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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Agency for Healthcare Research and Quality

Supplemental Evidence and Data Request on Diagnostic and Treatment of Clinical Alzheimer's-type Dementia (CATD)

AGENCY: Agency for Healthcare Research and Quality (AHRQ), HHS.

ACTION: Request for Supplemental Evidence and Data Submissions

SUMMARY: The Agency for Healthcare Research and Quality (AHRQ) is seeking scientific information submissions from the public. Scientific information is being solicited to inform our review of *Diagnostic and Treatment of Clinical Alzheimer's-type Dementia (CATD),* which is currently being conducted by the AHRQ's Evidence-based Practice Centers (EPC) Program. Access to published and unpublished pertinent scientific information will improve the quality of this review.

DATES: *Submission Deadline* on or before [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES:

E-mail submissions: epc@ahrq.hhs.gov.

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SUPPLEMENTARY INFORMATION:

The Agency for Healthcare Research and Quality has commissioned the Evidence-based Practice Centers (EPC) Program to complete a review of the evidence for *Diagnostic and Treatment of Clinical Alzheimer's-type Dementia (CATD)*. AHRQ is conducting this systematic review pursuant to Section 902(a) of the Public Health Service Act, 42 U.S.C. 299a(a).

The EPC Program is dedicated to identifying as many studies as possible that are relevant to the questions for each of its reviews. In order to do so, we are supplementing the usual manual and electronic database searches of the literature by requesting information from the public (e.g., details of studies conducted). We are looking for studies that report on *Diagnostic and Treatment of Clinical Alzheimer's-type Dementia (CATD)*, including those that describe adverse events. The entire research protocol, including the key questions, is also available online at: https://effectivehealthcare.ahrq.gov/topics/alzheimers-type-dementia/protocol.

This is to notify the public that the EPC Program would find the following information on *Diagnostic and Treatment of Clinical Alzheimer's-type Dementia (CATD)* helpful:

- A list of completed studies that your organization has sponsored for this indication. In the list, please *indicate whether results are available on ClinicalTrials.gov along with the ClinicalTrials.gov trial number*.
    - *For completed studies that do not have results on ClinicalTrials.gov*, please provide a summary, including the following elements: study number, study period, design, methodology, indication and diagnosis, proper use instructions, inclusion and exclusion criteria, primary and secondary outcomes, baseline characteristics, number of patients screened /eligible /enrolled /lost to follow-up /withdrawn /analyzed, effectiveness/efficacy, and safety results.
- *A list of ongoing studies that your organization has sponsored for this indication*. In the list, please provide the ClinicalTrials.gov trial number or, if the trial is not registered, the protocol for the study including a study number, the study period, design, methodology, indication and diagnosis, proper use instructions, inclusion and exclusion criteria, and primary and secondary outcomes.
- Description of whether the above studies constitute ALL Phase II and above clinical trials sponsored by your organization for this indication and an index outlining the relevant information in each submitted file.

Your contribution will be very beneficial to the EPC Program. Materials submitted must be publicly available or able to be made public. Materials that are considered confidential; marketing materials; study types not included in the review; or information on indications not included in the review cannot be used by the EPC Program. This is a voluntary request for information, and all costs for complying with this request must be borne by the submitter.

The draft of this review will be posted on AHRQ's EPC Program website and available for public comment for a period of 4 weeks. If you would like to be notified when the draft is posted, please sign up for the e-mail list at: https://www.effectivehealthcare.ahrq.gov/email-updates.

The systematic review will answer the following questions. This information is provided as background. AHRQ is not requesting that the public provide answers to these questions.

The Key Questions

KQ 1: In adults with CATD, what are the efficacy and harms of prescription pharmacological interventions versus placebo/inactive control for treatment of cognition, function, and quality of life?

KQ 1a: In adults with CATD, does the efficacy of prescription pharmacological 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 2: In adults with CATD, what are the efficacy and harms of nonprescription pharmacological interventions versus placebo/inactive control for treatment of cognition, function, and quality of life?

KQ 2a: In adults with CATD, does the efficacy of nonprescription pharmacological 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 3: In adults with CATD, what are the comparative effectiveness and harms of prescription pharmacological interventions versus other active interventions for treatment of cognition, function, and quality of life?

KQ 3a: In adults with CATD, what are the comparative effectiveness and harms of prescription pharmacological interventions versus other prescription pharmacological interventions for treatment of cognition, function, and quality of life?

KQ3b: In adults with CATD, what are the comparative effectiveness and harms of prescription pharmacological interventions versus nonprescription pharmacological interventions for treatment of cognition, function, and quality of life?

KQ3c: In adults with CATD, what are the comparative effectiveness and harms of prescription pharmacological interventions versus nonpharmacological interventions for treatment of cognition, function, and quality of life?

KQ 3d: In adults with CATD, does the comparative effectiveness of prescription pharmacological interventions versus other active interventions for treatment of cognition, function, and quality of life 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 and behavioral and psychological symptoms of dementia (BPSD), what are the efficacy and harms of prescription pharmacological interventions versus placebo/inactive control for treatment of BPSD?

KQ 4a: In adults with CATD and BPSD, what are the efficacy and harms of prescription pharmacological interventions versus placebo/inactive control for reducing frequency and severity of future BPSD?

KQ 4b: In adults with CATD and BPSD, does the efficacy of prescription pharmacological interventions versus placebo/inactive control for reducing frequency and severity of future BPSD vary as a function of patient characteristics (i.e., age, sex, race/ethnicity, depression, pre-treatment cognitive or functional level/CATD stage, pre-treatment BPSD severity, living setting)?

KQ 4c: In adults with CATD and BPSD, what are the efficacy and harms of prescription pharmacological interventions versus placebo/inactive control for acute treatment of BPSD?

KQ 4d: In adults with CATD and BPSD, does the efficacy of prescription pharmacological interventions versus placebo/inactive control for acute treatment of BPSD vary as a function of patient characteristics (i.e., age, sex, race/ethnicity, depression, pre-treatment cognitive or functional level/CATD stage, pre-treatment BPSD severity, living setting)?

KQ 5: In adults with CATD and BPSD, what are the efficacy and harms of nonprescription pharmacological interventions versus placebo/inactive control for treatment of BPSD in adults with CATD and BPSD?

KQ 5a: In adults with CATD and BPSD, what are the efficacy and harms of nonprescription pharmacological interventions versus placebo/inactive control for reducing frequency and severity of future BPSD?

KQ 5b: In adults with CATD and BPSD, does the efficacy of nonprescription pharmacological interventions versus placebo/inactive control for reducing frequency and severity of future BPSD vary as a function of patient characteristics (i.e., age, sex, race/ethnicity, depression, pre-treatment cognitive or functional level/CATD stage, pre-treatment BPSD severity, living setting)?

KQ 5c: In adults with CATD and BPSD, what are the efficacy and harms of nonprescription pharmacological interventions versus placebo/inactive control for acute treatment of BPSD?

KQ 5d: In adults with CATD and BPSD, does the efficacy of nonprescription pharmacological interventions versus placebo/inactive control for acute treatment of BPSD vary as a function of patient characteristics (i.e., age, sex, race/ethnicity, depression, pre-treatment cognitive or functional level/CATD stage, pre-treatment BPSD severity, living setting)?

KQ 6: In adults with CATD and BPSD, what are the comparative effectiveness and harms of prescription pharmacological interventions versus other active interventions for treatment of BPSD?

KQ 6a: In adults with CATD and BPSD, what are the comparative effectiveness and harms of prescription pharmacological interventions versus other prescription pharmacological interventions for reducing frequency and severity of future BPSD?

KQ 6b: In adults with CATD and BPSD, what are the comparative effectiveness and harms of prescription pharmacological interventions versus nonprescription pharmacological interventions for reducing frequency and severity of future BPSD?

KQ 6c: In adults with CATD and BPSD, what are the comparative effectiveness and harms of prescription pharmacological interventions versus

nonpharmacological interventions for reducing frequency and severity of future BPSD?

KQ 6d: In adults with CATD and BPSD, does the comparative effectiveness of prescription pharmacological interventions versus other active interventions for reducing frequency and severity of future BPSD vary as a function of patient characteristics (i.e., age, sex, race/ethnicity, depression, pre-treatment cognitive or functional level/CATD stage, pre-treatment BPSD severity, living setting)?

KQ 6e: In adults with CATD and BPSD, what are the comparative effectiveness and harms of prescription pharmacological interventions versus other prescription pharmacological interventions for acute treatment of BPSD?

KQ 6f: In adults with CATD and BPSD, what are the comparative effectiveness and harms of prescription pharmacological interventions versus nonprescription pharmacological interventions for acute treatment of BPSD?

KQ 6g: In adults with CATD and BPSD, what are the comparative effectiveness and harms of prescription pharmacological interventions versus nonpharmacological interventions for acute treatment of BPSD?

KQ 6h: In adults with CATD and BPSD, does the comparative effectiveness of prescription pharmacological interventions versus other active interventions for acute treatment of BPSD vary as a function of 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 suspected CATD, what are the accuracy, comparative accuracy, and harms of different individual cognitive diagnostic tests and their combinations for making the diagnosis of CATD as defined by full clinical evaluation and/or neuropsychological testing with explicit diagnostic criteria?

KQ 7a: Do the accuracy and comparative accuracy of cognitive tests for making the diagnosis of CATD as defined by full clinical evaluation and/or neuropsychological testing with explicit diagnostic criteria vary as a

function of patient characteristics (i.e., age, sex, race/ethnicity, education, pre-testing cognitive or functional level CATD stage)?

KQ 8: In adults with a clinical diagnosis of CATD, what are the accuracy, comparative accuracy, and harms of brain imaging, CSF, and blood tests for diagnosing pathologically confirmed Alzheimer's disease as the underlying etiology?

KQ 8a: Do the accuracy and comparative accuracy of brain imaging, CSF, and blood tests for pathologically confirmed Alzheimer's disease as the underlying etiology of CATD vary as a function of patient characteristics (i.e., age, sex, race/ethnicity, depression, education, pre-testing cognitive or functional level CATD stage)?

Table 1. PICOTS (Populations, Interventions, Comparators, Outcomes, Timing, Settings/Study Design)

KQ	Population	Intervention	Treatment Comparator or Diagnostic Reference Standard	Health Outcomes & Harms	Timing	Setting	Study Design
KQ 1-3: Drug treatment efficacy, comparative effectiveness & harms on cognition, function & quality of life	Adults with CATD ≥50 years of age Patient characteristics to be assessed as possible treatment effect modifiers Age Sex Race/ethnicity Depression Pre-treatment cognitive or functional level/CATD stage Living setting	Prescription pharmacologic (drug) treatment Cholinesterase inhibitors NMDA antagonists Nonprescription pharmacologic (drug) treatment OTC supplements Vitamins Herbals	For efficacy comparisons Placebo Other inactive control For comparative effectiveness comparisons Prescription drug treatment Nonprescription drug treatment Nondrug treatment	Efficacy and comparative effectiveness: Change in patient cognition (global screen, multidomain, memory, executive function, language, attention), function, or QOL on validated test Change in disease stage based on validated test Change in patient "at home" IADL or ADL function Change in patient residence to different level of independence	≥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 with ≥1000 participants, systematic review of any of these study designs
KQ	Population	Intervention	Treatment Comparator or Diagnostic Reference Standard	Health Outcomes & Harms	Timing	Setting	Study Design

				Harms: *General* FDA defined SAEs Withdrawals due to AEs *Psychiatric* Somnolence Confusion/Delirium *Nonpsychiatric* Falls Extrapyramidal symptoms Stroke Mortality (all-cause, CVD, non-CVD)			

KQ	Population	Intervention	Treatment Comparator or Diagnostic Reference Standard	Health Outcomes & Harms	Timing	Setting	Study Design
KQ 4-6: Drug treatment efficacy, comparative effectiveness & harms on BPSD	Adults with CATD ≥50 years of age with BPSD (studies specified BPSD inclusion criterion)	Prescription pharmacologic treatment Cholinesterase inhibitors NMDA antagonists Antipsychotics, second generation (any) and first generation (only haloperidol) Antidepressants	Efficacy comparisons Placebo Other inactive control Comparative effectiveness comparisons Prescription drug	Efficacy and comparative effectiveness: *Primary* Change in the frequency and/or severity of patient BPSD* on validated tests	Agitation, aggression, psychosis or Disinhibited sexual behavior outcomes: ≥2 weeks	Community-dwelling Assisted living Nursing home	Efficacy and comparative effectiveness: RCT, CCT, systematic review of RCTs or CCTs Harms: RCT, CCT,

	Patient characteristics to be assessed as possible treatment effect modifiers Age Sex Race/ethnicity Pre-treatment cognitive or functional level/CATD stage Pre-treatment BPSD severity Living setting	Anti-seizure/mood stabilizers Anxiolytics, benzodiazepine Anxiolytics, other Hormonal agents (Disinhibited sexual behavior only) Cannabinoids Combinations Nonprescription pharmacologic treatment OTC supplements Vitamins Herbals	treatment Nonprescription drug treatment Nondrug treatment	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 tests Depression Global stress/distress QOL Burden	Depression or anxiety outcomes: ≥24 weeks		controlled prospective cohort studies ≥1000 participants, systematic review of any of these study designs
KQ	Population	Intervention	Treatment Comparator or Diagnostic Reference Standard	Health Outcomes & Harms	Timing	Setting	Study Design
				Harms: *General* FDA defined			

				composite SAE outcome Withdrawals due to AE *Psychiatric* Somnolence Confusion/Delirium *Nonpsychiatric* Falls Extrapyramidal symptoms Stroke Mortality (all-cause, CVD, non-CVD)			

KQ	Population	Intervention	Treatment Comparator or Diagnostic Reference Standard	Health Outcomes & Harms	Timing	Setting	Study Design
KQ 7-8: Diagnostic test accuracy & harms (also see Table 2 below)	Cognitive tests: Adults ≥50 years of age with suspected CATD Biomarker tests only: Adults ≥50 years of age with clinical	Brief, validated cognitive tests: Global (brief screens, multi-domain batteries) Single domain tests (memory, executive, language, attention Biomarker tests: *Brain imaging* CT/MRI Medial temporal atrophy/hippocampal	Cognitive tests: Full clinical evaluation and/or neuropsychological testing with explicit diagnostic criteria Biomarker tests: Postmortem neuropathological confirmation of AD	Accuracy and comparative accuracy (e.g., TP, FP, TN, FN, sensitivity, specificity, PPV, NPV) Of cognitive tests for confirming clinical syndrome of CATD Of biomarker tests	Any	Community-dwelling Assisted living	Accuracy and comparative accuracy: Controlled observational studies (i.e., cross-sectional, retrospective cohort, case control); systematic

	syndrome of CATD <u>Patient characteristics to be assessed as possible effect modifiers of diagnostic test accuracy</u> Age Sex Race/ethnicity Education Depression Pre-test cognitive or functional level/ CATD stage	volume Cortical thickness DTI indices PET ^{18}F-FDG PET Amyloid PET ^{11}C-PiB and fluorinated tracers (e.g. florbetapir, flutemetamol, florbetaben) Tau PET fMRI: resting state and task specific activation SPECT: resting state cerebral perfusion *CSF tests* Aß42 Aß42/Aß40 ratio t-tau p-tau t-tau/Aß42 ratio p-tau/Aß42 ratio		for confirming that etiology of CATD is AD <u>Harms</u>: *Psychological or behavioral* True positive: Labeling stigma False positive: Incorrect diagnosis Labeling stigma Side effects of unneeded interventions (e.g., restrictions on independence) False negative: Unexplained symptoms Failure to make appropriate			review of controlled observational studies <u>Harms:</u> Controlled observational studies (i.e., cross-sectional, retrospective cohort, case control, prospective cohort); systematic review of controlled observational studies
KQ	Population	Intervention	Treatment Comparator or Diagnostic Reference Standard	Health Outcomes & Harms	Timing	Setting	Study Design
		neurofilament light protein*Blood tests* Aß42 Aß42/Aß40 ratio APP *Combinations*		interventions (e.g., safety precautions, future planning) Any test result: Patient or caregiver mental distress *Physical* Directly from diagnostic tests:			

				Pain Infection Headache Radiation			

*For this report, two psychological symptoms that are components of BPSD have been excluded due to their coverage in recent, high quality systematic reviews – apathy and sleep disturbances.[18, 19] In addition, wandering was also eliminated, as this symptom is usually treated with nonpharmacologic interventions, which are not covered as interventions in this review.

†Strength of evidence (SOE) will be evaluated for the 1-2 most commonly reported validated treatment efficacy outcomes for each of the following test categories: disease stage, global cognitive screening tests, global multidomain cognitive tests, memory, executive functioning, language, attention, function, quality of life, BPSD agitation/aggression, and the harms outcome of serious adverse events. Additional treatment outcomes will be considered for SOE grading when available data allow. For diagnostic tests, SOE will be graded for the 1-2 most commonly reported validated tests for each of the following categories: global cognitive screening tests, global multidomain cognitive tests, memory, MRI, PET, and CSF tests. Additional diagnostic testing outcomes will be considered for SOE grading when available data allow.

Aß = beta amyloid, AD = Alzheimer's dementia, ADL = activities of daily living, AE = adverse events, APOE = apolipoprotein E, 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, CVD = cardiovascular disease, DTI = diffusion tensor imaging, FDG = fluorodeoxyglucose, fMRI = functional magnetic resonance imaging, FN = false negative, FP = false positive, IADL = instrumental activities of daily living, MCI = mild cognitive impairment, MRI = magnetic resonance imaging, NMDA = N-methyl-D-aspartate, NPV = negative predictive value, OTC = over-the-counter, PET = positron emission tomography, PPV = positive predictive value, p-tau = abnormally phosphorylated tau, QOL = quality of life, RCT = randomized clinical trial, ROC = receiver operating characteristic, SAE = serious adverse events, SPECT = single-photon emission computed tomography, TN = true negative, TP = true positive, t-tau = total tau

Table 2. Prescription Drugs Used for Treatment of CATD Cognition, Function, Quality of Life 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

*US FDA approved indication for Alzheimer's dementia

†Excludes MAO-inhibitor, tricyclic and tetracyclic antidepressants.

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

References

1. Plassman BL, Langa KM, Fisher GG, et al. Prevalence of dementia in the United States: the aging, demographics, and memory study. Neuroepidemiology. 2007;29(1-2):125-32. doi: 10.1159/000109998. PMID: 17975326.
2. Langa KM, Larson EB, Crimmins EM, et al. A Comparison of the Prevalence of Dementia in the United States in 2000 and 2012. JAMA Intern Med. 2017 Jan 01;177(1):51-8. doi: 10.1001/jamainternmed.2016.6807. PMID: 27893041.
3. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011 May;7(3):263-9. doi: 10.1016/j.jalz.2011.03.005. PMID: 21514250.
4. Hurd MD, Martorell P, Delavande A, et al. Monetary costs of dementia in the United States. N Engl J Med. 2013 Apr 4;368(14):1326-34. doi: 10.1056/NEJMsa1204629. PMID: 23550670.
5. Zhao QF, Tan L, Wang HF, et al. The prevalence of neuropsychiatric symptoms in Alzheimer's disease: Systematic review and meta-analysis. J Affect Disord. 2016 Jan 15;190:264-71. doi: 10.1016/j.jad.2015.09.069. PMID: 26540080.
6. What is Alzheimer's? Alzheimer's Association. www.alz.org/alzheimers-dementia/what-is-alzheimers. Accessed on November 2, 2018.
7. Alzheimer's Disease. Centers for Disease Control and Prevention. www.cdc.gov/aging/aginginfo/alzheimers.htm. Accessed on November 2, 2018.
8. Association AP. Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-IIIR); 1987.
9. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of

Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology. 1984 Jul;34(7):939-44. PMID: 6610841.

10. Association AP. Diagnostic and Statistical Manual of Mental Disorders: DSM-5; 2013.

11. Cure S, Abrams K, Belger M, et al. Systematic literature review and meta-analysis of diagnostic test accuracy in Alzheimer's disease and other dementia using autopsy as standard of truth. J Alzheimers Dis. 2014;42(1):169-82. doi: 10.3233/JAD-131559. PMID: 24840572.

12. Frisoni GB, Boccardi M, Barkhof F, et al. Strategic roadmap for an early diagnosis of Alzheimer's disease based on biomarkers. Lancet Neurol. 2017 Aug;16(8):661-76. doi: 10.1016/S1474-4422(17)30159-X. PMID: 28721928.

13. Kane RLB, M.; Fink, H.A.; Brasure, M.; Davila, H.; Desai, P.; Jutkowitz, E.; McCreedy, E.; Nelson, V.A.; McCarten, J.R.; Calvert, C.; Ratner, E.; Hemmy, L.S.; Barclay, T. Interventions To Prevent Age-Related Cognitive Decline, Mild Cognitive Impairment, and Clinical Alzheimer's-Type Dementia. AHRQ Publication No. 17-EHC008-EF. Rockville, MD: Quality AfHRa; February 2017 2017. www.effectivehealthcare.ahrq.gov/reports/final.cfm

14. Reus VI, Fochtmann LJ, Eyler AE, et al. The American Psychiatric Association Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients With Dementia. Am J Psychiatry. 2016 May 1;173(5):543-6. doi: 10.1176/appi.ajp.2015.173501. PMID: 27133416.

15. Brasure M, Jutkowitz E, Fuchs E, et al. Nonpharmacologic Interventions for Agitation and Aggression in Dementia. Rockville (MD); 2016.

16. Qaseem A, Snow V, Cross JT, Jr., et al. Current pharmacologic treatment of dementia: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. Ann Intern Med. 2008 Mar 4;148(5):370-8. PMID: 18316755.

17. Kales HC, Gitlin LN, Lyketsos CG. Assessment and management of behavioral and psychological symptoms of dementia. BMJ. 2015 Mar 2;350:h369. doi: 10.1136/bmj.h369. PMID: 25731881.

18. Ruthirakuhan MT, Herrmann N, Abraham EH, et al. Pharmacological interventions for apathy in Alzheimer's disease. Cochrane Database Syst Rev. 2018 May 4;5:CD012197. doi: 10.1002/14651858.CD012197.pub2. PMID: 29727467.

19. McCleery J, Cohen DA, Sharpley AL. Pharmacotherapies for sleep disturbances in dementia. Cochrane Database Syst Rev. 2016 Nov 16;11:CD009178. doi: 10.1002/14651858.CD009178.pub3. PMID: 27851868.

20. Hackshaw A. Small studies: strengths and limitations. Eur Respir J. 2008 Nov;32(5):1141-3. doi: 10.1183/09031936.00136408. PMID: 18978131.

21. Viswanathan M, Ansari M, Berkman N, et al. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions AHRQ. 2012.

22. Methods Guide for Medical Test Reviews. AHRQ Publication No. 12-EC017. Rockville, MD: Quality AfHRa; June 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

23. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011 Oct 18;155(8):529-36. doi: 10.7326/0003-4819-155-8-201110180-00009. PMID: 22007046.

24. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008. doi: 10.1136/bmj.j4008. PMID: 28935701.

25. Fu R, Gartlehner G, Grant M, et al. Conducting quantitative synthesis when comparing medical interventions: AHRQ and the Effective Health Care Program. J Clin Epidemiol. 2011 Nov;64(11):1187-97. doi: 10.1016/j.jclinepi.2010.08.010. PMID: 21477993.

26. Takwoingi Y. Meta-analysis of test accuracy studies in Stata: a bivariate model approach. Version 1.1.

27. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions--agency for healthcare research and quality and the effective health-care program. J Clin Epidemiol. 2010 May;63(5):513-23. doi: S0895-4356(09)00093-6 [pii]

10.1016/j.jclinepi.2009.03.009. PMID: 19595577.

28. Singh S, Chang SM, Matchar DB, et al. Chapter 7: grading a body of evidence on diagnostic tests. J Gen Intern Med. 2012 Jun;27 Suppl 1:S47-55. doi: 10.1007/s11606-012-2021-9. PMID: 22648675.

29. Berkman ND, Lohr KN, Ansari M, et al. Grading the Strength of a Body of Evidence When Assessing Health Care Interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: An Update. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville (MD); 2008.

30. Atkins D, Chang S, Gartlehner G, et al. Assessing the Applicability of Studies When Comparing Medical Interventions. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville (MD); 2008.

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