Annals of Internal Medicine REVIEW

Pharmacologic Interventions to Prevent Cognitive Decline, Mild Cognitive Impairment, and Clinical Alzheimer-Type Dementia

A Systematic Review

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Background: Optimal treatment to prevent or delay cognitive decline, mild cognitive impairment (MCI), or dementia is uncertain.

Purpose: To summarize current evidence on the efficacy and harms of pharmacologic interventions to prevent or delay cognitive decline, MCI, or dementia in adults with normal cognition or MCI.

Data Sources: Several electronic databases from January 2009 to July 2017, bibliographies, and expert recommendations.

Study Selection: English-language trials of at least 6 months' duration enrolling adults without dementia and comparing pharmacologic interventions with placebo, usual care, or active control on cognitive outcomes.

Data Extraction: Two reviewers independently rated risk of bias and strength of evidence; 1 extracted data, and a second checked accuracy.

Data Synthesis: Fifty-one unique trials were rated as having low to moderate risk of bias (including 3 that studied dementia medications, 16 antihypertensives, 4 diabetes medications, 2 nonsteroidal anti-inflammatory drugs [NSAIDs] or aspirin, 17 hormones, and 7 lipid-lowering agents). In persons with normal cognition, estrogen and estrogen–progestin increased risk for dementia or a combined outcome of MCI or dementia (1 trial, low strength of evidence); high-dose raloxifene decreased risk for MCI but not for dementia (1 trial, low strength of evidence); and antihypertensives (4 trials), NSAIDs (1 trial), and statins (1 trial) did not alter dementia risk (low to insufficient strength of evidence). In persons with MCI, cholinesterase inhibitors did not reduce dementia risk (1 trial, low strength of evidence). In persons with normal cognition and those with MCI, these pharmacologic treatments neither improved nor slowed decline in cognitive test performance (low to insufficient strength of evidence). Adverse events were inconsistently reported but were increased for estrogen (stroke), estrogen–progestin (stroke, coronary heart disease, invasive breast cancer, and pulmonary embolism), and raloxifene (venous thromboembolism).

Limitation: High attrition, short follow-up, inconsistent cognitive outcomes, and possible selective reporting and publication.

Conclusion: Evidence does not support use of the studied pharmacologic treatments for cognitive protection in persons with normal cognition or MCI.

Primary Funding Source: Agency for Healthcare Research and Quality.

Ann Intern Med. 2018;168:39-51. doi:10.7326/M17-1529 **Annals.org**

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This article was published at Annals.org on 19 December 2017.

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Dementia is a clinical syndrome in which an acquired cognitive deficit interferes with a person's independence in daily activities (1). It adversely affects patient quality of life, burdens caregivers, increases institutionalization, and is costly to families and society (2). Alzheimer disease is the most common cause of dementia, although differentiation between when Alzheimer disease is present in isolation and when it is combined with another cause of dementia may not be possible in clinical settings. Mild cognitive impairment (MCI) is an acquired cognitive deficit in the absence of functional impairment (3, 4) and often leads to dementia (5).

Analyses have suggested that behavioral and pharmacologic interventions targeting potentially modifiable risk factors could substantially reduce Alzheimer disease prevalence (6). We did a systematic review of clinical trials to assess the most current evidence about the efficacy and safety of pharmacologic interventions for preventing or delaying cognitive decline, MCI, and dementia and whether effects differ by patient characteristics.

METHODS

We developed and followed a standard protocol (7). The full technical report (8) contains detailed findings.

Data Sources

We searched MEDLINE, PsycINFO, Embase, and the Cochrane Library for studies published between January 2009 and July 2017 (Part A of the **Supplement**, available at Annals.org). We identified earlier studies from a 2010 Agency for Healthcare Research and Quality (AHRQ) report on interventions for preventing Alzheimer disease and cognitive decline (9). We also

See also:

Related articles. 30, 52, 63
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searched reference lists of eligible studies and articles suggested by experts.

Study Selection

We included English-language randomized and nonrandomized controlled trials of adults without dementia (that is, with normal cognition or MCI) that compared U.S. Food and Drug Administration–approved prescription medications versus placebo or any control. Minimum follow-up was 6 months. Primary outcomes were cognitive diagnoses of MCI or dementia (Alzheimer disease or unspecified type, but excluding other specific causes, such as dementia attributable solely to a clinically recognized stroke). Secondary outcomes were measures of cognitive performance assessed by validated instruments. Two reviewers independently examined titles, abstracts, and full articles for eligibility and resolved discrepancies by consensus.

Data Extraction and Quality Assessment

For each study, 2 reviewers directly and independently rated risk of bias for outcomes of interest and the study overall as low, medium, or high on the basis of AHRQ criteria (10, 11). One reviewer extracted the study design, participant characteristics, pharmacologic interventions, and funding source from all eligible studies but extracted outcomes and adverse events only from studies with low or moderate risk of bias. A second reviewer checked the accuracy of the extracted data.

Data Synthesis and Analysis

We organized results by intervention type and categorized study participants by baseline cognitive status (normal or MCI). We grouped cognitive tests into memory tests; global cognitive screening tests (such as the Mini-Mental State Examination [MMSE]) or multidomain neuropsychological tests (such as the Alzheimer's Disease Assessment Scale–Cognitive Subscale); and tests of executive function, attention, and processing speed (Part B of the Supplement). We analyzed and reported cognitive test results by direction of effect and statistical significance because different cognitive tests were used, tests were analyzed and reported in many ways, and we were frequently unable to determine effect size or assess whether between-group differences in scores were clinically meaningful. Because of heterogeneity in study designs and outcomes, results were not pooled in meta-analyses.

When a treatment comparison had at least 2 studies or 1 large study (≥500 participants), 2 reviewers graded strength of evidence for each outcome on the basis of study limitations, directness, consistency, and precision (12); strength of evidence for single smaller trials was graded as insufficient. Assessments were confirmed by consensus.

Role of the Funding Source

This review was funded by the National Institute on Aging and AHRQ. These agencies and members of the National Academies Committee on Preventing Dementia and Cognitive Impairment helped refine the scope and reviewed the draft AHRQ report. The authors are solely responsible for the content of the manuscript and decision to submit it for publication.

RESULTS

We identified 102 eligible studies of pharmacologic treatments; 51 unique trials had low or medium risk of bias and were included in analyses (Appendix Figure, available at Annals.org). Of these, 32 received at least some industry funding. Trials in which baseline cognitive test results were essentially normal and those providing no baseline cognitive data were categorized as enrolling participants with normal baseline cognition. Most studies that enrolled participants with cognitive impairment (13–20) specified that participants had MCI defined by the Petersen criteria (13, 17–20). The Table shows main efficacy results for all interventions. Details on study and participant characteristics, including cognitive test characteristics, age, baseline cognition, risk-of-bias ratings, funding source, and strength-of-evidence ratings, are presented by pharmacologic intervention in Parts C to H of the Supplement.

Dementia Medications

Among 15 eligible references (13, 14, 19, 21–32), 3 unique trials had low to moderate risk of bias (13, 14, 19, 32) (Part C of the Supplement). These trials provided mostly low-strength evidence that acetylcholinesterase inhibitors do not reduce risk for dementia or improve cognitive test performance versus placebo in older adults with MCI; they gave insufficient evidence about persons with normal cognition.

Most evidence came from 1 trial of 512 adults (mean age, 73 years) with MCI who were randomly assigned to receive donepezil or placebo (13, 19). After 3 years, the treatment groups did not differ in progression to Alzheimer disease (HR, 0.80 [95% CI, 0.57 to 1.13]) (low strength of evidence) or in any cognitive test (insufficient to low strength of evidence). In participants with at least 1 apolipoprotein E ε4 allele, those assigned to donepezil progressed to Alzheimer disease less often than those assigned to placebo, although results were not statistically significant after correction for multiple comparisons. Participants who received donepezil were more likely to have adverse gastrointestinal symptoms, sleep disturbances, and arthritis.

Antihypertensive Medications

Antihypertensive Medication Versus Placebo

Among 14 eligible references (33–46), 8 unique trials had low to moderate risk of bias (33–44) (Part D of the Supplement). These trials enrolled 31 287 participants (mean age among 7 trials reporting, 70.2 years). Low-strength evidence in adults with normal cognition showed that antihypertensive treatment versus placebo does not reduce risk for dementia, and moderate-strength evidence showed no difference between these treatments on global cognitive screening tests. No trials reported data about persons with MCI.

Table. Effect of Pharmacologic Interventions Versus Control on Cognitive Outcomes in Adults With Normal Cognition and MCI

Outcome	Conclusion for Normal Cognition	Strength of Evidence (Justification)	Conclusion for MCI	Strength of Evidence (Justification)
Dementia medication vs. placebo (*k* = 3; *n* = 561)				
Dementia	No data	Insufficient	No benefit (RR, 0.80 [95% CI, 0.57–1.13]) (*k* = 1; *n* = 512; 3 y)	Low (SLM, UC)
MCI	No data	Insufficient	Not applicable	Not applicable
Brief cognitive test	No data	Insufficient	No benefit (*k* = 2; *n* = 533;1–3 y)	Low (SLM, ND, NC)
Multidomain tests	No data	Insufficient	No benefit (*k* = 1; *n* = 512; 3 y)	Low (SLM, ND, UC)
Executive function/attention/ processing speed	No benefit (*k* = 1; *n* = 26; 6 mo)	Insufficient (SLM, ND, NP)	No benefit	Insufficient (SLM, ND, NP)
Memory	No benefit (*k* = 1; *n* = 26; 6 mo)	Insufficient (SLM, ND, NP)	No benefit	Insufficient (SLM, ND, NP)
Antihypertensive medication vs. placebo (*k* = 8; *n* = 31 287)				
Dementia	Increased benefit in 1 of 4 trials (*k* = 4; *n* = 21 831; 2.2–4.3 y)	Low (SLM, NP, NC)	No data	Insufficient
MCI	No data	Insufficient	Not applicable	Not applicable
Incident cognitive impairment (dementia, cognitive impairment, or MMSE score <24)	No benefit (OR, 0.90 [95% CI, 0.80–1.01]) (*k* = 1; *n* = 5926; 4.7 y)	Low (SLM, ND, UC)	Not applicable	Not applicable
Brief cognitive test	No benefit (*k* = 4; *n* = 11 242; 2–4.7 y)	Insufficient (SLM, ND, NP)	No data	Insufficient
Multidomain tests	No data	Insufficient	No data	Insufficient
Executive function/attention/ processing speed	Increased benefit in 1 of 9 tests (*k* = 3; *n* = 3254; 9 mo–3.7 y)	Insufficient (SLM, ND, NP, NC)	No data	Insufficient
Memory	Increased benefit in 1 of 3 tests (*k* = 2; *n* = 2703; 9 mo–3.7 y)	Insufficient (SLM, ND, NP, NC)	No data	Insufficient
Intensive vs. standard antihypertensive medication treatment (*k* = 1; *n* = 1439)				
Dementia	No data	Insufficient	No data	Insufficient
MCI	No data	Insufficient	Not applicable	Not applicable
Brief cognitive test	No benefit (*k* = 1; *n* = 1439; 40 mo)	Low (SLM, ND, UC)	No data	Insufficient
Multidomain tests	No data	Insufficient	No data	Insufficient
Executive function/attention/ processing speed	No benefit (*k* = 1; *n* = 1439; 40 mo)	Low (SLM, ND, NP)	No data	Insufficient
Memory	No benefit (*k* = 1; *n* = 1439; 40 mo)	Low (SLM, ND, UC)	No data	Insufficient
Antihypertensive medication vs. antihypertensive medication (*k* = 9; *n* = 29 014)				
Dementia	No data	Insufficient	No data	Insufficient
MCI	No data	Insufficient	Not applicable	Not applicable
Incident cognitive impairment (dementia, cognitive impairment, or MMSE score <24)	No benefit (*k* = 1; *n* = 25 620; 4.7 y)	Low (SLM, ND, UC)	Not applicable	Not applicable
Brief cognitive test	Increased benefit in 2 of 6 tests (*k* = 3; *n* = 25 831; 1–4.7 y)	Insufficient (SLM, ND, NP, NC)	No data	Insufficient
Multidomain tests	No data	Insufficient	No data	Insufficient
Executive function/attention/ processing speed	No benefit (*k* = 3; *n* = 2614; 24 wk–9 mo)	Low (SLM, ND, NP)	No benefit (*n* = 81; 6 mo)	Insufficient (SLM, ND, NP, UC)
Memory	Increased benefit in 3 of 7 tests (*k* = 4; *n* = 2734; 24 wk–9 mo)	Insufficient (SLM, ND, NP, NC)	No benefit (*n* = 81; 6 mo)	Insufficient (SLM, ND, NP, UC)
Intensive vs. standard diabetes medication treatment (*k* = 2; *n* = 15 514)				
Dementia	No data	Insufficient	No data	Insufficient
MCI	No data	Insufficient	Not applicable	Not applicable

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Outcome	Conclusion for Normal Cognition	Strength of Evidence (Justification)	Conclusion for MCI	Strength of Evidence (Justification)
Incident cognitive impairment (incident dementia or MMSE score <24)	No benefit (HR, 0.93 [95% CI, 0.86–1.00]) (k = 1; n = 11 685; 6.2 y)	Low (SLH, UC)	No data	Insufficient
Brief cognitive test	No benefit (k = 2; n = 14 479; 3.3–6.2 y)	Low (SLM, ND, NP)	No data	Insufficient
Multidomain tests	No data	Insufficient	No data	Insufficient
Executive function/attention/processing speed	No benefit (k = 2; n = 14 479; 3.3–6.2 y)	Low (SLM, ND, NP)	No data	Insufficient
Memory	No benefit (k = 1; n = 2794; 3.3 y)	Low (SLM, ND, NP)	No data	Insufficient
Statin plus fenofibrate vs. statin (k = 1; n = 1538)				
Dementia	No data	Insufficient	No data	Insufficient
MCI	No data	Insufficient	Not applicable	Not applicable
Brief cognitive test	No difference (k = 1; n = 1538; 3.3 y)	Low (ND, UC)	No data	Insufficient
Multidomain tests	No data	Insufficient	No data	Insufficient
Executive function/attention/processing speed	No difference (k = 1; n = 1538; 3.3 y)	Low (ND, NP)	No data	Insufficient
Memory	No difference (k = 1; n = 1538; 3.3 y)	Low (ND, UC)	No data	Insufficient
NSAID vs. placebo (k = 1; n = 2528)				
Dementia	No benefit Celecoxib: HR, 1.03 (95% CI, 0.72–1.50) Naproxen: HR, 0.92 (95% CI, 0.62–1.35) (k = 1; n = 2117; 8 y)	Low (SLM, UC)	No data	Insufficient
MCI	No data	Insufficient	Not applicable	Not applicable
Brief cognitive test	No difference (k = 1; n = 2117; 4 y)	Insufficient (SLM, ND, NP, UC)	No data	Insufficient
Multidomain tests	No difference (k = 1; n = 2117; 4 y)	Low (SLM, ND, UC)	No data	Insufficient
Executive function/attention/processing speed	No difference (k = 1; n = 2117; 4 y)	Low (SLM, ND, NP)	No data	Insufficient
Memory	No difference (k = 1; n = 2117; 4 y)	Low (SLM, ND, NP)	No data	Insufficient
Aspirin vs. placebo (k = 1; n = 6377)				
Dementia	No data	Insufficient	No data	Insufficient
MCI	No data	Insufficient	Not applicable	Not applicable
Brief cognitive test	No difference (k = 1; n = 6377; 9.6 y)	Low (SLM, ND, UC)	No data	Insufficient
Multidomain tests	No difference (k = 1; n = 6377; 9.6 y)	Low (SLM, ND, UC)	No data	Insufficient
Executive function/attention/processing speed	No data	Insufficient	No data	Insufficient
Memory	No difference (k = 1; n = 6377; 9.6 y)	Low (SLM, ND, UC)	No data	Insufficient
Estrogen vs. placebo (k = 6; n = 4117)				
Dementia	No benefit (HR, 1.49 [95% CI, 0.83–2.66]) (k = 1; n = 2947; 5.2 y)	Low (SLM, UC)	No data	Insufficient
MCI	No benefit (HR, 1.34 [95% CI, 0.95–1.89]) (k = 1; n = 2947; 5.2 y)	Low (SLM, UC)	Not applicable	Not applicable
Dementia or MCI	Increased harm (HR, 1.38 [95% CI, 1.01–1.89]) (k = 1; n = 2947; 5.2 y)	Low (SLM, UC)	Not applicable	Not applicable
Brief cognitive test	Increased harm in 1 of 2 tests (k = 2; n = 3364; 2–5.4 y)	Low (SLM, ND, UC)	No data	Insufficient

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Outcome	Conclusion for Normal Cognition	Strength of Evidence (Justification)	Conclusion for MCI	Strength of Evidence (Justification)
Multidomain tests	No benefit (k = 1; n = 567; 2.5 y)	Insufficient (SLM, ND, UC)	No data	Insufficient
Executive function/attention/ processing speed	Increased benefit in 2 of 19 tests (k = 6; n = 4117; 6 mo–5.2 y)	Insufficient (SLM, ND, NP)	No data	Insufficient
Memory	Increased benefit in 2 of 35 tests (k = 6; n = 4117; 6 mo–5.2 y)	Insufficient (SLM, ND, NP)	No data	Insufficient
Estrogen plus progestin vs. placebo (k = 5; n = 6242)				
Dementia	Increased harm (HR, 2.05 [95% CI, 1.21–3.48]) (k = 1; n = 4532; 4.1 y)	Low (SLM, UC)	No data	Insufficient
MCI	No benefit (HR, 1.07 [95% CI, 0.74–1.55]) (k = 1; n = 4532; 4.1 y)	Low (SLM, UC)	Not applicable	Not applicable
Dementia or MCI	No benefit (HR, 1.37 [95% CI, 0.99–1.89]) (k = 1; n = 4532; 4.1 y)	Low (SLM, UC)	Not applicable	Not applicable
Brief cognitive test	Increased harm in 1 of 4 tests (k = 3; n = 4353; 3.2–5.4 y)	Low (SLM, ND, NC)	No data	Insufficient
Multidomain tests	No data	Insufficient	No data	Insufficient
Executive function/attention/ processing speed	Increased harm in 1 of 9 tests (k = 4; n = 4376; 6 mo–5.4 y)	Low (SLM, ND, NP)	No data	Insufficient
Memory	Increased harm in 4 of 16 tests (k = 5; n = 4518; 6 mo–5.4 y)	Low (SLM, ND, NP)	No data	Insufficient
SERM vs. placebo (k = 2; n = 7621)				
Dementia	No benefit Raloxifene, 60 mg/d: RR, 0.90 (95% CI, 0.47–1.74) Raloxifene, 120 mg/d: RR, 0.91 (95% CI, 0.47–1.76) (k = 1; n = 5386; 3 y)	Low (SLM, UC)	No data	Insufficient
MCI	No benefit for raloxifene, 60 mg/d: RR, 1.18 (95% CI, 0.85–1.64) Increased benefit for raloxifene, 120 mg/d: RR, 0.67 (95% CI, 0.46–0.98) (k = 1; n = 5386; 3 y)	Low (SLM, UC)	Not applicable	Not applicable
Dementia or MCI	No benefit Raloxifene, 60 mg/d: RR, 1.12 (95% CI, 0.84–1.49) Raloxifene, 120 mg/d: RR, 0.73 (95% CI, 0.53–1.01) (k = 1; n = 5386; 3 y)	Low (SLM, UC)	Not applicable	Not applicable
Brief cognitive test	No data	Insufficient	No data	Insufficient
Multidomain tests	No benefit (k = 2; n = 7621; 1–3 y)	Insufficient (SLM, ND, NP)	No data	Insufficient
Executive function/attention/ processing speed	No benefit (k = 2; n = 7621; 1–3 y)	Insufficient (SLM, ND, NP)	No data	Insufficient
Memory	No benefit (k = 2; n = 7621; 1–3 y)	Insufficient (SLM, ND, NP)	No data	Insufficient
Testosterone vs. placebo (k = 3; n = 565)				
Dementia	No data	Insufficient	No data	Insufficient
MCI	No data	Insufficient	Not applicable	Not applicable
Brief cognitive test	No benefit (k = 1; n = 50; 28 wk)	Insufficient (SLM, ND, UP, UC)	No benefit (k = 1; n = 493; 1 y)	Insufficient (ND, UC)
Multidomain tests	No data	Insufficient	No data	Insufficient
Executive function/attention/ processing speed	No data	Insufficient	No benefit (k = 2; n = 515; 6–12 mo)	Low (ND, NP)
Memory	No benefit (k = 1; n = 50; 28 wk)	Insufficient (SLM, ND, UP, UC)	No benefit (k = 2; n = 515; 6–12 mo)	Low (ND, NP)

HR = hazard ratio; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; NC = not consistent; ND = not direct; NP = not precise; NSAID = nonsteroidal anti-inflammatory drug; OR = odds ratio; RR = relative risk; SERM = selective estrogen receptor modulator; SLH = study limitations high; SLM = study limitations medium; UC = unknown consistency; UP = unknown precision.

Evidence on risk for dementia was based on 4 trials. With antihypertensive treatment, the Syst-Eur (Systolic Hypertension in Europe) trial reported a halving of incident dementia of marginal statistical significance (35, 36), although 3 subsequent and larger trials each reported no reduced risk for dementia (38, 42, 43). TRANSCEND (Telmisartan Randomised Assessment Study in Angiotensin Converting Enzyme Inhibitor Intolerant Subjects with Cardiovascular Disease) reported no difference between antihypertensive treatment and placebo in incident cognitive impairment, defined as a composite of incident dementia, incident cognitive impairment, or MMSE score less than 24 (low strength of evidence) (33). Four trials reported no difference between antihypertensive treatment and placebo in change on global cognitive screening tests (moderate strength of evidence) (33, 35, 36, 38, 43), whereas weaker evidence suggested no difference between treatment groups for other cognitive tests (34, 37–40). In the only trial that reported subgroup analyses, treatment effects on risk for incident cognitive impairment and cognitive test performance did not differ as a function of age or history of hypertension, stroke, or transient ischemic attack (33). In the 3 studies that reported adverse effects (38, 41, 43), other than for methyldopa (41) no consistent differences existed between active treatment and placebo.

Intensive Versus Standard Antihypertensive Treatment

One unique trial with moderate risk of bias randomly assigned 1439 adults (mean age, 62.4 years) with normal cognition, diabetes, and heightened cardiovascular risk to a systolic blood pressure target of less than 120 mm Hg or less than 140 mm Hg for 40 months. It reported no data on MCI or dementia outcomes and no between-group difference in any measured cognitive test (low strength of evidence) (47). Participants aged 70 years or older did better with intensive than standard treatment on a single evaluated memory test and 1 of 2 tests of executive function, attention, and processing speed; however, performance did not differ by sex, baseline cognition, cardiovascular disease history, or diabetes duration. Adverse events data were not reported.

Antihypertensive Medication Comparisons

Among 11 eligible references (15, 16, 33, 34, 41, 48–53), 9 unique trials (15, 16, 33, 34, 41, 48–52) had low to moderate risk of bias. These trials enrolled 28 933 adults with normal cognition (mean age, 66.6 years) and 81 with MCI (baseline MMSE score range, 20 to 28; mean age, 76.1 years) (15, 16). Findings suggest that antihypertensive regimens do not differ in cognitive test performance (low to insufficient strength of evidence). In adults with normal cognition, ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) (n = 25 620; mean age, 66.4 years; MMSE score range, 24 to 30) reported no statistically significant difference in risk for incident cognitive impairment (composite of incident dementia, incident cognitive impairment, or MMSE score <24) between active antihypertensive treatment groups (low strength of evidence) (33). Trials provided no information about relative effects of antihypertensive regimens on risk for MCI or dementia. The only trial that did subgroup analyses reported no differential effects of treatment on any cognitive outcomes as a function of age or history of hypertension, stroke, or transient ischemic attack (33). In the studies that reported adverse events (41, 48–50), other than for methyldopa (41) no consistent differences existed between antihypertensive treatment regimens.

Diabetes Medications

Among 8 eligible references (17, 20, 54–59), 4 unique trials had low to moderate risk of bias (17, 20, 54, 56, 59) (Part E of the Supplement). In adults with normal cognition, trials provided no evidence about whether intensive versus standard glucose control reduces risk for MCI or dementia and low-strength evidence that intensive diabetes treatment does not improve performance on cognitive tests.

Evidence for adults with normal cognition was based on the ACCORD-MIND (Action to Control Cardiovascular Risk in Diabetes–Memory in Diabetes) (54, 56) and ORIGIN (Outcome Reduction with Initial Glargine Intervention) (59) randomized trials, which collectively assigned 14 662 adults (mean age, 63.2 years) with diabetes and high risk for cardiovascular events to intensive versus standard glucose control for 3.3 and 6.2 years, respectively. The ORIGIN trial reported no difference between treatment groups in incident cognitive impairment (case report of dementia or MMSE score <24) (low strength of evidence). Both studies showed no between-treatment difference in change in any evaluated cognitive test (all low strength of evidence) (Supplement). ORIGIN reported no consistent difference in cognitive test performance as a function of age, sex, baseline diabetes severity, depression, or education. Neither trial reported adverse events, but the main ACCORD trial reported that participants assigned to intensive glucose control had increased risk for hypoglycemia, weight gain, and death (60).

Data from 2 small 6- to 12-month trials in overweight middle-aged and older adults with MCI provided insufficient evidence about the effect of diabetes treatment on cognitive performance tests in this population (17, 20).

Lipid-Lowering Medications

Among 10 eligible references (47, 61–69), 7 unique trials had low to moderate risk of bias (47, 61–64, 66, 67) (Part F of the Supplement). These trials enrolled 23 097 adults with normal cognition (mean age range, 46.4 to 76.3 years). They provided insufficient-strength evidence about whether treatment with HMG-CoA reductase inhibitors (statins) reduces risk for MCI or dementia and low-strength evidence that statins do not improve performance on cognitive tests. No trials provided data about persons with MCI.

Evidence about risk for dementia with statins versus placebo was based on a single 5-year randomized controlled trial (62) that assigned 20 536 persons to receive 40 mg of simvastatin or placebo daily. The trial reported no difference between treatment groups, but very few participants developed dementia. This trial and a smaller 6-month trial (66) reported no difference between statin and placebo in single tests of executive function, attention, and processing speed and global cognitive screening tests, respectively. However, 2 other small 6-month trials reported less improvement with statin than placebo in executive function, attention, and processing speed tests but no between-group differences in memory tests (63, 64). One trial reported that participants assigned to statins had an increased risk for abdominal pain or cramps (66), whereas 3 trials reported no differences in adverse events (62–64). None of these trials reported subgroup data.

A single trial that compared statin plus fenofibrate versus statin alone in 503 adults with diabetes reported that cognitive test performance did not differ between treatment groups (low strength of evidence) (47). The authors found no consistent differences in results for any participant characteristic evaluated and reported no adverse events. Trials comparing statin plus ezetimibe versus placebo in persons with atrial fibrillation (67) and statin versus α-tocopherol (61) enrolled fewer than 50 participants each and provided insufficient evidence about treatment differences in any cognitive outcome.

Nonsteroidal Anti-inflammatory Drugs

Among 8 eligible references (70–77), 2 unique trials had low to moderate risk of bias (70–74, 77) (Part G of the Supplement). In older adults with normal cognition, trials provided low-strength evidence that nonsteroidal anti-inflammatory drugs (NSAIDs) do not reduce risk for dementia and mostly low-strength evidence that neither NSAIDs nor aspirin improves cognitive test performance. No trials provided data about persons with MCI.

Evidence for NSAIDs was based on ADAPT (Alzheimer's Disease Anti-Inflammatory Prevention Trial), which randomly assigned 2528 older adults (median age, 74 years) with at least 1 first-degree relative with Alzheimer disease to receive naproxen, celecoxib, or placebo. Masked treatment was stopped after a median of 15 months (78), after which unmasked follow-up was continued. ADAPT reported no difference between either NSAID group and placebo in incident dementia at 8 years (low strength of evidence) or in any evaluated cognitive tests at 4 years (low to insufficient strength of evidence) (70–73, 77). Treatment results did not differ by apolipoprotein E ε4 status (77). Risks for 2 post hoc cardiovascular outcomes were significantly higher with naproxen than placebo but no different with celecoxib. Risk for hypertension was significantly higher in both NSAID groups than the placebo group (79).

Evidence for aspirin was based on a Women's Health Study substudy, in which 6377 participants were randomly assigned to receive low-dose aspirin or placebo (mean age at baseline cognitive assessment, 71.8 years) (74). Those assigned aspirin did no better than those assigned placebo in change over 4 years on either global cognitive screening or memory tests (low strength of evidence). Aspirin was associated with less cognitive decline than placebo in 2 of 14 subgroups (current smokers and participants with hyperlipidemia). Adverse events were not reported.

Hormone Therapy

Estrogen Only

Among 14 eligible references (80–93), 6 unique trials had low to moderate risk of bias (80–92) (Part H of the Supplement). In women with normal cognition, trials provided low-strength evidence that estrogen increases risk for a combined outcome of MCI or dementia and does not improve performance on cognitive tests. No trials gave data about women with MCI.

Evidence for the effect of estrogen on clinical diagnoses was based on WHIMS (Women's Health Initiative Memory Study) data. This trial randomly assigned 2947 women aged 65 years or older to receive estrogen or placebo for a mean of 5.2 years; those assigned estrogen had a significantly higher incidence of a combined outcome of MCI or dementia, although not of MCI or dementia as individual outcomes (low strength of evidence). Results did not differ as a function of any dementia risk factors examined at baseline. Brief cognitive test performance after 2 years was no different between women assigned estradiol, 0.014 mg/d, and those assigned placebo (92); however, women receiving estrogen, 0.625 mg/d, did slightly worse than those receiving placebo after a mean of 5.4 years (81). Across all trials, no between-group difference existed in any evaluated cognitive test (low strength of evidence). Although stroke risk seemed no different between groups in the WHIMS substudy (88), the main WHI (Women's Health Initiative) trial reported that women randomly assigned to estrogen had a 1.4-fold increased risk for stroke (94).

Estrogen Plus Progestin

Among 14 eligible references (80, 85–89, 95–102), 5 unique trials had low to moderate risk of bias (80, 85–89, 95–98) (Part H of the Supplement). In women with normal cognition, trials provided low-strength evidence that estrogen–progestin increases risk for dementia and does not improve cognitive test performance. No trials reported data about women with MCI.

Among 4532 women aged 65 years or older who were randomly assigned to receive estrogen–progestin or placebo for a mean of 4.1 years, those assigned estrogen–progestin had a significantly higher incidence of dementia but not of MCI or a combined outcome of MCI or dementia (low strength of evidence) (88, 103). These results did not differ as a function of any dementia risk factors examined at baseline (88). Across all trials, no between-group difference existed in any global cognitive screening test or executive function, attention, or processing speed test (low strength of evidence), but 4 of 16 memory tests favored placebo (low

strength of evidence). Results for memory tests seemed similar across subgroups (97). Although stroke risk did not differ between treatment groups in the WHIMS study (89), the main WHI trial reported that estrogen–progestin was associated with approximately 25% to 40% increased risks for stroke, coronary heart disease, and invasive breast cancer and a 2-fold increased risk for pulmonary embolism (104).

Selective Estrogen Receptor Modulators

Two unique trials with low to moderate risk of bias randomly assigned older women with osteoporosis to receive raloxifene (60 mg/d or 120 mg/d in both trials) or placebo (105–107) (Part H of the Supplement). A cognitive substudy of the MORE (Multiple Outcomes of Raloxifene Evaluation) trial (n = 7478; mean age, 66 years) (105, 106) reported that women with normal cognition assigned raloxifene, 120 mg/d, versus placebo had a lower risk for MCI but no reduction in Alzheimer disease, any dementia, or a combined outcome of MCI or dementia (low strength of evidence). By comparison, risk for these outcomes did not differ between women assigned raloxifene, 60 mg/d, and those assigned placebo (low strength of evidence). Results did not differ as a function of baseline estradiol level. Both trials reported no significant differences between treatment groups on executive function, attention, or processing speed or memory tests (low strength of evidence). The MORE cognitive substudy did not report adverse events, but the main MORE trial reported that raloxifene was associated with a 3-fold increased risk for venous thromboembolism, as well as increased risks for hot flashes, influenza syndrome, leg cramps, and peripheral edema (108). No trials reported data about women with MCI.

Testosterone

Three trials that randomly assigned older men to receive testosterone or placebo provided low-strength evidence that testosterone supplementation for 6 to 12 months does not improve cognitive test performance versus placebo among men with low testosterone levels at baseline and either age-associated memory impairment or MCI (18, 109) (Part H of the Supplement). Evidence was insufficient about effects in men with normal cognition (110). Men assigned testosterone were more likely to develop erythrocytosis (109).

DISCUSSION

In persons with normal baseline cognition, we found low-strength evidence that estrogen and estrogen–progestin increase risk for dementia or a combined outcome of MCI or dementia; low-strength evidence that high-dose raloxifene decreases risk for MCI but not for dementia; low- to insufficient-strength evidence that antihypertensive treatment, NSAIDs, and statins do not alter risk for dementia; and no evidence on the effect of aspirin, diabetes, or dementia medications on incident MCI or dementia. We also found mostly low-strength evidence that none of these pharmacologic treatments affect cognitive test performance in this population.

In persons with cognitive impairment not meeting dementia criteria (such as those with MCI), we found low-strength evidence that cholinesterase inhibitors do not reduce dementia risk, low-strength evidence that neither cholinesterase inhibitors nor testosterone slows decline of cognitive test performance, and insufficient to no evidence about the effect of other pharmacologic treatments on either risk for dementia or cognitive test performance.

On the basis of data from only a few studies, the effects of the evaluated pharmacologic treatments on cognitive outcomes did not seem to differ as a function of studied participant characteristics. Adverse effects were inconsistently reported, but risks for serious outcomes were significantly increased with estrogen, estrogen–progestin, and raloxifene compared with placebo.

These largely negative findings on cognitive outcomes are consistent with those reported in prior systematic reviews (identified in our searches) of randomized controlled trials of pharmacologic interventions to prevent cognitive decline in persons without dementia. Several systematic reviews and an American Heart Association scientific statement published between 2013 and 2016 concluded that cholinesterase inhibitors, antihypertensives, statins, and NSAIDs do not reduce risk for incident dementia (111–114), and we identified no eligible trials of these agents reporting dementia outcomes published since that time. Although findings that estrogen and estrogen–progestin increase risk for dementia and MCI were already published and reviewed in the 2010 AHRQ review (9), more recent trials included in the current review have strengthened the evidence that these treatments also do not improve cognitive test performance. We identified several recent randomized controlled trials of diabetes medication published after a 2010 systematic review on this topic (115), including trials of intensive versus standard diabetes control in patients with normal cognition and of diabetes medication versus inactive control in patients with MCI. Findings of these trials increased the strength of evidence to conclude that these diabetes treatments do not improve performance on cognitive tests.

Observational study results mostly showed that diabetes, midlife hypertension, and midlife hyperlipidemia were associated with increased dementia risk; that NSAID or statin use was associated with lower dementia risk; and that no association existed between postmenopausal hormone use and dementia risk (112, 116–121). The contrast between these results and the trial data results may be attributable to many factors, including that the risk and protective factors identified in observational studies are not causal and that results are confounded by differences in characteristics between users and nonusers of these medications. Even if some of these risk factors are causal, the negative trial results may have occurred in part because trials were too few or too small and because interventions were

introduced too late or treatment duration was too short to produce clinically meaningful differences in cognitive trajectories in persons with mostly normal baseline cognition. In addition, some of these persons were relatively young and at low risk for MCI or dementia during study follow-up. We found no trial data about whether pharmacologic interventions in midlife affect development of cognitive decline, MCI, or dementia in late life. With these limitations, determining whether insufficient or even low-strength evidence for no treatment benefit reflects inadequacy of the pharmacologic intervention or limitations in the study designs and data may be impossible. This review was further limited in that most trials were not designed to assess cognitive outcomes and represent only a few of the trials of these interventions, suggesting that published results could be subject to reporting bias.

Several of the evaluated pharmacologic interventions affect vascular disease and may have a greater effect on cognitive impairment attributable to vascular disease. However, to focus on the syndrome of dementia most typically seen in clinical settings, this review excluded trials that focused on dementia that attributed solely to a clinically recognized incident stroke. Still, if vascular risk factors in older adults were substantial contributors to common forms of late-life dementia, we would have hoped to see some signal of cognitive benefit in the trials reviewed, particularly because some trials saw large improvements in blood pressure, cholesterol, and glycemic control and reduced risk for stroke and other major cardiovascular events. The negative findings of the pharmacologic trials included in this review also may be due in part to each intervention addressing only 1 of many disease pathways that may contribute to cognitive decline.

Several large, single-intervention, pharmacologic randomized controlled trials registered at ClinicalTrials.gov are ongoing in mostly older adults without dementia and may better clarify the effects of statins, NSAIDs, and aspirin on cognitive outcomes, as well as provide new insights about the cognitive effects of insulin, solanezumab, and other experimental agents (Part J of the **Supplement**, available at Annals.org). Nevertheless, the optimal pharmacologic trial might need to simultaneously address many risk factors, begin in midlife, continue to late life with low attrition, measure effect on a clinically meaningful change in cognitive performance tests and rigorously adjudicated MCI and dementia outcomes, systematically collect harms data, and examine effects both overall and in a priori–selected subgroups. However, a trial with all of these components is not likely to be logistically or financially feasible. Identification of true surrogate outcomes for these clinically relevant outcomes may be a more realistic target.

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Disclaimer: Findings and conclusions are those of the authors, who are responsible for the article's contents; findings and conclusions do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or the U.S. Department of Health and Human Services.

Financial Support: This manuscript is based on research conducted by the Minnesota Evidence-based Practice Center under AHRQ contract 290-2015-00008-I.

Disclosures: Dr. Jutkowitz reports a contract with AHRQ during the conduct of the study. Drs. Hemmy and Barclay report grant support from AHRQ during the conduct of the study. Authors not named here have disclosed no conflicts of interest. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M17-1529.

Reproducible Research Statement: *Study protocol:* Available at https://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=2202. *Statistical code:* Not applicable. *Data set:* See Systematic Review Data Repository at https://srdr.ahrq.gov/.

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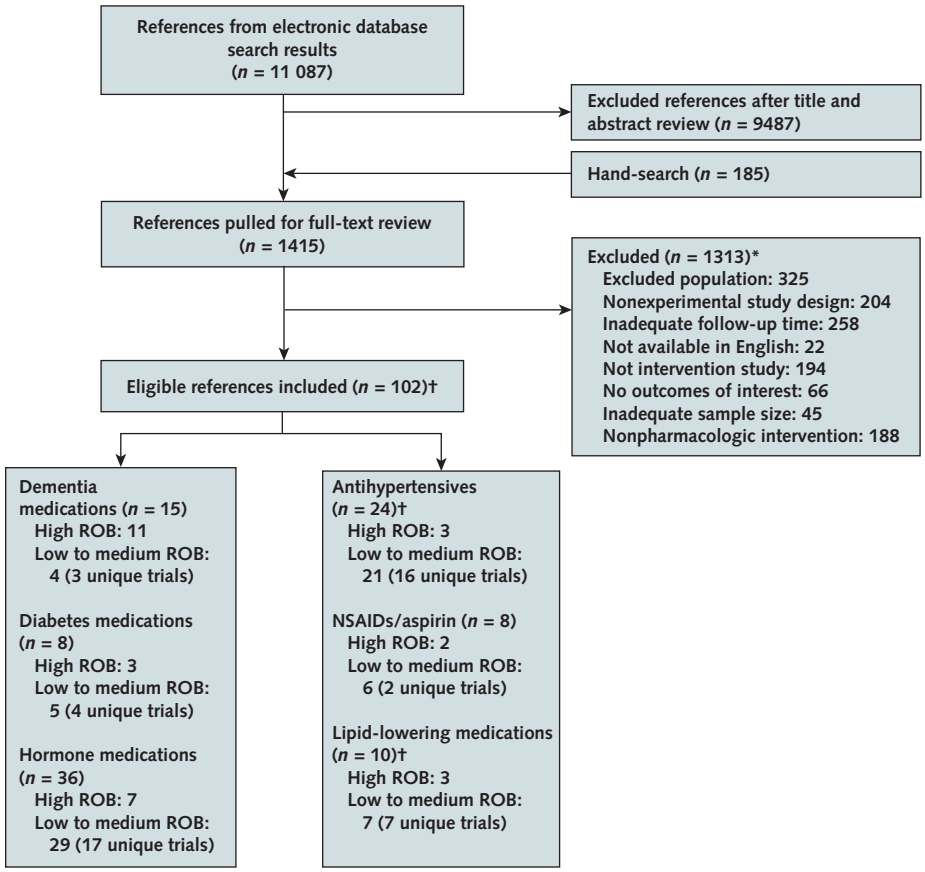
Appendix Figure. Evidence search and selection.



NSAID = nonsteroidal anti-inflammatory drug; ROB = risk of bias.
* Some studies were excluded for >1 reason.
† 1 eligible trial separately compared antihypertensive treatment and lipid-lowering medication versus placebo.