Components Frequency Duration	Outcome Timing	Outcome Domain [Instrument]
		13 Years Education MMSE 13		behavioral intervention arms		 Harms SAEs
De Deyn 1999[277] **RCT** **Multinational** **High**	229	Severity NR Mean Age 82 56% Female 99% White Education NR MMSE 8	Risperidone, 0.5-4mg/day	Placebo Additional active comparator arm	12 weeks	Agitation BEHAVE-AD CMAI Harms SAEs
Devanand 1998[278] **RCT** **US** **Medium 6 weeks** **High 12 weeks**	71	Severity NR Mean Age 72 65% Female 56% White Education NR Modified MMSE 19 (scoring range 0-57)	Haloperidol, 0.5-0.75mg/day No concomitant psychosocial intervention reported	Placebo Haloperidol, 2-3mg/day	6 weeks	Agitation BPRS SADS (psychosis and disorganization items) Behavioral Syndromes Scale for Dementia Harms SAEs
Auchus 1997[279] **RCT** **Canada** **High**	12	Severity NR Mean Age 76 67% Female Race NR 12 Years Education MMSE 15	Haloperidol, 3mg/day	Placebo Additional active comparator arm	3, 6 weeks	Agitation BEHAVE-AD CMAI Harms SAEs

Abbreviations: ABID=Agitated Behavior in Dementia Scale; AD=Alzheimer's Disease; BEHAVE-AD=Behavioral Pathology in Alzheimer's Disease Rating Scale; BPRS=Brief Psychiatric Rating Scale; BSSD=Behavioral Syndromes Scale for Dementia; C=control; CI=confidence interval; CMAI=Cohen-Mansfield Agitation Inventory; CMAI-SF=Cohen-Mansfield Agitation Inventory –Short Form; I=intervention; MG=milligrams; MMSE=Mini Mental State Exam; NPI=Neuropsychiatric Inventory; NPI-NH=Neuropsychiatric Inventory Nursing Home Version; NR=not reported; NS=not statistically significant; PANSS-EC=Positive and Negative Syndrome Scale; RCT=randomized controlled trial; RMBPC=Revised Memory and Behavior Problems Checklist; RoB=Risk of Bias; SADS=Schedule for Affective Disorders and Schizophrenia; SAEs=Serious Adverse Events; SD=standard deviation; UK=United Kingdom; US=United States

Appendix Table H.2. Risk of bias ratings: antipsychotics versus placebo

Study	Time	Selection Bias	Attrition Bias	Performance Bias	Detection Bias	Reporting Bias	Overall Rating* *Justification*
Ballard 2018[257] **Ballard 2019**[258]	6, 12 weeks	Medium	Medium 6 weeks Medium 12 weeks	Low	Low	Low	Medium
Ballard 2009[259]	1 year	Low	High	Low	Low	Low	High 22% participants lost before trial started. Adherence at 1 year 36%.
Mintzer 2007[260]	8 weeks	Medium	High	Medium	Low	Low	High
Zhong 2007 [261]	10 weeks	Low	High	Low	Low	Low	High
Mintzer 2006[262]	8 weeks	Medium	High	Low	Low	Low	High
CATIE Trial **Schneider 2006**[263] **Sultzer 2008**[264]	2, 4, 8, 12 weeks	Medium	Medium 2 weeks High 4+ weeks	Low	Low	Low	High *No efficacy outcomes reported before 12 weeks*
Tariot 2006[268]	10 weeks	Medium	High	Medium	Low	Low	High
Ballard 2005[269]	6 weeks, 26 weeks	Low	Medium 6 weeks Likely high 26 weeks	Low	Low	Low 6 weeks High 26 weeks	Medium 6 weeks High 26 weeks
Deberdt 2005[270]	10 weeks	Medium	High	Medium	Low	Low	High
De Deyn 2005[271]	10 weeks	Medium	Medium	Medium	Low	Low	Medium
De Deyn 2004[272]	10 weeks	Medium	High	Low	Low	Low	High
Street 2000[273] **Kennedy 2001**[274] **Mintzer 2001**[275]	6 weeks	Low	High	Low	Low	Low	High
Teri 2000[276]	16 weeks	Low	High	Medium	Low	Low	High
De Deyn 1999[277]	12 weeks	Medium	High	Low	Low	Low	High

Study	Time	Selection Bias	Attrition Bias	Performance Bias	Detection Bias	Reporting Bias	Overall Rating* *Justification*
Devanand 1998[278]	6, 12 weeks	Medium	Medium 6 weeks High 12 weeks	Low	Low	Low	Medium 6 weeks High 12 weeks
Auchus 1997[279]	3 weeks	Medium	High	Low	Low	Low	High

*Justifications provided when overall risk of bias rating deviating from guidance provided in tool (Appendix B)

Appendix Table H.3. Primary outcomes summary low and medium risk of bias studies: antipsychotics versus placebo

Drug Comparison	AD Severity	Study Followup RoB	General Behavior	Agitation	Aggression	Psychosis	Depression	Anxiety	Disinhibited sexual behavior	Harms
Aripiprazole vs. placebo	NR	De Deyn				BPRS-Core Mean Change from Baseline (SD) I: -3.9 (NR) C: -2.7 (NR) p=0.042 BPRS-Psychosis Mean Change from Baseline (SD) I: -1.93 (NR) C: -1.27 (NR) p=0.029 NPI-Psychosis Mean Change from Baseline (SD) I: -6.55 (NR) C: -5.52 (NR) p=0.169 Standardized mean difference could not be calculated.				SAEs I: 15% (16/106) C: 9% (9/102) p=NR Injurious falls I: 8% (8/106) C: 5% (5/102) Somnolence I: 8% (n=NR) C: 1% (n=NR) Withdrawal due to AEs I: 9% (10/106) C: 7% (7/102) Mortality I: 4% (4/106) C: 0 (0/102) Extrapyramidal Symptoms: Simpson-Angus Scale Mean Change from Baseline (SD) I: 0.71 (NR) C: 0.03 (NR) p=0.109 Abnormal Involuntary Movement

Drug Comparison	AD Severity	Study Followup RoB	General Behavior	Agitation	Aggression	Psychosis	Depression	Anxiety	Disinhibited sexual behavior	Harms
										Scale Mean Change from Baseline (SD) I: -0.13 (NR) C: -0.01 (NR) p=0.617 Barnes Akathisia Rating Scale Mean Change from Baseline (SD) I: -0.09 (NR) C: -0.06 (NR) p=0.470
Haloperidol vs. placebo **I1: 2-3mg** **I2: 0.5-0.75mg**	NR	Devanand		BSSD-Psychomotor Agitation Mean Change from Baseline (SD) I1: -1.0* (NR) I2: -0.1* (NR) C: -0.25* (NR) I1 vs. C: p<0.03 Favors I1 I2 vs. C: NR Standardized mean difference I1 vs. C: -0.59 (95%	BPRS-Hostile-Suspicious Mean Change from Baseline (SD) I1: -2.5* (NR) I2: -1.95* (NR) C: -1.35* (NR) I1 vs. C: p=NR (NS) I2 vs. C: NR Standardized mean difference I1 vs. C: -0.42 (95% CI -1.05, 0.21) I2 vs. C:	BPRS Mean Change from Baseline (SD) 1: -5.95* (NR) I2: -3.0* (NR) C: -2.95* (NR) I1 vs. C: p=NR Significance NR I2 vs. C: NR BPRS-Psychosis Mean Change from Baseline (SD) I1: -2.0* (NR) I2: -0.85* (NR) C: -0.85* (NR) I1 vs. C: p<0.02 Favors I1 I2 vs. C: NR				Extrapyramidal Symptoms I1 vs. C: p=0.08 I2 vs. C: NR Treatment Emergent Symptoms Scale I1 vs. C: p=NR (NS) I2 vs. C: NR

Drug Comparison	AD Severity	Study Followup RoB	General Behavior	Agitation	Aggression	Psychosis	Depression	Anxiety	Disinhibited sexual behavior	Harms
				CI -1.22, 0.05) I2 vs. C: 0.12 (95% CI -0.05, 0.74) <u>25% Reduction BSSD Psychomoto r Agitation</u> I1 55% (11/20) I2 25% (5/20) C 30% (6/20) I1 vs. C: p=0.11 I2 vs. C: p=NR I1 vs. C: RR 1.83 (95% CI 0.84, 3.99) I2 vs. C: RR 0.83 (95% CI 0.30, 2.29)	-0.23 (95% CI -0.85, 0.39) <u>BSSD- Physical Aggression</u> Mean Change from Baseline (SD) I1: -0.75* (NR) I2: -0.3* (NR) C: -0.25* (NR) I1 vs. C: p=NR (NS) I2 vs. C: p=NR Standardize d mean difference I1 vs. C: -0.40 (95% CI -1.03, 0.23) I2 vs. C: -0.04 (95% CI -0.66, 0.58)	25% Reduction <u>BPRS- Psychosis</u> I1 60% (12/20) I2 30% (6/20) C 30% (6/20) I1 vs. C: p<0.06 I2 vs. C: p=NR I1 vs. C: RR 2.00 (95% CI 0.94, 4.27) I2 vs. C: RR 1.00 (95% CI 0.39, 2.58) <u>SADS</u> Mean Change from Baseline (SD) I1: -3.35* (NR) I2: -1.6* (NR) C: -1.85* (NR) I1 vs. C: p=NR (NS) I2 vs. C: p=NR 25% Reduction SADS Target Symptoms I1 55% (11/20) I2 35% (7/20) C 25% (5/20) I1 vs. C: p<0.06 I2 vs. C: NR I1 vs. C: RR 2.20 (95% CI 0.93, 5.18) I2 vs. C: RR 1.4 (95% CI 0.53, 3.68)				

Drug Comparison	AD Severity	Study Followup RoB	General Behavior	Agitation	Aggression	Psychosis	Depression	Anxiety	Disinhibited sexual behavior	Harms
Pimavanserin vs. placebo **NR** **Severe psychosis subgroup (NPI-NH≥12)**	Ballard 2018[280] 6 weeks efficacy 12 weeks harms Medium		CMAI-SF Total Score *Full study sample* Adjusted mean change from baseline (95% CI) 0·30 (–2·04 to 2·63) *Severe psychosis subgroup* Adjusted mean change from baseline I: -5.22 C: -3.97 p=0.618 CMAI-SF Verbally Agitated Behavior *Full study sample* Adjusted mean change from baseline (95% CI) –0·17 (–1·35 to 1·02) *Severe*	CMAI-SF Aggressive Behavior *Full study sample* Adjusted mean change from baseline (95% CI) 0·30 (–0·52 to 1·11) *Severe psychosis subgroup* Adjusted mean change from baseline I: -1.11 C: -1.02 p=0.919	NPI-NH Psychosis Full study sample Adjusted mean change from baseline (SE) I: -3.76 (0.65) C: -1.93 (0.63) Delta -1.84 (95% CI -3.64 to -0.04) Cohen's d -0.32 p=0.045 (SMD, -0.30, [95% CI, -0.59 to -0.01])* ≥20% Decrease in NPI-NH Psychosis Score I: 59% (53/90) C: 46% (42/91) p=0.094 ≥30% Decrease in NPI-NH Psychosis Score				SAEs *Full study sample* I: 17% (15/90) C: 11% (10/91) RR* 1.25 (95% CI 0.87 to 1.79) Withdrawal due to AEs *Full study sample* I: 9% (8/90) C: 12% (11/91) RR* 0.83 (95% CI 0.48 to 1.44)	SAEs *Full study sample* I: 17% (15/90) C: 11% (10/91) RR* 1.25 (95% CI 0.87 to 1.79) Withdrawal due to AEs *Full study sample* I: 9% (8/90) C: 12% (11/91) RR* 0.83 (95% CI 0.48 to 1.44) Mortality *Full study sample* I: 4% (4/90) C: 4% (4/91) RR* 1.01 (95% CI 0.26 to 3.92) Falls *Full study sample* I: 23% (21/90) C: 23% (21/91) RR* 1.01 (95% CI 0.60 to 1.72)

Drug Comparison	AD Severity	Study Followup RoB	General Behavior	Agitation	Aggression	Psychosis	Depression	Anxiety	Disinhibited sexual behavior	Harms
			psychosis subgroup Adjusted mean change from baseline I: -3.23 C: -1.87 p=0.230 <u>NPI-NH Agitation/ Aggression</u> *Full study sample* Adjusted mean change from baseline (95% CI) –0·66 (–1·80 to 0·48) *Severe psychosis subgroup* Adjusted mean change from baseline I: -2.38 C: -2.12 p=0.829		I: 55% (48/90) C: 37% (34/91) p=0.016 ≥50% Decrease in NPI-NH Psychosis Score I: 51% (46/90) C: 34% (31/91) p=0.024 ≥75% Decrease in NPI-NH Psychosis Score I: 28% (25/90) C: 17% (15/91) p=0.066 ≥100% Decrease in NPI-NH Psychosis Score I: 13% (12/90) C: 10% (9/91) p=0.55 AA Severe					

Drug Comparison	AD Severity	Study Followup RoB	General Behavior	Agitation	Aggression	Psychosis	Depression	Anxiety	Disinhibited sexual behavior	Harms
					psychosis subgroup Mean change from baseline (95% CI) I: -10.15 (-12.50 to -7.80) C: -5.72 (-8.14 to -3.30) Delta -4.43 (95% CI -7.81 to -1.04) Cohen's d -0.73 p=0.011 In severe psychosis subgroup: ≥20% Decrease in NPI-NH Psychosis Score I: 96.3% (n/N NR) C: 53.5% p<0.001 ≥30% Decrease in NPI-NH Psychosis Score I: 88.9% (n/N NR)					

Drug Comparison	AD Severity	Study Followup RoB	General Behavior	Agitation	Aggression	Psychosis	Depression	Anxiety	Disinhibited sexual behavior	Harms
					C: 43.3% p<0.001 ≥50% Decrease in NPI-NH Psychosis Score I: 77.8% (n/N NR) C: 43.3% p<0.008 ≥75% Decrease in NPI-NH Psychosis Score I: 40.7% (n/N NR) C: 16.7% p=0.038 100% Decrease in NPI-NH Psychosis Score I: 11.1% (n/N NR) C: 10.0% p=0.884					

Drug Comparison	AD Severity	Study Followup RoB	General Behavior	Agitation	Aggression	Psychosis	Depression	Anxiety	Disinhibited sexual behavior	Harms
Quetiapine vs. placebo	Severe AD	Ballard 2005[269] 6 weeks Medium		CMAI Mean change from baseline (SD) I: -4.0 (15.4) C: -6.2 (17.6) Mean difference 3.5 (95% CI -3.7, 10.8) p=0.3 Standardized mean difference 0.26 (95% CI -0.27, 0.79)						SAEs I: 0 (0/31) C: 3% (1/31) Mortality I: 6% (2/31) C: 0 (0/31)

*Calculated by EPC

Abbreviations: AD=Alzheimer's Disease; BPRS=Brief Psychiatric Rating Scale; BSSD=Behavioral Syndromes Scale for Dementia; C=control; CI=confidence interval; CMAI=Cohen-Mansfield Agitation Inventory; I=intervention; NPI=Neuropsychiatric Inventory; NR=not reported; NS=not statistically significant; RoB=Risk of Bias; SADS=Schedule for Affective Disorders and Schizophrenia; SAEs=Serious Adverse Events; SD=standard deviation

Appendix Table H.4. Primary outcomes summary low and medium risk of bias studies: antipsychotics dose response

Drug Comparison	AD Severity	Study Followup RoB	General Behavior	Agitation	Aggression	Psychosis	Depression	Anxiety	Disinhibited sexual behavior	Harms
Haloperidol high vs. low dose **I1: 2-3mg** **I2: 0.5-0.75m**	NR	Devanand 1998[278] 6 weeks Medium		BSSD-Psychomotor Agitation Mean Change from Baseline (SD) I1: -1.0* (NR) I2: -0.1* (NR) p<0.02 Favors I1 25% Reduction	BPRS-Hostile-Suspicious Mean Change from Baseline (SD) I1: -2.5* (NR) I2: -1.95* (NR) p=NR (NS) Standardized mean difference -	BPRS Mean Change from Baseline (SD) I1: -5.95* (NR) I2: -3.0* (NR) p=NR BPRS-Psychosis Mean Change from Baseline				Extrapyramidal Symptoms p<0.08 (NS) Treatment Emergent Symptoms Scale p=NR (NS)

Drug Comparison	AD Severity	Study Followup RoB	General Behavior	Agitation	Aggression	Psychosis	Depression	Anxiety	Disinhibited sexual behavior	Harms
				BSSD Psychomotor Agitation I1 55% (11/20) I2 25% (5/20) NS p<0.06	0.20 (95% CI -0.82, 0.42) BSSD-Physical Aggression Mean Change from Baseline (SD) I1: -0.75* (NR) I2: -0.3* (NR) p=NR (NS) Standardized mean difference -0.36 (95% CI -0.98, 0.27)	(SD) I1: -2.0* (NR) I2: -0.85* (NR) p=0.05 Standardized mean difference -0.45 (95% CI -1.08, 0.17) 25% Reduction BPRS-Psychosis I1 60% (12/20) I2 30% (6/20) NS p<0.06 RR 2.0 (95% CI 0.94, 4.27) SADS Mean Change from Baseline (SD) I1: -3.35* (NR) I2: -1.6* (NR) p=NR (NS) Standardized mean difference -0.68 (95% CI -1.32, -0.04) 25% Reduction SADS Target Symptoms I1 55%				

Drug Comparison	AD Severity	Study Followup RoB	General Behavior	Agitation	Aggression	Psychosis	Depression	Anxiety	Disinhibited sexual behavior	Harms
						(11/20) I2 35% (7/20) p=0.20 RR 1.57 (95% CI 0.77, 3.22)				

*Calculated by EPC

Abbreviations: AD=Alzheimer's Disease; BPRS=Brief Psychiatric Rating Scale; BSSD=Behavioral Syndromes Scale for Dementia; C=control; I=intervention; NR=not reported; NS=not statistically significant; RoB=Risk of Bias; SADS=Schedule for Affective Disorders and Schizophrenia; SAEs=Serious Adverse Events; SD=standard deviation

Appendix Table H.5. Summary of strength of evidence: aripiprazole versus placebo

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
NPI	NR	10 weeks	1 RCT (n=203)	No difference	Medium	Unknown	Direct	Imprecise	Insufficient
BPRS	NR	10	1 RCT (n=195)	No difference	Medium	Unknown	Direct	Imprecise	Insufficient
BPRS-Core	NR	10	1 RCT (n=198)	Favors aripiprazole	Medium	Unknown	Direct	Precise	Insufficient
BPRS Psychosis	NR	10	1 RCT (n=192)	Favors aripiprazole	Medium	Unknown	Direct	Precise	Insufficient
NPI Psychosis	NR	10	1 RCT (n=203)	No difference	Medium	Unknown	Direct	Imprecise	Insufficient

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Withdrawal SAEs	NR	10	1 RCT (n=208)	No difference	Medium	Unknown	Direct	Imprecise	Insufficient
SAEs		10	1 RCT (n=208)	No difference	Medium	Unknown	Direct	Imprecise	Insufficient

Abbreviations: AD=Alzheimer's Disease; BPRS=Brief Psychiatric Rating Scale; NPI=Neuropsychiatric Inventory; RCT=randomized controlled trial; SAEs=serious adverse events

Appendix Table H.6. Summary of strength of evidence: haloperidol versus placebo

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
BSSD-Psychomotor Agitation NR		6 weeks	1 RCT (n=40)	Favors Haloperidol	Medium	Unknown	Direct	Precise	Insufficient
BPRS Hostile Suspicious NR		6 weeks	1 RCT (n=40)	No Difference	Medium	Unknown	Direct	Imprecise	Insufficient
BSSD Physical Aggression NR		6 weeks	1 RCT (n=40)	No Difference	Medium	Unknown	Direct	Imprecise	Insufficient
BPRS NR		6 weeks	1 RCT (n=40)	Not gradable					

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
BPRS Psychosis NR		6 weeks	1 RCT (n=40)	Favors	Medium	Unknown	Direct	Precise	Insufficient
SADS NR		6 weeks	1 RCT (n=40)	No Difference	Medium	Unknown	Direct	Imprecise	Insufficient (No Difference)

Abbreviations: AD=Alzheimer's Disease; BPRS=Brief Psychiatric Rating Scale; BSSD=Behavioral Syndromes Scale for Dementia; NPI=Neuropsychiatric Inventory; RCT=randomized controlled trial; SADS=Schedule for Affective Disorders and Schizophrenia; SAEs=serious adverse events

Appendix Table H.7. Summary of strength of evidence: pimavanserin versus placebo

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
CMAI-SF Agitation	NR	6 weeks	1 RCT (n=181)	No Difference	Medium	Direct	Imprecise	Insufficient	CMAI-SF Agitation NR
CMAI-SF Aggression	NR	6 weeks	1 RCT (n=181)	No Difference	Medium	Direct	Precise	Insufficient	CMAI-SF Aggression NR
NPI-NH Psychosis	NR	6 weeks	1 RCT (n=181)	Favors Pimavanserin	Medium	Unknown	Direct	Imprecise	Insufficient
SAEs	Severe AD	6 weeks	1 RCT (n=181)	No difference	Medium	Unknown	Direct	Imprecise	Insufficient
Withdrawal Due to AEs		12 weeks	1 RCT (n=181)	No difference	Medium	Unknown	Direct	Imprecise	Insufficient

Abbreviations: AD=Alzheimer's Disease; CMAI=Cohen-Mansfield Agitation Inventory; CMAI-SF=Cohen-Mansfield Agitation Inventory Short Form; NPI-NH=Neuropsychiatric Inventory for Nursing Homes; RCT=randomized controlled trial; SAES=serious adverse events

Appendix Table H.8. Summary of strength of evidence: quetiapine versus placebo

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
CMAI	Severe AD	6 weeks	1 RCT (n=54)	No difference	Medium	Unknown	Direct	Imprecise	Insufficient
SAEs	Severe	6 weeks	1 RCT (n=54)	No difference	Medium	Unknown	Direct	Imprecise	Insufficient

Abbreviations: AD=Alzheimer's Disease; CMAI=Cohen-Mansfield Agitation Inventory; RCT=randomized controlled trial; SAES=serious adverse events

Appendix Table H.9. Summary of strength of evidence: haloperidol standard dose (2-3 mg) versus low dose (0.5-0.75 mg)

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
BSSD-Psychomotor Agitation	NR	6 weeks	1 RCT (n=40)	Favors Standard Dose	Medium	Unknown	Direct	Precise	Insufficient
BPRS-Hostile Suspicious	NR	6 weeks	1 RCT (n=40)	No Difference	Medium	Unknown	Direct	Imprecise	Insufficient
BSSD-Physical Aggression	NR	6 weeks	1 RCT (n=40)	No Difference	Medium	Unknown	Direct	Imprecise	Insufficient
BPRS	NR	6 weeks	1 RCT (n=40)	Not gradable					
BPRS-Psychosis	NR	6 weeks	1 RCT (n=40)	No Difference	Medium	Unknown	Direct	Imprecise	Insufficient
SADS	NR	6 weeks	1 RCT (n=40)	No Difference	Medium	Unknown	Direct	Imprecise	Insufficient

Abbreviations: AD=Alzheimer's Disease; BPRS=Brief Psychiatric Rating Scale; BSSD=Behavioral Syndromes Scale for Dementia; NPI=Neuropsychiatric Inventory; RCT=randomized controlled trial; SADS=Schedule for Affective Disorders and Schizophrenia; SAEs=serious adverse events

Antidepressants Versus Placebo

Appendix Table H.10. Characteristics of eligible studies: antidepressants versus placebo

Study Characteristics: **Author/Year** **Design** **Country** **Risk of Bias**	**N=**	**Population:** **AD Severity** **Mean Age** **% Female** **% White** **Education (mean yrs.)** **Baseline Cognition** **Baseline BPSD**	**Intervention:** **Intervention mode** **Components** **Frequency** **Duration**	**Comparison:** **Comparison mode** **Components** **Frequency** **Duration**	**Outcome Timing**	**Outcome Domain [Instrument]**
Zhou 2019[281] **RCT** **China** **Medium**	80	Severity NR Mean Age 71 59% Female Race NR 6 Years Education MMSE 15 NPI 35	Citalopram, 30 mg/day All treatment groups received memantine (~20 mg/day)	Placebo All treatment groups received memantine (~20 mg/day)	12 weeks	Agitation NPI Agitation Psychosis NPI Delusions NPI Hallucinations
Porsteinsson 2014[282] **RCT** **USA/Canada** **Low** **Leonpacher 2016** [283] **RCT** **USA** **Medium**	186	Probable AD Mean Age 78 46% Female 65% White 23% Received High School Diploma Baseline Cognition: MMSE 15.7 Baseline CMAI: 28.2	Citalopram, 30 mg/day All treatment groups received concomitant psychosocial intervention	Placebo All treatment groups received concomitant psychosocial intervention	9 weeks	Agitation CMAI mADCS-CGIC NBRS-A NPI-agitation subscale Psychosis NPI-delusion subscale
Banerjee 2011[284] **RCT** **UK** **Medium**	219	Probable or possible AD Mean Age 79 68% Female 93% White Education not reported Baseline Cognition: MMSE 18.1 Baseline CSDD: 13.06	Mirtazapine, 45/mg day No concomitant psychosocial intervention reported	Placebo	39 weeks	Behavior NPI Depression CSDD Quality of life DEMQOL EQ5D

Study Characteristics: **Author/Year** **Design** **Country** **Risk of Bias**	**N=**	**Population:** **AD Severity** **Mean Age** **% Female** **% White** **Education (mean yrs.)** **Baseline Cognition** **Baseline BPSD**	**Intervention:** **Intervention mode** **Components** **Frequency** **Duration**	**Comparison:** **Comparison mode** **Components** **Frequency** **Duration**	**Outcome Timing**	**Outcome Domain [Instrument]**
Banerjee 2011[284] **RCT** **UK** **Medium**	218	Probable or possible AD Mean Age 79 68% Female 93% White Education not reported Baseline Cognition: MMSE 18.1 Baseline CSDD: 13.21	Sertraline, 150 mg/day No concomitant psychosocial intervention reported	Placebo	39 weeks	Behavior NPI Depression CSDD Quality of life DEMQOL EQ5D
Finkel 2004[285] **RCT** **USA** **Medium**	244	Probable or possible AD Mean Age 76 61% Female Race not reported Education not reported Baseline Cognition: MMSE 17.8 Baseline NPI: 30.8	Sertraline, 25-200 mg/day Donepezil 5-10 mg/day for both arms No concomitant psychosocial intervention reported	Placebo	12 weeks	Agitation CMAI
Levkovitz 2001 [286] **RCT** **Israel** **High**	20	Unspecified AD Mean Age 78 45% Female Race not reported Education not reported BPRS ≥ 18	Fluvoxamine, 50 mg/day	Placebo plus Perphenazine, 4mg 3x/day	7 weeks	Psychosis BPRS

Abbreviations: AD=Alzheimer's Disease; BPRS=Brief Psychiatric Rating Scale; CMAI=Cohen-Mansfield Agitation Inventory; CSDD=Cornell Scale for Depression in Dementia; DEMQOL=DEM Quality of Life; EQ5D=EuroQol 5D. GHQ-12=General Health Questionnaire; HDRS=Hamilton Depression Rating Scale; mADCS-CGIC=modified Alzheimer Disease Cooperative Study-Clinical Global Impression of Change; NBRS-A=Neurobehavioral Rating Scale; NPI=Neuropsychiatric Inventory; RoB=Risk of Bias; SAEs=Serious Adverse Events

Appendix Table H.11. Risk of bias ratings: antidepressant versus placebo

Study	Time	Selection Bias	Attrition Bias	Performance Bias	Detection Bias	Reporting Bias	Overall Rating
Zhou 2019[281]	12 weeks	Medium	Low	Low	Low	Low	Medium
Porsteinsson 2014[282] **Leonpacher 2016**[283]	9 weeks	Low	Low	Low	Medium	Medium	Medium
Banerjee 2011 [284]	39 weeks	Low	Medium	Medium	Low	Medium	Medium
Finkel 2004 [285]	12 weeks	Medium	Medium	Low	Medium	Medium	Medium
Levkovitz 2001 [286]	7 weeks	Medium	Low	Medium	High	High	High

Appendix Table H.12. Primary outcomes summary low and medium risk of bias studies: antidepressant versus placebo

Drug Comparison	AD Severity	Study Characteristics: Author/Year Followup Risk of Bias	General Behavior	Agitation	Aggression	Psychosis	Depression	Anxiety	Disinhibited Sexual Behavior	Harms	Quality of Life
Citalopram vs. Placebo	Probable AD	Porsteinsson 2014 [282] Leonpacher 2016 [283] 9 weeks Medium	NR	CMAI Estimated treatment effect, mean (95% CI) -2.38 (-4.13 to -0.63) mADCS-CGIC Estimated treatment effect, mean (95% CI) 2.13 (1.23 to 3.69)' Moderate	NR	NPI-delusions subscale ≥50% improvement in domain score C: 54% I: 38%	NR	NR	NR	Confusion I: 76.7 % (69/90) C: 83.7% (72/86) p=0.24 Falls I: 16.7% (15/90) C: 11.6% (10/86) p=0.34 Somnolence I: 52.2% (47/90) C: 48.8% (42/86) p=0.65	

Drug Comparison	AD Severity	Study Characteristics: Author/Year Followup Risk of Bias	General Behavior	Agitation	Aggression	Psychosis	Depression	Anxiety	Disinhibited Sexual Behavior	Harms	Quality of Life
				or marked improvement I: 40% C: 26% NBRS-A Estimated treatment effect, mean (95% CI) -0.93 (-1.80 to -0.06) NPI-agitation subscale Estimated treatment effect, mean (95% CI) -0.78 (-1.77 to 0.21) ≥50% improvement in domain score C: 64% I: 43%							
	Zhou 2019[281] 12 weeks Medium		NPI Agitation/ Aggression Mean change from	See adjacent cell	NPI Hallucinations Mean change from baseline (SD)				SAEs "Similar" rates between groups, no data reported.		

Drug Comparison	AD Severity	Study Characteristics: Author/Year Followup Risk of Bias	General Behavior	Agitation	Aggression	Psychosis	Depression	Anxiety	Disinhibited Sexual Behavior	Harms	Quality of Life
			baseline (SD) I: -2.77 (1.22) C: -2.03 (0.96) p=0.004 (SMD, 0.67 [95% CI, 0.22 to 1.13])*		I: -0.08 (0.35) C: -0.10 (0.45) p=0.78 (SMD, -0.05 [95% CI, -0.49 to 0.39])* <u>NPI Delusions</u> Mean change from baseline (SD) I: -0.08 (0.27) C: -0.05 (0.22) p=0.649 (SMD, 0.12, [95% CI, -.032 to 0.57])*						
Mirtazapine vs. Placebo	Probable or possible AD	Banerjee 2011[284] 39 weeks Medium	<u>NPI</u> Estimated treatment effect, mean (95% CI) -1.51 (-6.25 to 3.24)	NR	NR	NR	<u>CSDD</u> Mean difference from placebo (95% CI) -0.66 (-2.12 to 0.79)	NR	NR	<u>Overall</u> Number of participants (number of events) I: 44 (96) C: 29 (58) p=0.031	<u>DEMQOL</u> Mean treatment effect: -0.03 [95% CI -3.80, 3.75] p=0.99 EQ5D Mean difference from placebo -1.18 [95%

Drug Comparison	AD Severity	Study Characteristics: Author/Year Followup Risk of Bias	General Behavior	Agitation	Aggression	Psychosis	Depression	Anxiety	Disinhibited Sexual Behavior	Harms	Quality of Life
											CI -9.25, 6.89] p=0.78 (self-report); -1.11 [95% CI -7.44, 5.21] p=0.73 (carer-report)
Sertraline vs. Placebo	Probable or possible AD	Banerjee 2011[284] 39 weeks Medium	NPI Estimated treatment effect, mean (95% CI) 2.02 (-2.94 to 6.97)	NR	NR	NR	CSDD Mean difference from placebo (95% CI) 0.37 (-1.12 to 0.87)	NR	NR	Overall Number of participants (number of events) I: 46 (86) C: 29 (58) p=0.01	DEMQOL: Mean treatment effect: -1.76 [95% CI -5.75, 2.23] p=0.39 EQ5D Mean difference from placebo -4.34 [95% CI -12.56, 3.88] p=.30 (self-report); -0.27 [95% CI -6.77, 6.24] p=0.94 (carer-report)
Donepezil + Sertraline vs.	Probable or possible AD	Finkel 2004 [285] 12 weeks Medium	NR	CMAI Mean change		NR	NR	NR	NR	NR	

Drug Comparison	AD Severity	Study Characteristics: Author/Year Followup Risk of Bias	General Behavior	Agitation	Aggression	Psychosis	Depression	Anxiety	Disinhibited Sexual Behavior	Harms	Quality of Life
Donepezil + Placebo				score I: -3.6 ± 1.4 C: -2.7 ± 1.2							

***Calculated by EPC**

Abbreviations: AD=Alzheimer's Disease; RoB=Risk of Bias; C=Control; CMAI=Cohen-Mansfield Agitation Inventory; CSDD=Cornell Scale for Depression in Dementia; I=Intervention; GHQ-12=General Health Questionnaire 12; mADCS-GCIC=modified Alzheimer Disease Cooperative Study-Clinical Global Impression of Change; NBRAS-A=Neurobehavioral Rating Scale Agitation subscale; NPI=Neuropsychiatric Inventory; SE=Standard Error; SAEs=Serious Adverse Events

Appendix Table H.13. Secondary outcomes summary low and medium risk of bias studies: antidepressant versus placebo

Drug Comparison	AD Severity	Study Characteristics: Author/Year Followup Risk of Bias	Change in Caregiver or Staff Outcomes
Citalopram vs. Placebo	Probable AD	Porsteinsson 2014[282], Leonpacher 2016[283] 9 weeks Medium	Addition of Citalopram compared with placebo significantly reduced caregiver distress (NPI-caregiver distress subscore estimated treatment effect -2.70 (-4.94 to -0.47), p=0.02; favors drug.
		Zhou 2019[281] 12 weeks Medium	Addition of citalopram compared with placebo significantly reduced caregiver distress (NPI caregiver distress subscore mean change from baseline 3.18 [SD 1.57] vs. 1.59 [SD 1.35], p<0.001).
Mirtazapine vs. Placebo	Probable or possible AD	Banerjee 2011 [284] 39 weeks Medium	Mirtazapine vs. placebo favored scores associated with carer burden (Zarit) and physical life quality (SF-PCS 12; physical). Mirtazapine vs. placebo worsened scores associated with carer mental health (GHQ) and carer mental life quality (SF-12 MCS; mental).
Sertraline vs. Placebo	Probable or possible AD	Banerjee 2011 [284] 39 weeks Medium	No significant difference for caregiver burden outcomes (carer burden (Zarit), CHQ, SF-12 MCS, SF-12 PCS).
Donepezil + Sertraline vs. Donepezil + Placebo	Probable or possible AD	Finkel 2004[285] 12 weeks Medium	No significant between-treatment group efficacy differences for caregiver burden outcomes (CBQ). Mean change score from baseline CBQ was -1.3±0.9 and 0.3±0.8 (p=0.12) for the sertraline + donepezil and donepezil + placebo group, respectively.

Abbreviations: AD=Alzheimer's Disease; NPI=Neuropsychiatric Inventory; CBQ=Caregiver Burden Questionnaire; CGI-S=Clinical Global Impression Severity scale; GHQ=General Health Questionnaire; PCS=Physical Composite Score; MCS-Mental Composite Score; NR=Not Reported; RoB=Risk of Bias; SF=Short-Form Health Survey

Appendix Table H.14. Summary of strength of evidence: citalopram versus placebo

Antidepressant vs. Placebo Outcome AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Agitation Probable AD	9 weeks	1 RCT (n=186)	Favors citalopram	Medium	Unknown	Direct	Imprecise	Insufficient
Agitation*	12 weeks	Agitation/ Aggression	Favors citalopram	Medium	Unknown	Direct	Precise	Insufficient
Psychosis*	12 weeks	Psychosis	No difference	Medium	Unknown	Direct	Imprecise	Insufficient

*Citalopram studies not pooled as all participants in 12-week study (Zhou 2019) received memantine.
Abbreviations: AD=Alzheimer's Disease; RCT=Randomized Controlled Trial

Appendix Table H.15. Summary of strength of evidence: donepezil and sertraline versus donepezil and placebo

Antidepressant vs. Placebo Outcome AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Agitation Probable or possible AD	12 weeks	1 RCT (n=244)	No difference	Medium	Unknown	Direct	Imprecise	Insufficient

Abbreviations: AD=Alzheimer's Disease; RCT=Randomized Controlled Trial

Appendix Table H.16. Summary of strength of evidence: mirtazapine versus placebo

Antidepressant vs. Placebo Outcome AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
General behavior Probable or possible AD	39 weeks	1 RCT (n=218)	No difference	Medium	Unknown	Direct	Imprecise	Insufficient
Depression Probable or possible AD	39 weeks	1 RCT (n=218)	No difference	Medium	Unknown	Direct	Imprecise	Insufficient

Abbreviations: AD=Alzheimer's Disease; RCT=Randomized Controlled Trial

Appendix Table H.17. Summary of strength of evidence: sertraline versus placebo

Antidepressant vs. Placebo Outcome AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
General behavior Probable or possible AD	39 weeks	1 RCT (n=219)	No difference	Medium	Unknown	Direct	Imprecise	Insufficient
Depression Probable or possible AD	39 weeks	1 RCT (n=219)	No difference	Medium	Unknown	Direct	Imprecise	Insufficient

Abbreviations: AD=Alzheimer's Disease; RCT=Randomized Controlled Trial

Donepezil Versus Placebo

Appendix Table H.18. Risk of bias ratings: donepezil versus placebo

Study	Time	Selection Bias	Attrition Bias	Performance Bias	Detection Bias	Reporting Bias	Overall Rating
Howard 2007[287]	12 weeks	Low	Medium (CMAI) High (NPI; NPI Caregiver Distress)	Low	Low	Low	Medium (CMAI) High (NPI; NPI Caregiver Distress)

Abbreviations: CMAI=Cohen-Mansfield Agitation Inventory; NPI=Neuropsychiatric Inventory

Appendix Table H.19. Characteristics of eligible studies: donepezil versus placebo

Study Characteristics: **Author/Year** **Design** **Country** **Risk of Bias**	**N=**	**Population Characteristics**	**Intervention:** **Intervention mode** **n/group** **Maximum dose** **Frequency** **Duration**	**Comparison:** **Comparison mode** **n/group** **Dose** **Frequency** **Duration**	**Outcome Timing**	**Outcome Domain [Instrument]**
Howard 2007[287] **RCT** **UK**	259	AD Severity NR Mean Age 84.7 85% Female 97% White Education 10.5 years Baseline Cognition: MMSE 8.2 Baseline BPSD: NPI 23.7 CMAI 61.6 Eligible participants had no response to a prior psychosocial program	Donepezil, 10mg/day, titrated in 5mg/day increments, for 12 weeks No concomitant psychosocial intervention reported	Placebo No concomitant psychosocial intervention reported	12 weeks	<u>Agitation</u> Cohen-Mansfield Agitation Inventory <u>Adverse Events</u> Falls Stroke Death

Abbreviations: AD=Alzheimer's Disease

Appendix Table H.20. Primary outcomes summary low and medium risk of bias studies: donepezil versus placebo

Drug Comparison	AD Severity	Study Characteristics: Author/Year Followup Risk of Bias	Agitation	Aggression	Hypersexuality	Harms
Donepezil vs. Placebo	NR	Howard, 2007[287] 12 weeks Medium	Proportion making 30% reduction in baseline CMAI score I: 19.5% C: 20.4%; RR=0.96; 95% CI=0.56 to 1.62 CMAI, change in total score, difference in mean change (adjusting for baseline CMAI score and stratification variables) (95% CI): -0.18 (-4.59 to 4.22) p = 0.94 CMAI, change in total score, standardized mean difference in (adjusting for baseline CMAI score and stratification variables) (95% CI): 0.00 (-0.24, 0.25)	N/A	N/A	Falls I: 2 C: 2 p-value not reported Stroke I: 1 C: 0 p-value not reported Death I: 3 C: 4 p-value not reported

Abbreviations: AD=Alzheimer's Disease

Appendix Table H.21. Summary of strength of evidence: donepezil versus placebo

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Cohen-Mansfield Agitation Inventory	NR	12 weeks	1 RCT	Proportion making 30% reduction in baseline CMAI score: I: 19.5% C: 20.4%; RR=0.96; 95% CI=0.56 to 1.62 CMAI, total score, difference in mean change (adjusting for baseline CMAI score and stratification variables): (95% CI): -0.18 (-4.59 to 4.22) p = 0.94 CMAI, change in total score, standardized mean difference in (adjusting for baseline CMAI score and stratification variables) (95% CI): 0.00 (-0.24, 0.25)	Medium	Unknown	Direct	Imprecise	Low

Anticonvulsants Versus Placebo

Appendix Table H.22. Risk of bias ratings: anticonvulsants versus placebo for treatment of BPSD

Study	Time		Selection Bias	Attrition Bias	Performance Bias	Detection Bias	Reporting Bias	Overall Rating
Tariot 2005[288]	6 weeks		Low	Medium	Medium	Medium	Low	Medium

BPSD=behavioral and psychological symptoms of dementia

Appendix Table H.23. Characteristics of eligible studies: anticonvulsants versus placebo for treatment of BPSD

Study Characteristics: **Author/Year** **Design** **Country** **Risk of Bias**	**N=**	**Population Characteristics**	**Intervention:** **Intervention mode** **Components** **Frequency** **Duration**	**Comparison:** **Comparison mode** **Components** **Frequency** **Duration**	**Outcome Timing**	**Outcome Domain [Instrument]**
Tariot 2005[288] **RCT** **US**	153	AD Severity NR Mean Age 86.0 69% Female 92% White Education NR Baseline Cognition: MMSE 10.7 Baseline BPSD: BPRS, total score 33.7 BPRS agitation score 8.3 CMAI, 36.5	Divalproex Sodium, target dose of 750mg/day, titrated in 250mg/day increments every 3 days, for 12 weeks (6 weeks double blind; 6 weeks open label) No concomitant psychosocial intervention reported	Placebo No concomitant psychosocial intervention reported	6 weeks	Agitation Brief Psychiatric Rating Scale, agitation factor Cohen-Mansfield Agitation Inventory Adverse Events Falls Psychiatric disorders*

*Composite outcome that included somnolence, but also agitation and aggression.
AD=Alzheimer's Disease; BPRS=Brief Psychiatric Rating Scale; BPSD=behavioral and psychological symptoms of dementia; MMSE=Mini-Mental State Exam; NPI=Neuropsychiatric Inventory; CMAI=Cohen-Mansfield Agitation Inventory

Appendix Table H.24. Primary outcomes summary low and medium risk of bias studies: anticonvulsants versus placebo for treatment of BPSD

Drug Comparison	AD Severity	Study Followup RoB	Agitation	Aggression	Hypersexuality	Harms
Divaloprex Sodium vs. Placebo	NR	Tariot 2005[288] 4 weeks Medium	BPRS, Agitation Factor, 6-Week Change (SD) From Baseline I: -2.08 (3.1) C: -1.72 (3.1) 95% CI for Difference: -1.4 to 0.6 Standard Mean Difference (95% CI) -0.12 (-0.44 to 0.21) CMAI I: -3.5 (14.5) C: -6.7 (15.6) 95% CI for Difference: -8.0 to 1.4 Standard Mean Difference (95% CI) -0.21 (-0.54 to 0.11)	N/A	N/A	Falls I: 21% divalproex vs. C: 17% placebo p=0.54 "Psychiatric disorders"*: I: 23% divalproex C: 15% placebo p=0.30

AD=Alzheimer's Disease; BPRS=Brief Psychiatric Rating Scale; BPSD=behavioral and psychological symptoms of dementia;MMSE=Mini-Mental State Exam; NPI=Neuropsychiatric Inventory; CMAI=Cohen-Mansfield Agitation Inventory

Appendix Table H.25. Summary of strength of evidence: anticonvulsants versus placebo for treatment of BPSD

Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Agitation (BPRS Agitation; CMAI)		6 weeks	1 RCT	No significant difference between groups on either of two tests (BPRS, CMAI)	Medium	Unknown	Direct	Imprecise	Insufficient

BPSD=behavioral and psychological symptoms of dementia

Memantine Versus Placebo

Appendix Table H.26. Risk of bias ratings: memantine versus placebo for treatment of BPSD

Study	Time	Selection Bias	Attrition Bias	Performance Bias	Detection Bias	Reporting Bias	Overall Rating
Fox 2012[289]	6 weeks	Low	High	Low	Low	Low	High
Hermann 2013[183]	24 weeks	Medium	Medium	High	Low	High	High

Appendix Table H.27. Characteristics of eligible studies: memantine versus placebo for treatment of BPSD

Study Characteristics: Author/Year Design Country Risk of Bias	N=	Population Characteristics	Intervention: Intervention mode Components Frequency Duration	Comparison: Comparison mode Components Frequency Duration	Outcome Timing	Outcome Domain [Instrument]
Fox 2012[289] **RCT** **United Kingdom** **High**	153	Moderate to Severe AD Mean Age 85 74% Female 98% White Education NR Baseline Cognition: MMSE 7.3 Baseline BPSD: CMAI 68.3 NPI 36.6	Memantine, 20mg/day in 2 doses, titrated in 10mg/day increments, for 12 weeks	Placebo	6 and 12 weeks	Agitation CMAI General BPSD NPI Adverse Events Death
Hermann 2013[183] **RCT** **Canada**	369	AD Severity NR Mean Age 75 58% Female Race NR Education NR Baseline Cognition: MMSE 11.9 Baseline BPSD: CMAI (physical): 16 NPI: 30	Memantine, 20mg/day in 1 dose, titrated in 5 mg/day increments, for 24 weeks	Placebo	24 weeks	Agitation CMAI General BPSD NPI Adverse Events Falls

NR=not reported

Estrogen Versus Placebo

Appendix Table H.28. Risk of bias ratings: estrogen versus placebo

Study	Time	Selection Bias	Attrition Bias	Performance Bias	Detection Bias	Reporting Bias	Overall Rating
Hall 2005[290]	8 weeks	Low	High	Low	Low	Medium	High
Kyomen 1999[291]	4 weeks	Medium	Low	High	High	High	High

Appendix Table H.29. Characteristics of eligible studies: estrogen versus placebo

Study Characteristics: Author/Year Design Country Risk of Bias	N=	Population Characteristics	Intervention: Intervention mode Components Frequency Duration	Comparison: Comparison mode Components Frequency Duration	Outcome Timing	Outcome Domain [Instrument]
Hall 2005[290] **RCT** **Australia**	27	AD Severity NR Mean Age 78.5 0% Female Race NR Education NR Baseline Cognition: MMSE 17.2 Baseline BPSD: Rating Scale for Aggressive Behavior in Elderly (RAGE) 22.5	Estrogen patch, 10mcg/day, titrated in 5mcg/day increments	Placebo	8 weeks	Aggression Rating Scale for Aggressive Behavior in the Elderly (RAGE) Adverse Events The study did not report data for any of the harms of interest specified in this systematic review protocol.
Kyomen 1999[291] **RCT** **US**	14	Moderate to Severe AD Mean Age 83.7 85.7% Female Race NR Education NR Baseline Cognition: MMSE 4.72 Baseline BPSD NR	Estrogen pill, 2.5 mg/day, titrated in 0.625mg doses	Placebo	4 weeks	Aggression Overt Aggression Scale, modified: physical and verbal aggression domains Disinhibited Sexual Behavior Overt Aggression Scale, modified: sexually aggressive domain Adverse Events The study did not report data for any of the harms of interest specified in this systematic review protocol.

Appendix I. Key Question 7: Efficacy and Harms of Supplements Versus Placebo for Behavioral and Psychological Symptoms of Dementia

Appendix Table I.1. Characteristics of eligible studies: supplements versus placebo

Study Characteristics: Author/Year Design Country Risk of Bias	**N=**	**Population Characteristics**	**Intervention: Intervention mode Components Frequency Duration**	**Comparison: Comparison mode Components Frequency Duration**	**Outcome Timing**	**Outcome Domain [Instrument]**
Furukawa 2017[292] RCT Japan	145	Probable CATD Mean Age 78.4 57.9 % Female Race NR Education NR Baseline Cognition: MMSE 19.4 Baseline BPSD: NPI-Q 9.5	Yokukansan, 7.5 g/day No concomitant psychosocial intervention reported	Placebo No concomitant psychosocial intervention reported	4 weeks	Agitation NPI-Q Agitation/Aggression Subscale Aggression NPI-Q Agitation/Aggression Subscale Psychosis NPI-Q Delusion Subscale NPI-Q Hallucination Subscale Disinhibited Sexual Behavior NPI-Q Disinhibition Subscale Adverse Events Common Terminology Criteria for Adverse Events, Version 4.0

Abbreviations: CATD=Clinical Alzheimer's Type Dementia; MMSE=Mini-Mental State Examination; NPI=Neuropsychiatric Inventory; NPI-I=Neuropsychiatric Inventory Questionnaire; NR=Not Reported

Appendix Table I.2. Outcome instruments used in low/medium risk of bias studies: supplement versus placebo

Drug Comparison	Study	RoB	AD Severity	General Behavior	Agitation	Aggression	Psychosis	Depression	Anxiety	Disinhibited Sexual Behavior	Quality of Life
Yokukansan vs. Placebo	Furukawa 2017 [292] RCT Japan	Low	Probable CATD per NINCDS-ADRDA criteria	NR	NPI-Q Agitation/ Aggression subscale	NPI-Q Agitation/Aggression subscale	NPI-Q Delusion subcale, NPI-Q Hallucination subscale	NR	NR	NR	NR
	TOTAL			0	1	1	2	0	0	0	1

Abbreviations: AD=Alzheimer's disease; CATD=Clinical Alzheimer's Type Dementia; NPI=Neuropsychiatric Inventory; NR=Not Reported; RCT=Randomized Controlled Trial

Appendix Table I.3. Risk of bias ratings: supplement versus placebo

Intervention	Study	Time	Selection Bias	Attrition Bias	Performance Bias	Detection Bias	Reporting Bias	Overall Rating
Yokukansan	Furukawa 2017 [292]	4 weeks	Low	Low†	Low	Low	Medium	Low

†Attrition was 45%, but 136 of 145 (93.8%) were analyzed for efficacy. Authors did not state how much missing data were present and how missing data were handled.

Appendix Table I.4. Primary outcomes summary low and medium risk of bias studies: supplement versus placebo

Study	Drug Comparison	AD Severity	Follow up	RoB	General Behavior	Depression	Anxiety	Agitation	Aggression	Psychosis	Disinhibited Sexual Behavior	Harms	Quality of Life
Furukawa 2017[292]	Yokukansan vs. Placebo	Probable CATD	4 weeks	Low	NR	NR	NR	NPI-Q Agitation/ Aggression Subscale No statistically significant difference between groups	NPI-Q Agitation/Aggression Subscale No statistically significant difference between groups	NPI-Q Delusion Subscale No statistically significant difference between groups NPI-Q Hallucination Subscale No statistically significant difference between groups	NR	Adverse Events No significant difference in number of adverse events between arms	NR

Abbreviations: CATD=Clinical Alzheimer's Type Dementia; DEMQOL=DEM Quality of Life; MMSE=Mini-Mental State Examination; NPI=Neuropsychiatric Inventory; NPI-I=Neuropsychiatric Inventory Questionnaire; NR=Not Reported

Appendix Table I.5. Summary of strength of evidence: antidepressants versus placebo

Study	Drug Comparison	Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Furukawa 2017[292]	Yokukansan vs. Placebo	Agitation	Probable CATD	4 weeks	1 RCT (n=145)	No difference	Low	Consistency unknown (single study)	Direct	Imprecise	Insufficient
Furukawa 2017[292]	Yokukansan vs. Placebo	Aggression	Probable CATD	4 weeks	1 RCT (n=145)	No difference	Low	Consistency unknown (single study)	Direct	Imprecise	Insufficient

Study	Drug Comparison	Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Furukawa 2017[292]	Yokukansan vs. Placebo	Psychosis	Probable CATD	4 weeks	1 RCT (n=145)	No difference	Low	Consistency unknown (single study)	Direct	Imprecise	Insufficient
Furukawa 2017[292]	Yokukansan vs. Placebo	Harms	Probable CATD	4 weeks	1 RCT (n=145)	No difference	Low	Consistency unknown (single study)	Direct	Imprecise	Insufficient

Abbreviations: AD=Alzheimer's Disease; RCT=Randomized Controlled Trial

Appendix J. Key Question 8: Comparative Effectiveness and Harms of Prescription Drug Treatment Versus Other Active Treatment for Behavioral and Psychological Symptoms of Dementia

Appendix Table J.1. Characteristics of eligible studies: drug versus drug

Study Characteristics: **Author/Year** **Design** **Country** **Risk of Bias**	**N=**	**Population:** **AD Severity** **Mean Age** **% Female** **% White** **Education (mean yrs.)** **Baseline Cognition**	**Intervention:** **Intervention mode** **Components** **Frequency** **Duration**	**Comparison:** **Comparison mode** **Components** **Frequency** **Duration**	**Outcome Timing**	**Outcome Domain [Instrument]**
Auchus 1997[279] **RCT** **Canada** **High**	12	Severity NR Mean Age 76 67% Female Race NR 12 Years Education MMSE 15	Haloperidol, 3 mg/day	Fluoxetine, 20 mg/day Additional placebo arm	6 weeks	Agitation BEHAVE-AD CMAI Harms SAEs
Ballard 2005[269] **RCT** **UK and Norway** **High**	62	Severity NR Mean Age 84 82% Female Race NR Education NR Cognition NR	Quetiapine, 25-50 mg/twice daily for 12 weeks, 50 mg/twice daily after	Rivastigmine, 3-6mg/twice daily for 12 weeks, 9+ mg/twice daily after Additional placebo arm	26 weeks	Agitation CMAI Harms SAEs
Ballard 2015[247] **RCT** **UK** **Medium**	199	Probable or possible AD Mean Age 83 69% Female Race NR Education NR MMSE 8	Antipsychotics pooled (various) No concomitant psychosocial intervention reported	Memantine, 10 mg/twice daily No concomitant psychosocial intervention reported	24 weeks	Behavior NPI Agitation CMAI Harms SAEs Mortality

Study Characteristics: **Author/Year** **Design** **Country** **Risk of Bias**	**N=**	**Population:** **AD Severity** **Mean Age** **% Female** **% White** **Education (mean yrs.)** **Baseline Cognition**	**Intervention:** **Intervention mode** **Components** **Frequency** **Duration**	**Comparison:** **Comparison mode** **Components** **Frequency** **Duration**	**Outcome Timing**	**Outcome Domain [Instrument]**
Banerjee 2011 [284] **RCT** **UK** **Medium**	215	Probable or possible AD Mean Age 79 70% Female 93% White Education not reported Baseline Cognition: MMSE 18.0 Baseline CSDD: 12.65	Sertraline, 150 mg/day No concomitant psychosocial intervention reported	Mirtazapine, 45 mg/day No concomitant psychosocial intervention reported	39 weeks	Behavior NPI Depression CSDD Quality of life DEMQOL EQ5D Harms SAE Mortality
Chan 2001[293] **RCT** **China** **High**	58	Severity NR Mean Age 81 72% Female 100% Chinese Education NR MMSE (Cantonese) 8	Risperidone, 0.5-2mg/day	Haloperidol, 0.5-2mg/day	12 weeks	Agitation BEHAVE-AD CMAI Harms SAEs
Deberdt 2005[270] **RCT** **Multinational** **High**	400	Severity NR Mean Age 78 64% Female 84% White Education NR MMSE 14	Olanzapine, 2.5-10 mg/day	Risperidone, 0.5-2 mg/day Additional placebo arm	10 weeks	Behavior BPRS NPI Agitation CMAI NPI-Psychosis Harms SAEs
De Deyn 1999[277] **RCT** **Multinational** **High**	230	Severity NR Mean Age 82 56% Female 99% White Education NR MMSE 8	Risperidone, 0.5-4 mg/day	Haloperidol, 0.5-4 mg/day Additional placebo arm	12 weeks	Agitation BEHAVE-AD CMAI Harms SAEs

Study Characteristics: **Author/Year** **Design** **Country** **Risk of Bias**	**N=**	**Population:** **AD Severity** **Mean Age** **% Female** **% White** **Education (mean yrs.)** **Baseline Cognition**	**Intervention:** **Intervention mode** **Components** **Frequency** **Duration**	**Comparison:** **Comparison mode** **Components** **Frequency** **Duration**	**Outcome Timing**	**Outcome Domain [Instrument]**
Fontaine 2003[294] **RCT** **USA** **High**	39	Severity NR Mean Age 83 67% Female 87% White Education NR MMSE 8	Olanzapine, 2.5, 5, 10 mg/daily	Risperidone, 0.5, 1, 2 mg/daily	2 weeks	Behavior NPI Agitation E-BEHAVE-AD Harms SAEs
Holmes 2007[295] **RCT** **UK** **High**	6	Severe AD Mean Age 86 74% Female Race NR Education NR MMSE 8	Risperidone, 0.5 mg/daily for two weeks, then twice daily	Rivastigmine, 1.5 mg/twice daily for two weeks, then 3mg/twice daily	6 weeks	Agitation CMAI Harms SAEs
Tariot 2006[268] **RCT** **USA** **High**	171	Severity NR Mean Age 83 73% Female 91% White Education NR MMSE 13	Quetiapine, 25 mg/day	Haloperidol, 0.5 mg/day Additional placebo arm	10 weeks	Behavior BPRS NPI-NH14 Agitation BPRS subscales NPI-NH14 subscales Harms SAEs
Teri 2000[276] **RCT** **USA** **High**	71	Severity NR Mean Age 75 73% Female 86% White 13 Years Education MMSE 13	Haloperidol, 0.5 mg/day	Trazodone, 50 mg/day Additional placebo arm	16 weeks	Agitation ABID CMAI RMBPC Harms SAEs

Study Characteristics: Author/Year Design Country Risk of Bias	N=	Population: AD Severity Mean Age % Female % White Education (mean yrs.) Baseline Cognition	Intervention: Intervention mode Components Frequency Duration	Comparison: Comparison mode Components Frequency Duration	Outcome Timing	Outcome Domain [Instrument]
Viscogliosi 2017[296] **RCT** **Italy** **High**	50	Severity NR Mean Age NR % Female NR Race NR Education NR Cognition NR	Olanzapine, 2.5+mg/day Quetiapine, 25+mg/day	Citalopram, 10+mg/day Additional placebo arm	24 weeks	Agitation NPI-Agitation Harms SAEs

Abbreviations: ABID= Agitated Behavior in Dementia scale; AD=Alzheimer's Disease; BEHAVE-AD=Behavioral Pathology in Alzheimer's Disease rating scale; BPRS= Brief Psychiatric Rating Scale; CMAI=Cohen Mansfield Agitation Inventory; CSDD= Cornell Scale for Depression in Dementia; DEMQOL=DEM Quality of Life; E-BEHAVE-AD=Empirical Behavioral Pathology in Alzheimer's Disease rating scale; EQ5D=EuroQol 5D; NPI=Neuropsychiatric Inventory; NR=Not Reported; RMBPC= Revised Memory and Behavior Problem Checklist; RoB=Risk of Bias; SAEs=Serious Adverse Events

Appendix Table J.2. Risk of bias ratings: drug versus drug

Study	Time	Selection Bias	Attrition Bias	Performance Bias	Detection Bias	Reporting Bias	Overall Rating* *Justification*
Auchus 1997[279]	6 weeks	Medium	High	Low	Low	Low	High
Ballard 2005[269]	26 weeks	Low	High	Low	Low	Low	High
Ballard 2015[247]	24 weeks	Medium	Medium	Medium	Low	Low	Medium
Banerjee 2011 [284]	39 weeks	Low	Medium	Medium	Low	Medium	Medium
Chan 2001[293]	10 weeks	Medium	Low	Medium	Low	High	High *Data poorly reported, largely unusable.*
Deberdt 2005[270]	10 weeks	Medium	High	Medium	Low	Low	High
De Deyn 1999[277]	12 weeks	Medium	High	Low	Low	Low	High
Fontaine 2003[294]	2 weeks	Medium	Medium	High	Low	Low	High

Study	Time	Selection Bias	Attrition Bias	Performance Bias	Detection Bias	Reporting Bias	Overall Rating* *Justification*
Holmes 2007[295]	6 weeks	Medium	High	Low	Low	Low	High
Tariot 2006 [268]	10 weeks	Medium	High	Medium	Low	Low	High
Teri 2000[276]	16 weeks	Low	High	Medium	Low	Low	High
Viscogliosi 2017[296]	24 weeks	Medium	Low	High	High	Medium	High

*Justifications provided when overall risk of bias rating deviating from guidance provided in tool (Appendix B)

Appendix Table J.3. Primary outcomes summary low and medium risk of bias studies: drug versus drug

Drug Comparison	AD Severity	Study Characteristics: Author/Year Followup Risk of Bias	General Behavior	Agitation	Aggression	Psychosis	Depression	Anxiety	Disinhibited Sexual Behavior	Harms	Quality of Life
Sertraline vs. Mirtazapine	Probable or possible AD	Banerjee 2011 [284] 39 weeks Medium	NPI Estimated treatment effect, mean (95% CI) 3.53 (-1.44 to 8.49) SMD 0.23 [95% CI, -0.09 to 0.56]	NR	NR	NR	CSDD Mean difference from mirtazapine (95% CI) 1.04 (-0.45 to 2.53) SMD 0.23 [95% CI, -0.10 to 0.56]	NR	NR	Overall Number of participants (number of events) S: 46 (86) M: 44 (96)	DEMQOL SMD -0.14 [95% CI, -0.47 to 0.19] DEMQOL-proxy SMD -0.07 [95% CI, -0.40 to 0.26] Self-reported EQ5D Mean difference from mirtazapine -3.16 [95% CI -9.25, 6.89] p=0.45 SMD -0.07 [95% CI, -0.40 to 0.26] Carer-reported EQ5D Mean difference from mirtazapine 0.85 [95% CI -5.86, 7.56] p=0.80 SMD 0.04 [95% CI, -0.29 to 0.37]

Memantine vs. Antipsychotics	Probable or possible AD	Ballard 2015[247] 24 weeks Medium	<u>NPI</u> Mean Change from Baseline (SD) M: 17.90 (16.25) A: 14.01 (13.53) Mean Change Between Groups (95% CI) 3.63 (-1.40, 8.67) p=0.157 SMD 0.22 [95% CI, -0.08 to 0.53] <u>Relapse (30% worsening in NPI scores)</u> Odds ratio (95% CI) M: 39.2% A: 29.6% OR 1.99 (1.17, 3.40) p=0.01 Favors antipsychotics	<u>CMAI</u> Mean Change from Baseline (SD) M: 52.42 (17.98) A: 46.58 (12.47) Mean Change Between Groups (95% CI) 4.09 (-0.35, 8.53) p=0.0711 SMD 0.28 [95% CI, -0.02 to 0.59]	NR	NR	NR	NR	NR	<u>SAEs</u> M: 18/NR A: 25/NR p=NR <u>Mortality</u> M: 9/NR A: 4/NR p=NR	NR

Abbreviations: AD=Alzheimer's Disease; CMAI=Cohen-Mansfield Agitation Inventory; CI=confidence interval; CSDD=Cornell Scale for Depression in Dementia; I=Intervention; EQ5D=EuroQol 5D; M=Mirtazapine; NPI=Neuropsychiatric Inventory; S=Sertraline; SAEs=Serious Adverse Events; SD=standard deviation; SE=Standard Error

Appendix Table J.4. Secondary outcomes summary low and medium risk of bias studies: drug versus drug

Drug Comparison	AD Severity	Study Characteristics: Author/Year Followup Risk of Bias	Change in Caregiver or Staff Outcomes
Sertraline vs. Mirtazapine	Probable or possible AD	Banerjee 2011 [284] 39 weeks Medium	No significant difference for caregiver burden outcomes (carer burden (Zarit), GHQ, SF-12 MCS, SF-12 PCS) between groups. Carer burden (Zarit) SMD 0.21 [95% CI, -0.11 to 0.54 GHQ SMD 0.22 [95% CI, -0.11 to 0.55] SF-12 MCS SMD 0.04 [95% CI, -0.29 to 0.37] SF-12 PCS SMD -0.12 [95% CI, -0.45 to 0.21]
Memantine vs. Antipsychotics	Probable or possible AD	Ballard 2015 [247] 24 weeks Medium	NR

Abbreviations: AD=Alzheimer's Disease; GHQ=General Health Questionnaire; PCS=Physical Composite Score; MCS-Mental Composite Score; NR=Not Reported; RoB=Risk of Bias; SF=Short-Form Health Survey

Appendix Table J.5. Summary of strength of evidence: drug versus drug

Antidepressant vs. Placebo	Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Sertraline vs. Mirtazapine	General behavior	Probable or possible AD	39 weeks	1 RCT (n=215)	No difference	Medium	Unknown	Direct	Imprecise	Insufficient
Sertraline vs. Mirtazapine	Depression	Probable or possible AD	39 weeks	1 RCT (n=215)	No difference	Medium	Unknown	Direct	Imprecise	Insufficient
Memantine vs. Antipsychotics	General behavior	Probable or possible AD	24 weeks	1 RCT (n=166)	No difference	Medium	Unknown	Direct	Imprecise	Insufficient
Memantine vs. Antipsychotics	Agitation	Probable or possible AD	24 weeks	1 RCT (n=166)	No difference	Medium	Unknown	Direct	Imprecise	Insufficient

Antidepressant vs. Placebo	Outcome	AD Severity	Timing	# Studies/ Design (n analyzed)	Finding or Summary Statistic	Study Limitations	Consistency	Directness	Precision	Overall Grade/ Conclusion
Sertraline vs. Mirtazapine	SAEs	Probable or possible AD	39 weeks	1 RCT (n=215)	No difference	Medium	Unknown	Direct	Imprecise	Insufficient
Memantine vs. Antipsychotics	SAEs	Probable or possible AD	24 weeks	1 RCT (n=166)	No difference	Medium	Unknown	Direct	Imprecise	Insufficient

Abbreviations: AD=Alzheimer's Disease; RCT=Randomized Controlled Trial

Appendix K. Background Tables

Appendix Table K.1. Cognitive tests to be assessed for classification accuracy

Cognitive Test Categories	Cognitive Test Names	Cognitive Domains Evaluated	Approximate Administration Time
Brief Standalone Tests (< 30min) Global Instruments	Cognitive Abilities Screening Instrument (CASI)	Global	15-20 min
	Mini-Cog	Global	< 5 min
	Mini-Mental State Exam (MMSE)	Global	5-10 min
	Montreal Cognitive Assessment (MoCA, also MoCA-Blind version)	Global	10-15 min
	St. Louis University Mental Status (SLUMS)	Global	5-10 min
	Short Test of Mental Status (STMS)	Global	5-10 min
	Telephone Interview for Cognitive Status (TICS & TICS-M)	Global	10 min
	Clock Drawing	Global	<5 min
Brief Multidomain Batteries	Alzheimer's Disease Assessment Scale-Cognition (ADAS-Cog)	Global	30-40 min
	CERAD Battery	Global	30-40 min
	Mattis Dementia Rating Scale (DRS & DRS-2)	Global	30-40 min (both)
	Repeatable Battery for the Assessment of Neuropsychological Status (RBANS, multiple versions)	Global	30-40 min
	Computer administered (e.g., CogState, CANS-MCI)	Global	Varies by test
Individual Test Types Administered as Part of Longer Battery (cognitive domains evaluated)	Trail making tests (e.g., TMT part B, DKEFS)	Attention, Executive Function	Varies by test
	Coding tasks (e.g., Digit symbol [WAIS], symbol digit)	Executive Function	Varies by test
	Design and figure fluency tasks (e.g., DKEFS)	Executive Function	Varies by test
	Concept formation switching and rule attainment (e.g., Wisconsin Card Sort)	Executive Function	Varies by test
	Figure recall tasks (e.g., BVRT, RCFT, Taylor)	Visuospatial Memory	Varies by test
	List-learning tests (e.g., CVLT, Buschke, Hopkins, RAVLT)	Verbal Memory	Varies by test
	Prose/paragraph recall (e.g., Boston story, Logical Memory)	Verbal Memory	Varies by test
	Confrontation naming (e.g., BNT)	Language	Varies by test
	Verbal fluency-letter/phonemic (e.g., FAS, CFL, includes COWAT)	Language, Executive Function	Varies by test
	Verbal fluency–category/semantic (e.g., names, animals)	Language, Executive Function	Varies by test

Abbreviations: ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognition; BNT=Boston Naming Test; BVRT=Benton Visual Retention Test; CASI=Cognitive Abilities Screening Instrument; CERAD=Consortium to Establish a Registry for Alzheimer's Disease; COWAT=Controlled Oral Word Association Test; CPT=Continuous Performance Test; CVLT=California Verbal Learning Test; DKEFS=Delis-Kaplan Executive Function System; DRS=Dementia Rating Scale; MMSE=Mini-Mental State Exam; MoCA=Montreal Cognitive Assessment; RAVLT=Rey Auditory Verbal Learning Test; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status; RCFT=Rey-Oosterrieth Complex Figure Test; SLUMS=St. Louis University Mental Status; STMS=Short Test of Mental Status; TICS=Telephone Interview for Cognitive Status; TMT=Trail Making Test; TOVA=Tests of Variables of Attention; WAIS=Wechsler Adult Intelligence Scale

Appendix Table K.2. Drugs used for treatment of CATD cognition, function, QOL, or BPSD

Class of Drug	Drug Name(s)
Cholinesterase inhibitor	Donepezil*, rivastigmine*, galantamine*
NMDA receptor antagonist	Memantine*
Cholinesterase inhibitor/NMDA receptor antagonist combination	Donepezil/ Memantine*
1st generation (typical) antipsychotic	only Haloperidol
2nd generation (atypical) antipsychotic	e.g., Risperidone, quetiapine, olanzapine, aripiprazole, clozapine
Anti-depressant, selective serotonin-reuptake inhibitor (SSRI)	e.g., Citalopram, escitalopram, sertraline, fluoxetine, fluvoxamine, paroxetine
Anti-depressant, serotonin-norepinephrine reuptake inhibitor (SNRI)	e.g., Duloxetine, venlafaxine
Anti-depressant, other†	e.g., Trazodone, bupropion, mirtazapine
Anti-seizure/mood stabilizer	e.g., Valproate, gabapentin, carbamazepine, lamotrigine
Anti-anxiety, benzodiazepine	e.g., Clonazepam, diazepam, lorazepam, temazepam, alprazolam
Anti-anxiety, other	Buspirone
Mixed	Dextromethorpan/quinidine
Hormones (antiandrogens, estrogens, gonadotropin-releasing hormone analogues)	e.g., Medroxyprogesterone acetate, cyproterone acetate, leuprolide
Cannabinoids	e.g., Medical marijuana

Abbreviations: BPSD=behavioral and psychological symptoms of dementia; CATD=clinical Alzheimer's-type dementia; NMDA=N-methyl-D-aspartate; SSRI=selective serotonin reuptake inhibitor; SNRI=selective norepinephrine reuptake inhibitor
*US FDA approved indication for Alzheimer's dementia
†Excludes MAO-inhibitor, tricyclic and tetracyclic antidepressants.

Appendix L. Excluded References

Excluded References: Cognitive Testing

1. . Erratum: A subtest analysis of the Montreal Cognitive Assessment (MoCA): Which subtests can best discriminate between healthy controls, mild cognitive impairment and Alzheimer's disease? (International Psychogeriatrics (2016) 28:5 (825-832) DOI: 10.1017/S1041610215001982). International Psychogeriatrics. 2017 01 Apr;29(4):701. PMID: 613758350 **Tests not administered in English**

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181. Davis C, Heidler-Gary J, Gottesman RF, et al. Action versus animal naming fluency in subcortical dementia, frontal dementias, and Alzheimer's disease. Neurocase. 2010 Jun;16(3):259-66. PMID: 20104387 **No outcomes of interest**

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184. Davis PB, Morris JC, Grant E. Brief screening tests versus clinical staging in senile dementia of the Alzheimer type. Journal of the American Geriatrics Society. 1990 Feb;38(2):129-35. PMID: 1990-20129-001 **No outcomes of interest**

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198. Delprado J, Kinsella G, Ong B, et al. Clinical measures of prospective memory in amnestic mild cognitive impairment. Journal of the International Neuropsychological Society. 2012 Mar;18(2):295-304. PMID: 22264396 **Not CATD diagnosis**

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No outcomes of interest

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Index test not eligible

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Tests not administered in English

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864. Toepper M, Steuwe C, Beblo T, et al. Deficient symbol processing in alzheimer disease. Alzheimer Disease and Associated Disorders. 2014 04 Dec;28(4):340-6. PMID: 600686497 **Tests not administered in English**

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