

Practice guideline update: Mild cognitive impairment

Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the
American Academy of Neurology

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AUTHOR CONTRIBUTION

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M. Armstrong serves on the Level of Evidence editorial board for *Neurology* (but is not compensated financially) and serves as an evidence-based medicine methodologist for the American Academy of Neurology (AAN).

T. Getchius was an employee of the AAN and has nothing to disclose.

M. Ganguli has served on the data safety and monitoring board for Indiana University and on the advisory committee for Biogen Inc., and has received research support from the National Institute on Aging of the NIH.

D. Gloss serves as an evidence-based medicine methodologist for the AAN.

G. Gronseth serves as associated editor for *Neurology*, serves on the editorial advisory board for *Neurology Now*, and is compensated by the AAN for methodologic activities.

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ABBREVIATIONS

AAN: American Academy of Neurology
AD: Alzheimer disease
ADAMS: Aging, Demographics, and Memory Study
ADAS-Cog: Alzheimer's Disease Assessment Scale–Cognitive Subscale
ADLs: activities of daily living
AEs: adverse events
Alzheimer's Disease Assessment Scale–Cognitive Subscale
aMCI: amnesic MCI
CDR: Clinical Dementia Rating scale
CDR-SB: CDR Sum of Boxes
CGIC: Clinical Global Impression of Change
CGIC-MCI: Clinical Global Impression of Change Scale for MCI
CIND: cognitively impaired no dementia
HR: hazard ratio
HRS: Health and Retirement Study
IADLs: instrumental activities of daily living
ITT: intention-to-treat
MCI: mild cognitive impairment
MMQ: Multifactorial Memory Questionnaire
MMSE: Mini-Mental State Examination
MoCA: Montreal Cognitive Assessment
NP: neuropsychological
NYU: New York University
RCTs: randomized control trials
RD: risk difference
RR: relative risk

ABSTRACT

Objective: To update the 2001 American Academy of Neurology (AAN) guideline on mild cognitive impairment (MCI).

Methods: The guideline panel systematically reviewed MCI prevalence, prognosis, and treatment articles according to AAN classification of evidence criteria, and based recommendations on evidence and modified Delphi consensus.

Results: MCI prevalence was 6.7% for ages 60–64, 8.4% for 65–69, 10.1% for 70–74, 14.8% for 75–79, and 25.2% for 80–84. Cumulative dementia incidence was 14.9% in individuals with MCI older than age 65 years followed for 2 years. No high-quality evidence exists to support pharmacologic treatments for MCI. In patients with MCI, exercise training (6 months) is likely to improve cognitive measures and cognitive training may improve cognitive measures.

Major recommendations: Clinicians should assess for MCI with validated tools in appropriate scenarios (Level B). Clinicians should evaluate patients with MCI for modifiable risk factors, assess for functional impairment, and assess for and treat behavioral/neuropsychiatric symptoms (Level B). Clinicians should monitor cognitive status of patients with MCI over time (Level B). Cognitively impairing medications should be discontinued where feasible and behavioral symptoms treated (Level B). Clinicians may choose not to offer cholinesterase inhibitors (Level B); if offering, they must first discuss lack of evidence (Level A). Clinicians should recommend regular exercise (Level B). Clinicians may recommend cognitive training (Level C). Clinicians should discuss diagnosis, prognosis, long-term planning, and the lack of effective medicine options (Level B), and may discuss biomarker research with patients with MCI and families (Level C).

Mild cognitive impairment (MCI) is a condition in which individuals demonstrate focal or multifocal cognitive impairment with minimal impairment of instrumental activities of daily living (IADLs) that does not cross the threshold for dementia diagnosis.^{e1–e3} Although MCI can be the first cognitive expression of Alzheimer disease (AD), it can also be secondary to other disease processes (i.e., other neurologic, dementing, systemic, or psychiatric disorders) that can cause cognitive deficits.^{e4} The term *amnesic MCI* (aMCI) describes persons with a syndrome in which memory dysfunction predominates, whereas nonamnesic MCI refers to individuals whose impairment of other cognitive features (e.g., language, visuospatial, executive) is more prominent.^{e2} This practice guideline focuses on MCI of presumed idiopathic or neurodegenerative origin rather than mild cognitive changes relating to potentially reversible causes such as metabolic, vascular, systemic, or psychiatric disorders.

This practice guideline updates a 2001 American Academy of Neurology (AAN) practice parameter with recommendations for clinicians concerning the diagnosis and treatment of MCI.^{e5} At that time, the literature available was relatively sparse, but there was sufficient Class II evidence to recommend that clinicians should monitor patients with MCI because of an increased risk of progressing to dementia.

On the basis of the increase in studies on MCI since 2001, the importance of MCI for clinical practice, and the study of associated therapeutics in randomized control trials (RCTs), the AAN developed this update to the 2001 practice parameter on MCI for clinicians.

This practice guideline reviews current scientific evidence regarding the diagnosis of MCI and addresses the following clinical questions:

1. What is the prevalence of MCI in the general population?
2. What is the prognosis for patients diagnosed with MCI for progression to a diagnosis of dementia, and how does this compare with an age-matched general population?
3. What pharmacologic treatments are effective for patients diagnosed with MCI?
4. What nonpharmacologic treatments are effective for patients diagnosed with MCI?

The guideline authors anticipate a progression to disease-specified MCI types as biomarker measures such as amyloid PET imaging and CSF biomarkers (e.g., amyloid β 42, total tau, phosphorylated tau) are more clearly linked to specific pathologic outcomes (e.g., MCI-Alzheimer disease or MCI-Lewy body disease). The authors also anticipate that the evolving field of biomarker research will lead to improved specificity as to the underlying causes of the MCI syndrome; however, this guideline does not review this rapidly changing area of research. Furthermore, the authors specifically excluded Parkinson disease-MCI and vascular cognitive impairment, as these may have different epidemiologic and treatment spectra than AD. In addition, the potential psychological distress of a diagnosis of MCI (which has been discussed in the literature) was not one of the questions reviewed by the expert panel for this guideline.^{e6}

DESCRIPTION OF THE ANALYTIC PROCESS

This practice guideline principally follows the methodologies described in the 2004 edition of the AAN's guideline development process manual.^{e7} Conclusions and recommendations were

developed in accordance with the process outlined in the 2011 guideline development process manual, as amended to include the updated scheme for classifying therapeutic articles.^{e8} In 2008, after reviewing potential members' conflict of interest statements and curriculum vitae, the AAN Guideline Development, Dissemination, and Implementation Subcommittee (appendices e-1 and e-2) convened a multidisciplinary panel of experts in MCI to develop this guideline. The original panel consisted of 6 neurologists (R.C.P., O.L., D.G., G.S.G., J.S., A.R.-G.), 1 geriatric psychiatrist (M.G.), 1 neuropsychologist (D.M.), 1 geriatrician (M.S.), and 1 AAN staff member (T.S.D.G.). Additional assistance was later provided by 2 guideline methodology specialists (M.J.A., T.P.) and another guideline subcommittee member (G.S.D.). The panel determined at project initiation that the literature on "biomarkers" to predict progression to AD is changing rapidly and should be the subject of a future guideline or systematic review. This view was reaffirmed in 2016. The panel developed research questions in PICO format: patient, intervention, comparison, outcome.

The guideline panel included articles in humans related to MCI and cognitively impaired no dementia (CIND) under the headings of prevalence, prognosis, treatment (both pharmacologic and nonpharmacologic). The panel excluded pharmacologic treatment trials with fewer than 50 participants. The complete search strategy is presented in appendix e-3. The panel engaged a medical librarian to search the MEDLINE, CINAHL, EMBASE, and PsycInfo databases from January 2000 to December 2008. An updated literature search was completed from January 2008 to April 2014. An additional updated search was performed in December 2015 to include prevalence, prognosis, and cognitive therapy articles. Two panel members working independently of each other reviewed each of the 11,530 abstracts retrieved for basic inclusion criteria: (1) article was relevant to at least one of the clinical questions; (2) article described MCI, cognition disorders, or memory disorders, unrelated to dementia; (3) study population was greater than or equal to 50 to reduce the likelihood of spurious results due to small samples; (4) article was not a single-patient case report, review, or editorial. Of the 11,530 abstracts reviewed, the panelists identified 315 as pertinent, for which they obtained and reviewed the full-text articles. Of the 315 reviewed articles, 68 met inclusion criteria and were reviewed and classified by 2 panel members, working independently of each other, for quality of evidence on the basis of the AAN screening (frequency), prognostic, and therapeutic classification schemes rating risk of bias pertaining to study characteristics (appendix e-4). Discrepancies were reconciled between the 2 reviewers or by a third reviewer. Appendix e-5 presents the rules for determining confidence in the evidence.

For the prevalence and prognosis questions, the guideline panel excluded from analysis articles that reanalyzed cohorts (substudies) or assessed secondary outcomes of a parent treatment study. For the treatment question, the guideline authors excluded articles that assessed mixed populations (e.g., persons with MCI or dementia). Also excluded were pharmacologic treatment studies totaling fewer than 50 participants and cognitive intervention studies lacking control groups and totaling fewer than 50 participants. Class III studies are discussed in the guideline text only when no Class I or Class II studies were identified. Class IV studies were excluded from consideration because of their high risk of bias.

The panelists noted that various definitions of MCI, and of related terms, such as CIND, were used in the reviewed literature. Variation was based on different ascertainment methods,

different neuropsychological (NP) measures, different measure thresholds, and requirements for different cognitive deficits. There also was variation in the use of aMCI and nonamnesic MCI in these studies. To address these discrepancies, the panelists reflected the specific definition used for a study where feasible in the evidence table and guideline text, and provided specific comments on the potential effect of differing definitions.

The guideline panel used a modified form of the Grading of Recommendations Assessment, Development and Evaluation process to develop conclusions (see appendix e-6 for evidence synthesis tables) and a modified Delphi process to achieve consensus regarding recommendations.^{e8} In accordance with the 2011 guideline manual, recommendations were based not only on the evidence in the systematic review, but also on strong related evidence, established principles of care, and inferences. The level of obligation for each recommendation was based on the strength of these premises and the risk–benefit ratio of following the recommendation, with adjustments based on importance of outcomes, variation in patient preferences, feasibility/availability, and patient costs. Consensus was determined by a modified Delphi voting process in accordance with prespecified rules.^{e8} Appendix e-7 delineates the steps and rules for formulating recommendations, and appendix e-8 presents the rationale of factors considered during recommendation development. This guideline was subjected to external review in accordance with the 2004 AAN guideline process.^{e7} AAN methodologists (M.J.A., G.S.G., T.P.) supported the development of this guideline, the processes of which were described earlier and are delineated more fully in the 2004 and 2011 guideline development process manuals.^{e7,e8}

ANALYSIS OF EVIDENCE

In the initial search, 7,850 abstracts were reviewed, and the full-text articles of 193 (68 frequency, 102 prognosis, and 23 treatment) were obtained and reviewed. Articles excluded through systematic search of the results were review articles, duplicates, editorials, case reports, and animal studies. The 2 search updates (performed in April 2014 and December 2015) identified 3,680 abstracts (1,587 frequency, 1,498 prognosis, 595 treatment). Of these, the full-text articles of 62 were obtained and reviewed. In the final analysis, the guideline panel used Class I and Class II data for the frequency question and Class I data for the prognosis question, as this high-level evidence drove recommendations. For the treatment question, the panel included Class I–III articles. In its final selection of rated articles, the panel included 34 frequency, 9 prognosis, 14 pharmacologic treatment, and 7 nonpharmacologic treatment.

1. What is the prevalence of MCI in the general population? (Prevalence question)

Background

Various definitions of MCI have been used over time, reflecting an evolution of thought from primarily focusing on amnesia to including other cognitive deficits. Because memory deficits are the clinical hallmark of AD, some groups used criteria for MCI that required the presence of memory deficits in isolation (e.g., aMCI),^{e3,e9,e10} and others included a broader definition that included either single-domain nonamnesic deficits or deficits in multiple cognitive domains, either with memory impairment (multidomain aMCI) or without (multidomain nonamnesic

MCI).^{e1,e2,e11} The definition of MCI is also affected by the psychometric properties of, and norms for, the tests used to identify thresholds between cognitive decline from normal aging and MCI. Table e-1 presents the characteristics of various definitions of MCI used in the literature evaluated here.

Analysis

Thirty-four studies were included in the final analysis, of which 20 were rated as Class I and 14 were rated as Class II.

Class I evidence

Twenty studies had Class I evidence for prevalence of MCI in a population.^{e9,e10,e12–e29} A confounding issue was the wide variance of MCI and CIND definitions used in these studies. Although many studies used variations of Petersen criteria^{e2,e3} others referenced an operationalized definition of MCI^{e21} or other sources. Definitions that were referenced are listed in table e-1.

In all Class I studies, specific geographic areas were defined, population-based random-sampling techniques were used, all participants without dementia in the sample were included in the sampling frame, and parameters were defined for diagnosis of MCI or CIND and for dementia ascertainment. Age inclusion criteria varied for these studies, ranging from 55 years and older^{e22} to 75 years and older.^{e20} Most had a lower age limit of 60 or 65 years. Evaluated populations had a worldwide distribution, including white Australian,^{e12} Chinese,^{e10,e28} Finnish,^{e14} white French,^{e18} German,^{e17,e20} Italian,^{e13,e29} Indian,^{e21} Spanish,^{e22} US rural,^{e9,e16,e26} and US urban white populations.^{e19,e23}

Class II evidence

Fourteen studies were classified as Class II evidence.^{e30–e43} These studies encompassed a broad range of participants in geographically based cohort studies focused on ages 55 years and older.

Summary of Class I evidence

Persons meeting the criteria described in the definition for MCI or CIND were present in all cohorts reported. Prevalence of MCI or CIND varied among the Class I studies. The panel identified 2 types of MCI definitions: “narrow” definitions address a specific amnesic deficit with various definitions of cutoff criteria, and “broad” definitions address both amnesic and nonamnesic deficits with various definitions of cutoff criteria (i.e., using NP age-matched cutoffs of 1.5 SDs rather than 1.0 SD^{e20}) (table e-2). Where narrow criteria for MCI were used,^{e12,e13,e20} prevalence estimates and incidence rates were lower. With use of narrow criteria, prevalence rates varied from 3.2%–25%. With use of broad criteria, prevalence rates varied from 13.4%–42.0%. A meta-analysis of all studies with individuals aged 65 years and older resulted in a prevalence of 16.62% (95% CI 11.59%–26.9%, I^2 23.54) vs a narrow study prevalence of 10.5% (95% CI 4.8%–21.5%, I^2 20.4).

Eight of the Class I studies showed that a lower education level was significantly associated with a higher prevalence of MCI.^{e9,e10,e14,e18,e21,e24,e27,e28} Two of the Class I studies indicated that male sex was associated with the presence of MCI,^{e13,e24} but other studies found similar baseline prevalence in both male and female participants.^{e14,e15,e27}

To further assess the effect of age on MCI prevalence, a guideline methodologist [T.P.] performed a random-effects meta-analysis. Class I and II studies confirmed an increased prevalence with cohort age. The all-studies estimate for individuals aged 60–64 years was 6.7% (95% CI 3.4%–12.7%, I^2 11.0); for those aged 65–69, 8.4% (95% CI 5.2%–13.4%, I^2 0); for ages 70–74, 10.1% (95% CI 7.5%–13.5%, I^2 5.2); for ages 75–79, 14.8% (95% CI 10.1%–21.1%, I^2 60.7); and for ages 80–84, 25.2% (95% CI 16.5%–36.5%, I^2 0) (see table e-3). The sole study that provided data on the 55-years-and-older age group was excluded from analysis.^{e19}

Data from 3 studies could not be included in the meta-analysis of prevalence studies because data were not presented in 5-year age groups. In a cohort study^{e40} of 1,169 participants in a defined population with a mean age of 74.4 years (SD 3.9), MCI was seen in 7.0%. In a Health and Retirement Study (HRS)–completed assessment of 856 participants aged 71 years and older, 28% (241) had cognitive impairment without dementia.^{e44} In a sample of persons from a population aged 70–89 years, 16.7% (329/1,969) had MCI at initial assessment.^{e45}

Conclusions

Patients with MCI and CIND are present worldwide in populations aged 60 years and older. Prevalence was 6.7% for those aged 60–64 years, 8.4% for those aged 65–69 years, 10.17% for those aged 70–74 years, 14.8% for those aged 75–79 years, 25.2% for those aged 80–84 years, and 37.6% for those aged 85 years and older (95% CI 28.1%–48.0%, I^2 24.8). MCI is common in older populations, and its prevalence increases with age (high confidence, multiple Class I and Class II studies, consistent meta-analysis) and lower educational level (high confidence, 8 Class I studies). More stringent criteria for MCI diagnosis reduce the frequency of reported MCI in patients aged 65 years and older (high confidence, multiple Class I studies).

2. What is the prognosis for patients diagnosed with MCI for progression to a diagnosis of dementia, and how does this compare with an age-matched general population? (Prognosis question)

The guideline panel found 9 Class I studies on prognosis for individuals with MCI.^{e9,e13,e19,e23,e27,e42,e44–e47}

Analysis

Class I evidence

The Rush Memory and Aging project is an ongoing community-based cohort health study in Chicago^{e19} reporting on the likelihood of participants with MCI in this cohort progressing to dementia. Participants were recruited from 40 senior housing facilities in the Chicago metropolitan area, including subsidized housing facilities, retirement communities, and

retirement homes. A total of 786 participants had at least one follow-up evaluation over an average of 2.5 years. Criteria for MCI diagnosis were “individuals who were found to have cognitive impairment by the neuropsychologist but who, in the judgment of the examining clinician, did not meet criteria for dementia.” Of the 786 individuals eligible for analysis, 221 (28.1%) had MCI according to these criteria. MCI increased the relative risk (RR) of developing Alzheimer dementia significantly (risk difference [RD] 21.7%; RR 6.75 [95% CI 4.11–11.09]) compared with the cognitively intact state of comparator group at baseline. Over an average of 2.5 years of follow-up, 57 participants with MCI (25.8%) and 23 participants without cognitive impairment (4.1%) developed AD.

The Italian Longitudinal Study on Aging evaluated persons diagnosed with CIND and MCI^{e13} as part of a large population-based cohort study of a random sampling of 5,632 individuals aged 65–84 years living in the community or an institution (data obtained from population registers of 8 Italian municipalities). The cohort included a broad range of at-risk individuals. Participants were defined as having CIND and MCI by use of specific NP scores. The dementia diagnosis was based on a structured clinical assessment. The analysis included a total of 2,202 individuals with CIND or MCI with evaluable endpoints (mean follow-up of 3.9 ± 0.7 years). Participants with MCI at baseline had a hazard ratio (HR) of 2.90 for developing dementia compared with those with normal cognition at baseline (95% CI 1.59–5.31).

The Monongahela Valley Independent Elderly Survey evaluated individuals for presence of cognitive impairment and impaired activities of daily living (ADLs) using the Consortium to Establish a Registry for Alzheimer’s Disease protocol for the Clinical Dementia Rating (CDR) scale.^{e9} The CDR scale is a validated clinically based instrument^{e48} (incorporating findings from clinical examination that may include bedside NP testing) that stages cognitive and functional decline as very mild dementia (0.5), mild dementia (1.0), moderate dementia (2.0), and severe dementia (3.0). A global CDR score of 0.5 is often used to indicate the presence of MCI but does not adhere to the more commonly used definitions.^{e42}

This large prospective study randomly selected a community sample aged 65 years and older for biennial cognitive screening followed by a standardized clinical evaluation. Retrospective application of MCI criteria enabled an assessment of progression to dementia in individuals defined as having aMCI by Petersen criteria.^{e2,e3} Participants were assessed over the course of 10 years, and a cohort of 1,248 participants was available for analysis. Participants with aMCI had an increased HR of 3.9 for development of dementia (95% CI 2.1–7.2).

The Cardiovascular Health Study Cognition Study (conducted at multiple US sites: Forsyth County, North Carolina [mixed rural/urban]; Sacramento County, California [mixed rural/urban]; Washington County, Maryland [mixed rural/urban]; Pittsburgh, Pennsylvania [urban]) evaluated persons for the presence of “MCI amnesic-type” or “MCI multiple cognitive deficits-type” as part of a prospective cohort study of participants aged 75 years and older (2,470 participants, mean follow-up 3.2 years).^{e23,e27} The dementia diagnosis was based on a deficit in performance in 2 or more cognitive domains that were of sufficient severity to affect the participants’ ADL in individuals with a history of normal intellectual function before the onset of cognitive abnormalities. Results for progression to dementia were reported as incidence rather than RR. The dementia incidence among individuals who were cognitively intact at baseline was 38 per

1,000 person-years (95% CI 29.9–48.2). The incidence of dementia among all individuals with MCI was 147 per 1,000 person-years (95% CI, 113.3–189.6). Both participants with “MCI amnesic-type” and those with “MCI multiple cognitive deficits-type” had an increased dementia incidence (MCI amnesic-type 170 per 1,000 person-years, [95% CI 91.5–316.1]; MCI multiple cognitive deficits-type 143 per 1,000 person-years, [95% CI 121.3–270.0]).

The Kungsholmen Project (Stockholm, Sweden) evaluated persons for the presence of CIND and the future progression to AD.^{e46} This was a prospective cohort study of all inhabitants of the Kungsholmen district of Stockholm aged 75 years and older on October 1, 1987 (718 individuals without dementia, average follow-up 3.4 ± 0.5 years). Cutoff scores of 1–2 SDs below Mini-Mental State Examination (MMSE) age- and education-specific means only were used to define CIND, making the CIND definition analogous but not necessarily synonymous with various definitions of MCI. Results were reported for mild CIND (1 SD below MMSE age- and education-specific means), moderate (1.5 SDs below), and severe (2 SDs below), but not for the group as a whole. The RR of dementia at 6-year follow-up for mild CIND was 1.7 (95% CI 1.3–2.2); for moderate CIND, 1.5 (95% CI 1.0–2.1); and for severe CIND, 1.8 (95% CI 1.2–2.7). The study authors noted a small group of “improvers” with mild CIND; their RR for dementia was not significantly increased compared with participants who were never impaired (RR 1.4, 95% CI 0.7–3.0).

A study in persons aged 75 years and older recruited from 4 US communities (Hagerstown, Maryland; Pittsburgh, Pennsylvania; Sacramento, California; Winston-Salem and Greensboro, North Carolina; urban vs rural not defined), included 3,063 elderly community-dwelling participants without dementia, with a mean follow-up at 6.1 years (no reported SD).^{e42} Participants were categorized into 4 groups based on NP assessment and CDR (0 or 0.5): Group 1 participants classified as normal by NP and CDR; Group 2 participants classified as normal by NP but MCI by CDR; Group 3 participants classified as MCI by NP but normal by CDR; and Group 4 participants classified as MCI by both NP and CDR criteria. The study reported a higher rate of progression to dementia in groups meeting any of the 3 MCI criteria vs age-matched participants (age-matched participants, 7.4% converted; meeting CDR MCI alone, 17.2% [RD 9.8%]; meeting NP alone, 22.8% [RD 15.4%]; meeting both criteria, 41.5% converted [RD 34.1%] [χ^2 307.4, $p < 0.001$]).

The Cache County Study on memory health and aging^{e47} followed county residents aged 65 years and older (4,491 baseline phase participants without dementia, 3-year follow-up, no mean follow-up duration statistics available). In comparison with the neurologically intact group, higher percentages of participants categorized as prodromal AD (corresponding to aMCI) progressed to dementia (normal group 3.3%, 59.4% prodromal AD group, RD 56.1% [χ^2 467.15, $df = 2$, $p < 0.0001$]).

The Aging, Demographics, and Memory Study (ADAMS) included participants aged 71 years and older drawn from the nationally representative HRS.^{e44} Of 1,770 selected individuals, 856 completed initial assessment, and of 241 selected individuals, 180 completed 16- and 18-month assessments. Of participants who completed follow-up assessment, 11.7% with MCI progressed to dementia annually. The study used its own criteria for CIND, operationalizing the definition

on the basis of analyses of both NP data and an objective measure of daily function from participants with this diagnosis in other studies done by the ADAMS group.

The Mayo Clinic Study of Aging is a population-based, prospective study evaluating the prevalence, incidence, and natural history of cognitive decline.^{e45} Using the records linkage system of the Rochester Epidemiology Project, the authors constructed a sampling frame of residents of Olmsted County, Minnesota, aged 70–89 years on October 1, 2004. Of 4,398 eligible individuals, 61.8% participated. The risk of dementia increased in those who had ever had MCI vs those who never had MCI (HR 23.2; 95% CI 14.4–37.2).

Summary of analysis

All Class I studies showed an increased risk of progression to dementia in persons with MCI using various definitions compared with age-matched participants without MCI (high confidence in the evidence, multiple Class I studies). A meta-analysis of these studies showed that, in individuals with MCI/CIND older than age 65 years followed for 2 years, the cumulative incidence for the development of dementia was 14.9% (95% CI 11.6%–19.1%, random-effects analysis, $I^2 = 0$). In those with MCI/CIND vs age-matched participants at 2–5 years after, the RR of dementia (all types) was 3.3 (95% CI 2.5–4.5, $I^2 = 4.9$). In those with MCI/CIND vs in age-matched participants at 2–5 years after, the RR of the diagnosis of Alzheimer dementia was 3.0 (95% CI 2.1–4.8, $I^2 = 17.3$).

Reversion to normal cognition in individuals with MCI

The guideline panel assessed whether participants diagnosed with MCI within these studies could revert to normal cognition. Four Class I studies commented on reversion to normal.^{e9,e19,e23,e45} These studies showed a reversion to normal cognition on follow-up in 14.4%,^{e19} 33.3%,^{e9} 19%,^{e23} and 38%^{e45} in participants diagnosed with MCI. Five of the Class II studies also documented a subset of participants with MCI who were cognitively normal at follow-up.^{e18,e49–e52} However, 2 studies documented increased rates of ultimate conversion to dementia in participants who had been diagnosed with MCI but then reverted to normal cognition, suggesting that individuals who revert remain at a higher risk of progression again to MCI or dementia than individuals who have never received an MCI diagnosis (in these studies 65%^{e45} and 55% ultimately converted to dementia^{e52}).

Conclusions

Persons with MCI are at higher risk of progressing to dementia than age-matched controls (high confidence, multiple concordant Class I studies, meta-analysis). In individuals with MCI/CIND older than age 65 years followed for 2 years, the cumulative incidence for the development of dementia is 14.9% (95% CI 11.6%–19.1%, random-effects analysis, $I^2 = 0$). In those with MCI/CIND vs age-matched participants at 2–5 years after, the RR of dementia (all types) is 3.3 (95% CI 2.5–4.5, $I^2 = 4.9$). In those with MCI/CIND vs age-matched participants at 2–5 years after, the RR of the diagnosis of presumed Alzheimer dementia is 3.0 (95% CI 2.1–4.8, $I^2 = 17.3$). Persons diagnosed with MCI may remain stable, return to neurologically intact, or progress to dementia (multiple Class I studies, 14.4%–55.6% reverting to normal).

Clinical context

Variation in definitions of MCI and its subtypes, as well as for the diagnosis of dementia (see table e-1), likely increased the variability among studies and predictive value of the diagnosis of MCI and its subtypes, although heterogeneity in the meta-analysis was low. Differences in the operational definition of dementia (i.e., what level of functional impairment defines dementia) may also increase variability among studies in progression to dementia. Inclusion of specific biomarker data in future population studies may modify these results.

3. What pharmacologic treatments are available for patients diagnosed with MCI, and are these treatments effective on cognitive measures of progression to dementia, excluding other symptomatic effects? (Treatment question)

Analysis

The guideline panel found 14 studies (1 Class I, 10 Class II, and 3 Class III) addressing the issue of pharmacologic treatment of MCI. The panel reports the studies by type of agent used. Specific data on criteria used for the diagnosis of MCI are available in the text where specific to the study.

Donepezil

The guideline panel found 3 Class II studies addressing the use of donepezil in persons with MCI. Pooling of results was not possible because of different trial durations and different outcome measures.

A large, 3-arm, randomized, multicenter, double-blind, placebo-controlled, parallel group study^{e53} had a primary outcome of time to development of possible or probable AD. Participants were randomized to 1 of 3 treatments: 1) 2,000 IU of vitamin E, placebo donepezil, and multivitamin daily; 2) 10 mg of donepezil, placebo vitamin E, multivitamin daily; or 3) placebo vitamin E, placebo donepezil, multivitamin daily. All treatments were provided for 3 years. This study was rated Class II owing to < 80% completion rate (70% of total group completed). A total of 769 individuals participated in the study. There was no significant difference among groups in the primary outcome measure (HR 0.80; 95% CI 0.57–1.13).

A Class II multicenter, randomized, double-blind, placebo-controlled, parallel group study^{e54} in persons with MCI reported on participants randomized to a 3-week single-blind placebo run-in period followed by a 48-week double-blind period. During the 48-week double-blind period, participants were assigned to treatment with donepezil (5 mg/d for 6 weeks followed by 10 mg/d) or placebo. The study was rated Class II because < 80% of study participants completed the study (55% of the participants who received donepezil, and 66% of the participants who received placebo). The dual primary efficacy measures were the modified Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) and the CDR Sum of Boxes (CDR-SB). Eight hundred twenty-one participants were randomized to donepezil 10 mg/d or placebo. At study endpoint, the difference between treatment groups on the modified ADAS-Cog score was

small and favored donepezil (change from baseline to endpoint donepezil -1.0, ± 0.4 [95% CI -1.04 to -0.96]; placebo -0.13, ± 0.4 [95% CI -0.17 to -0.089]). Changes from baseline in CDR-SB scores were minimal in each group and were not significantly different between groups at any time point. Adverse events (AEs) with a 2-or-more-times greater rate in the donepezil group than placebo included diarrhea, muscle spasms, nausea, insomnia, abnormal dreams, and headache.

Another Class II multicenter, randomized, double-blind, placebo-controlled, parallel group study in persons with MCI reported on efficacy of donepezil.^{e55} Participants were randomized to donepezil titrated up to 10 mg/d vs placebo for 24 weeks. Study authors enrolled 270 participants: 67.7% completed donepezil and 83.2% completed placebo. Two primary measures were used, New York University (NYU) Delayed Paragraph Recall Test score and least squares mean Clinical Global Impression of Change Scale for MCI (CGIC-MCI) score. No significant effect on NYU Delayed Paragraph Recall Test was observed (intention-to-treat [ITT] change from baseline donepezil 0.8 [95% CI 0.95–0.85]; placebo 0.5 (95% CI 0.47–0.53)). There was no significant difference on least squares mean CGIC-MCI scores in the ITT population (*p* value and CIs not reported). The study was rated Class II owing to < 80% completion rate.

Conclusions

In patients with MCI, donepezil use over 3 years is possibly ineffective for reducing the chances of a progression to possible or probable Alzheimer dementia (low confidence in the evidence, single Class II study). In patients with MCI, it is unknown whether donepezil slows progression on various cognitive scales (very low confidence in the evidence based on 2 Class II studies with limited precision and small magnitude of effect). Study CIs could not exclude an important effect, and the ADAS-Cog score change was statistically significant but not clinically meaningful.^{e55}

Galantamine

Two Class II studies addressed the use of galantamine in persons with MCI defined as “gradual onset and slow progression of declining cognitive ability by history, a CDR score of 0.5 and CDR memory score of ≥ 0.5 , and insufficient impairment of cognition and activities of daily living to meet diagnostic criteria for dementia”; these study results were reported together.^{e56} The studies were identical in design, with the exception of inclusion of MRI measures (included in one, excluded in the other). These were multicenter, randomized, double-blind, placebo-controlled studies comparing galantamine titrated 4 mg orally twice a day to 8 mg orally to 12 mg orally, depending on tolerance, vs placebo for 24 months. The studies were rated as Class II owing to less than 80% of participants completing the studies. In the first study, the galantamine arm was 47% and the placebo arm was 52%; in the second study, the galantamine arm was 45% and the placebo arm was 54%. The primary outcome was the number and percentage of participants progressing from MCI to dementia at month 24. In the first study, 995 participants were randomized to galantamine (497) and placebo (498). In the second study, 1,062 participants were randomized to galantamine (532) or placebo (530). There was no difference in the primary outcome measure between participants treated with galantamine and those treated with placebo in these studies (reported as Kaplan-Meier estimates for progression to dementia over 2 years,

study 1 = 22.9% for galantamine, 22.6% for placebo, difference 0.3% [95% CI -0.1% to 0.7%), and study 2 = 25.4% galantamine vs 31.2% placebo, difference -5.8% [95% CI -28.7% to 17.1%]).

Conclusion

In patients with MCI, galantamine use over 24 months is probably ineffective for reducing progression to dementia (moderate confidence in the evidence based on 2 Class II studies).

Rivastigmine

A single Class II multicenter, randomized, double-blind, placebo-controlled study compared oral rivastigmine titrated to 3–12 mg/d, depending on tolerance, vs placebo.^{e57} The study was rated as Class II because less than 80% of participants completed the study (61% rivastigmine, 67% placebo). Coprimary measures for the study were time to progress to Alzheimer dementia and difference between rivastigmine and placebo in cumulative z score between baseline and endpoint on a 10-test NP battery. Evaluations for dementia were performed every 3 months. A total of 1,018 persons with MCI participated in the study. There was no statistical difference in mean time to Alzheimer dementia diagnosis (1,318 days in rivastigmine group, 1,289 in placebo group). There was no significant difference between the rivastigmine and placebo groups on the standardized z score for the cognitive test battery measured as mean change from baseline to endpoint (-0.10 , 95% CI -0.63 to 0.44). Over a 3- to 4-year study period, there was no significant difference in the number of participants progressing to a diagnosis of Alzheimer dementia (17.3% of participants on rivastigmine and 21.4% of those on placebo progressed to Alzheimer dementia [HR 0.85, 95% CI 0.64–1.12]).

Conclusion

In patients with MCI, rivastigmine use up to 48 months is possibly ineffective for reducing the rate of progression to possible or probable Alzheimer dementia (low confidence in the evidence based on a single Class II study).

Flavonoid-containing drink

A Class II trial^{e58} (rating based on lack of description of allocation concealment and no defined primary outcome) reported on the use of high- and intermediate-dose flavonoid-containing drink in persons with MCI. This was a single-center, randomized, double-blind, parallel-arm study comparing a daily drink containing about 990 mg of flavonoids vs about 520 mg vs 45 mg (high, intermediate, low), with 30 participants in each study arm. The trial duration was 8 weeks. MCI was diagnosed according to the revised Petersen criteria.^{e2} The authors used a composite cognitive measure that was an “integrated measure of overall cognitive function, a composite cognitive z score.” This score was significantly better in participants in the high-dose flavonoids group vs the low-dose flavonoids group but not in the intermediate-dose flavonoids group ($p < 0.05$, no CIs available). MMSE score did not significantly change in relation to the 3 treatments during the study ($p = 0.13$).

Conclusion

In patients with MCI, there is insufficient evidence to support or refute the cognitive benefits of a drink with high-dose flavonoids (about 990 mg) on an integrated measure (cognitive z score) of overall cognitive function at 8 weeks (very low confidence in the evidence based on a single Class II study with CIs including unimportant effects; evidence of a dose response was also unclear).

Homocysteine-lowering B vitamin treatment

A single Class II trial reported on the use of 3 homocysteine-lowering B vitamins in persons with MCI.^{e59} This was a single-center, double-blind RCT of oral folic acid (0.8 mg/d), vitamin B₁₂ (0.5 mg/d), and vitamin B₆ (20 mg/d) vs placebo in individuals with MCI. Treatment duration was 24 months. The study was rated Class II owing to less than 80% of participants having had 2 evaluable MRI images to measure the primary endpoint (group mean rate of change of atrophy per year) using a fully automated, validated, quantitated measure, the Structural Image Evaluation, using Normalization, of Atrophy.^{e59} A total of 271 individuals entered the study. Eighty-five of 138 randomized to vitamins (61.1%) and 83 of 133 randomized to placebo (62.4%) had serial MRI scans technically suitable for analysis. After adjustment for age, the rate of brain atrophy per year was less in the active treatment group (0.76% [95% CI 0.63%–0.90%]) vs the placebo group (1.08% [95% CI 0.94%–1.22%]), difference -0.32% (95% CI -0.51% to -0.13%).

Conclusion

In patients with MCI, there is insufficient evidence to support or refute the use of homocysteine-lowering therapies in patients with MCI (very low confidence in the evidence based on a single Class II study with decreased confidence in the evidence owing to use of a primary endpoint with unclear clinical significance).

Nicotine patch, transdermal

A single Class I trial reported on the use of transdermal nicotine patches in individuals with aMCI.^{e60} This was a multisite randomized, double-blind, placebo-controlled trial in individuals with aMCI who do not smoke. Participants with aMCI were randomized to receive either a transdermal nicotine patch (titrating to 15-mg patch daily by day 21) or a matching placebo for 26 weeks. Seventy-four participants were randomized, of whom 67 completed the double-blind phase (90%). The primary outcome measure was the reaction time standard error performance on the Connors Continuous Performance Test. Secondary cognitive measures included the Cognitive Drug Research computerized battery, NYC Immediate and Delayed Paragraph Recall Test, and Digit Symbol Substitution Task, with the CGIC-MCI as a clinical measure. The primary outcome measure showed significantly improved performance with nicotine treatment compared with placebo treatment ($F_{1,54} = 14.96$, $p = 0.0003$). There was no statistical difference between treatment groups in the distribution of participants rated improved or not improved. There was no significant difference between treatment groups on Clinical Global Impression of Change (CGIC) in participants rated improved or not improved ($p = 0.13$; CIs not reported).

Conclusion

Six months of transdermal nicotine (15 mg/d) use possibly improves cognitive test performance but not CGIC in patients with aMCI who do not smoke (low confidence in the evidence based on 1 Class I study with decreased confidence in the evidence owing to uncertain clinical significance of the outcome of hit reaction time).

Piribedil

Piribedil is an antiparkinsonian agent and piperazine derivative that acts as a D2 and D3 receptor agonist. A single Class III study reported on the use of oral piribedil in individuals with MCI.^{e61} This was a single-center, randomized, double-blind, placebo-controlled trial of piribedil 50 mg oral daily vs placebo for 90 days. The study was rated as Class III owing to a lack of full description of baseline characteristics of the treatment arms. Ninety percent of participants receiving treatment and 80% of participants receiving placebo completed the study. The primary outcome measure was change in MMSE scores. Improved MMSE scores at 3 months were present in 63.3% of participants receiving piribedil and 26.7% of participants receiving placebo (RD 36.6%, $p < 0.01$). Mean MMSE increase between baseline and 90 days was 1.23 for participants receiving piribedil and was stated to be “significantly greater than for participants receiving placebo”; however, data for participants receiving placebo were not reported.

Conclusion

Data are insufficient to support or refute an effect of piribedil on cognitive measures in MCI (very low confidence in the evidence based on 1 Class III study).

Rofecoxib

A single Class II study reported on the use of oral rofecoxib in individuals with MCI.^{e62} This was a multicenter, randomized, double-blind, placebo-controlled study with parallel groups. The study was rated Class II because less than 80% of participants completed the blinded phase of the study. Participants with aMCI as defined in the study protocol were randomized to receive rofecoxib 25 mg once daily or placebo once daily for up to 4 years. The primary study endpoint was the cumulative incidence of possible or probable Alzheimer dementia (criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association).^{e63} Participants with dementia from other causes were censored in the analysis. A total of 1,457 participants was randomized to placebo (732) or rofecoxib 25 mg (725). In the placebo arm, 301 of 732 participants completed the study on the drug (41%); in the rofecoxib arm, 287 of 725 completed the study (39%). In the rofecoxib group, 107 of 725 participants (14.8%) developed AD over a 4-year study period vs 82 of 732 (11.2%) of the placebo group (HR 1.46 [95% CI 1.09–1.94]). AEs were reported in the study document and were consistent with the packaging label for rofecoxib.

Conclusion

Rofecoxib possibly increases the risk of progression to AD in patients with MCI (low confidence in the evidence based on 1 Class II study).

Clinical context

Rofecoxib was removed from the market worldwide in September 2004. There are no data on whether other anti-inflammatory medications are effective or harmful in persons with MCI.

Tesamorelin/Growth hormone–releasing hormone)

A single-phase II Class II study reported on the use of tesamorelin injections (growth hormone–releasing hormone) in individuals with aMCI.^{e64} This was a single-center, randomized, double-blind, placebo-controlled trial. The study was rated as Class II because of multiple measures reported as the “primary measure.” Results both for healthy participants and for those with aMCI were grouped, thereby confounding interpretation of the study. Sixty-one participants with aMCI were randomized in this study. The authors indicated that the treated aMCI group had multiple positive results on various cognitive measures, and explained that “treatment with GHRH had a favorable effect on cognition ($F_{3,125} = 5.26, p = 0.002$), and even though the healthy adults outperformed those with MCI overall ($F_{3,125} = 11.15, p = 0.001$), the cognitive benefit relative to placebo was comparable for both groups (no treatment x diagnosis interaction; $p = 0.57$).”^{e64}

Conclusion

In patients with MCI, treatment with tesamorelin injections over 20 weeks is possibly effective to improve performance on various cognitive measures (low confidence in the evidence based on 1 Class II study).

Clinical context

It is unclear from this study whether this effect is sustained beyond 20 weeks.

V0191

A single phase II Class III study^{e65} reported on the use of V0191 in individuals with prodromal AD (in this study the definition of prodromal AD correlated with standard definitions of aMCI).^{e2} V0191 was defined as a procholinergic drug, a derivative of a proprietary medicinal product (DEBRUMYL). This multicenter trial was conducted using a randomized, double-blind, placebo-controlled, parallel group design in male and female community-dwelling individuals with prodromal AD. The study was rated Class III because of a lack of definitive masking of raters. Two hundred forty-two participants were randomized to 1,500 mg of V0191 once daily orally vs matching placebo for 24 weeks. The primary study endpoint was the proportion of improvement on the ADAS-Cog at the end of 24 weeks. There were multiple secondary NP measures. The primary outcome measure showed no statistical difference between participants treated with V0191 and those treated with placebo in response rate on the ADAS-Cog (6 of 121

participants in treatment group [5%] had a decrease of ≥ 4 points on the ADAS-Cog score, and 9 of 120 [7.5%] of the placebo group had a decrease of ≥ 4 points [odds ratio 0.63, 95% CI 0.22–1.81]. No secondary endpoint measures were significantly different between groups.

Conclusion

Data are insufficient to support or refute an effect of V0191 use on ADAS-Cog response rates in patients with MCI (very low confidence in the evidence based on 1 Class III study).

Vitamin E

A large, 3-arm, randomized, multicenter, double-blind, placebo-controlled, parallel group study^{e53} (Class II, also described earlier in the donepezil section) reported on participants with MCI who were randomized to 1 of 3 treatments: treatment 1 consisted of 2,000 IU of vitamin E, placebo donepezil, and multivitamin daily; treatment 2 consisted of 10 mg of donepezil, placebo vitamin E, and multivitamin daily; and treatment 3 consisted of placebo vitamin E, placebo donepezil, and multivitamin for 3 years. This study was rated Class II because of a $< 80\%$ completion rate (70% of total group completed). A total of 769 individuals participated in the study. The primary study outcome measure was time to progression to possible or probable Alzheimer dementia. There was no significant difference between groups in the primary outcome measure (HR 0.80, 95% CI 0.57–1.13).

Conclusion

In patients with MCI, use of vitamin E 2,000 IU daily is possibly ineffective for reducing progression to AD (low confidence in the evidence based on a single Class II study).

Vitamin E and vitamin C

One Class III single-center randomized trial^{e66} of vitamin E 300 mg and vitamin C 400 mg daily was performed in individuals with MCI aged 60–75 years. After adjustment for covariate effects, MMSE scores at 6 and 12 months did not differ between the treatment and control groups.

Conclusion

In patients with MCI, combined use of oral vitamin E 300 mg and vitamin C 400 mg daily over 12 months is of uncertain efficacy (very low confidence in the evidence based on single Class III study).

4. What nonpharmacologic treatments are effective for patients diagnosed with MCI? (Treatment question)

The guideline panel identified and reviewed 7 studies (3 Class II and 4 Class III) addressing the issue of nonpharmacologic treatment of MCI.

Exercise interventions

Two Class II studies were reviewed that used exercise as an intervention in individuals with MCI.^{e67,e68}

A Class II study reported results of twice-weekly resistance training or twice-weekly aerobic training for 26 weeks in participants with MCI.^{e67} This was a single-blind (examiner) RCT. Participants were randomized to resistance training, aerobic training, or a balance and tone class twice a week. Eighty-six community-dwelling women aged 70–80 years with MCI were entered in the study. The primary outcome measure was Stroop test performance (executive function task); secondary measures included trail-making tests, verbal digit tests, an everyday problems test, fMRI (during an associative memory task, not further defined), a short physical performance battery, and cardiovascular testing. The study was rated Class II because of lack of concealed allocation and lack of statement about ITT; overall completion rate was 89%. The resistance-training group showed significantly improved results on Stroop test and associative memory tests ($p = 0.03$ vs balance class group for Stroop, $p = 0.04$ vs balance class for associative memory tests, no other statistics provided).

The other Class II study reported results of exercise as an intervention in individuals with MCI.^{e68} This was a randomized single-blind trial comparing a multicomponent exercise program (90 min/d, 2 d/wk, 40 times over 6 months) vs an education control group (2 education classes). Participants were substratified into “other” MCI and aMCI groups as part of the randomization. Data collection was obtained by study personnel who were blinded to randomization assignment. Completion rate was 94% in the exercise group and 90% in the education group. This study was rated Class II because of lack of a specifically defined primary outcome measure. MMSE scores differed at end of study between the participants with aMCI in the exercise group vs those in the education group (p value analysis of variance [ANOVA] for repeated measures 0.03), but not for the overall MCI group (overall group effect ANOVA $p = 0.1$, mean between-group MMSE difference from baseline 1.7). ADAS-Cog did not show significant differences (-0.8 [95% CI -1.4 to 0.2] exercise overall MCI group vs -0.2 [95% CI -0.08 to 0.4] “control group” at 6 months).

Conclusion

In patients with MCI, treatment with exercise training for 6 months is likely to improve cognitive measures (moderate confidence in the evidence based on 2 Class II studies).

Cognitive interventions

Nonpharmacologic interventions involving various approaches to cognitive rehabilitation or training were considered as a group, although different approaches were used. Exact interventions are described briefly for each study. One Class II and 4 Class III studies investigated the use of various cognitive interventions.

A single Class II study^{e69} reported on the results of a memory intervention in 54 individuals with aMCI. This was a single-blind RCT of a memory intervention vs wait list controls with aMCI.

The intervention was a set of 5 weekly 1.5-hour sessions of a memory intervention with clinical neuropsychologists and an occupational therapist, in which “[s]essions used a problem-solving approach to illustrate common everyday memory problems and practice in strategies to respond to these problems.” This study was rated Class II because of a lack of concealed allocation and defined primary outcome. Although point estimates often favored the intervention group, the study authors found no statistically significant improvements^{e69} associated with the intervention (as assessed by ANCOVA analyses) at 2-week or 4-month follow-up when using the prospective memory index and the Multifactorial Memory Questionnaire (MMQ) ability subscale or when considering self-reported strategy knowledge. Self-report of memory strategies was improved at 2 weeks in the intervention group compared with the wait list controls ($p = 0.047$) but not at 4-month follow-up. Data were insufficient to calculate mean differences and CIs between groups, but the small sample size may have limited the study’s ability to detect a statistically significant effect.

Because of these results, the same group performed a follow-up study (Class III) using a similar intervention consisting of six 2-hour weekly sessions conducted by an experienced occupational therapist, neuropsychologist, or cofacilitator and providing information on changing memory, approaches to compensating for memory changes, problem solving, and coping strategies.^{e70} The study randomized 106 participants with aMCI to either early intervention or late intervention (wait list control). The study included multiple primary outcomes in the domains of strategy knowledge, strategy use, memory ability, and well-being. The intervention was associated with improvements in strategy knowledge as measured by the Strategy Repertoire Test (mean postintervention difference 3.3 [95% CI 0.4–6.2], $p < 0.05$ using an ANCOVA with pretest score as a covariate), use of internal strategies as measured by the MMQ 19-item strategy subscale for internal strategies (mean postintervention difference 4.3 [95% CI 1.8–6.9], $p < 0.01$ using an ANCOVA with pretest score as a covariate), and well-being as measured by the MMQ contentment subscale (mean postintervention difference 2.7 [95% CI -1.9 to 7.3], $p < 0.05$ using an ANCOVA with pretest score as a covariate). There was no difference between groups when study authors considered the outcomes of external strategies as measured by the MMQ strategy subscale for external strategies (mean postintervention difference -0.4 [95% CI -3.0 to 2.3], $p > 0.05$ using an ANCOVA with pretest score as a covariate) or memory as measured by the MMQ ability subscale (mean postintervention difference 2.2 [95% CI -2.0 to 6.3], $p > 0.05$ using an ANCOVA with pretest score as a covariate), the Cambridge Assessment of Prospective Memory total score (mean postintervention difference 0.04 [95% CI -3.4 to 3.5], $p > 0.05$ using an ANCOVA with pretest score as a covariate), or the California Verbal Learning Test-Second Edition long-delay recall score (mean postintervention difference 0.95 [95% CI -0.5 to 2.4], $p > 0.05$ using an ANCOVA with pretest score as a covariate).

Another Class III study^{e71} reported on the use of a multidimensional therapy including cognitive training with attention and executive tasks, cognitive stimulation targeting different types of memory, and psychotherapeutic techniques such as progressive muscle relaxation. Participants receiving the intervention attended 60 total sessions, with each weekly day center visit including 3 sessions, 1 of each type (cognitive training, cognitive stimulation, and psychotherapy). This was a randomized trial of multidimensional therapy for 6 months in participants with MCI ($n = 104$) vs a wait list control without therapy ($n = 72$). The study was rated Class III because of all of the following factors: undescribed concealed allocation, lack of statement on ITT, lack of

primary outcome measure, lack of functional performance difference identified vs no therapy, and differences on various NP measures between groups at the end of the treatment period. After 6 months, scores were significantly better in the treatment group on the MMSE (27.06 in the untreated group vs 29.00 in the treated group, mean difference 1.9 [95% CI 0.6–3.2]), Montreal Cognitive Assessment (MoCA) (22.45 in the untreated group vs 24.71 in the treated group, mean difference 2.3 [95% CI 1.0–3.5]), Functional Cognitive Assessment Scale planning subscale (6.18 in the untreated group vs 6.04 in the treated group, mean difference -0.14 [95% CI -0.3 to 0.002]), MoCA delayed recall (2.38 in the untreated group vs 3.19 in the treated group, mean difference 0.8 [95% CI 0.3–1.3]), Rey-Osterrieth Complex Figure Test-Delayed Recall (29.18 in the untreated group vs 31.53 in the treated group, mean difference 2.4 [95% CI 0.4–4.3]), MoCA clock drawing (2.3 in the untreated group vs 2.6 in the treated group, mean difference 0.3 [95% CI 0.05–0.5]), and the Functional Rating Scale of Symptoms of Dementia (3.91 in the untreated group vs 2.67 in the treated group, mean difference -1.2 [95% CI -1.9 to 0.6]). Per the study, each of these remained statistically significant after a Bonferroni correction.

A cluster-randomized Class III study^{e72} reported on 127 participants aged older than 74 years with CDR of 0.5 randomized to cognitive interventions (questions, puzzles, and games particularly targeting executive function and attention), physical activities (walking and step aerobics), or reminiscence (reality orientation and then reminiscing). All interventions included 12 weekly group sessions and 12 homework assignments. In the per-protocol analysis, of the measures performed, the only cognitive measure with between-group differences were the MMSE ($df = 2$, $F = 6.42$, $p = 0.002$), with post hoc paired t-tests showing improvement in the MMSE score in the cognitive intervention and physical activities group but not the reminiscence group, although interpretation of this is limited by the fact that the reminiscence group had a higher MMSE score at baseline ($p < 0.01$). The Quality of Life Face Scale score also had between-group differences on ANOVA analysis ($df = 1$, $F = 7.61$, $p = 0.007$), but the interaction with intervention type was not significant. Other measures showed pre- and posttest differences within groups but were not associated with between-group differences.

Another cluster-randomized Class III study^{e73} randomized 555 community-dwelling persons with either single-domain MCI ($n = 260$) or multidomain MCI ($n = 295$) to either physical exercise (stretching and toning, mind–body exercise, and aerobic exercise), cognitive activity (e.g., reading and discussing newspapers, playing board games), integrated cognitive and physical exercise (1 cognitive activity and 2 mind–body exercise activities each week), or social activity (e.g., tea, movies) groups, each consisting of 1 hour of structured activities 3 times per week. For the 423 participants (62%) who completed the 12-month assessment, there was no difference between groups in the primary outcome measure, which was the CDR-SB score, in terms of change over time ($p = 0.92$) or intervention by time ($p = 0.61$). There were also no differences in the IADL subscale scores of the Chinese Disability Assessment for Dementia (change over time $p = 0.15$, intervention by time $p = 0.80$) or the Cantonese version of the MMSE (change over time $p = 0.16$, intervention by time $p = 0.23$). When the single- and multidomain MCI groups were considered separately, participants with single-domain MCI receiving the integrated cognitive and physical intervention performed better on the ADAS-Cog (intervention by time $p = 0.02$), category verbal fluency test (intervention by time $p = 0.006$), and delayed recall (intervention by time $p = 0.02$). In participants with multidomain MCI, those receiving the

integrated cognitive and physical intervention performed better on the category verbal fluency test (intervention by time $p = 0.009$) but not on other measures.

Conclusions

There is insufficient evidence to support or refute the use of any individual cognitive intervention strategy (very low confidence in the evidence; 1 Class II study with results that are not statistically significant and with suspected imprecision, 4 Class III studies, each examining a different cognitive intervention strategy). When various cognitive interventions are considered as a group, for patients with MCI, cognitive interventions may improve select measures of cognitive function (low confidence in the evidence based on 1 Class II study^{e69} with insufficient precision, 1 Class III study showing improvements in strategy knowledge, internal strategy use, and well-being but not external strategy or memory,^{e70} 1 Class III study^{e71} showing improvement on multiple cognitive measures, 1 Class III study^{e72} showing improvement on the MMSE but with some limitations, and 1 Class III study^{e73} showing no differences when all patients with MCI are considered, but with improvements in the integrated cognitive–physical training groups when the ADAS-Cog, fluency, and recall are considered in patients with single-domain MCI and fluency in patients with multidomain MCI).

PUTTING THE EVIDENCE INTO CLINICAL CONTEXT

Care for persons with cognitive impairment meeting various MCI criteria continues to evolve, with the area of biomarker research changing particularly rapidly. Even in the context of an evolving field, clinicians can provide high-quality care focusing on counseling, treatment, and comorbidity management. Where clinicians are not proficient in caring for the cognitive or behavioral/psychiatric needs of persons with MCI, referral to appropriate specialists is an important part of the treatment paradigm in line with the following recommendations.

PRACTICE RECOMMENDATIONS

Section A: Recommendations for assessing for MCI

1. Recommendation A1

Rationale

Appropriate diagnosis of MCI is important because MCI becomes increasingly common as individuals age and is associated with an increased risk of progression to dementia, suggesting that this condition reflects a pathologic disease state rather than normal cognitive aging. Appropriate diagnosis of MCI is important in order to assess for reversible causes of cognitive impairment, to help patients and families understand the cause of their cognitive concerns, and to discuss the prognostic possibilities with the provider so they can plan accordingly, although sharing the diagnosis must be balanced with the potential harm of anxieties from diagnosing a patient with a condition that may not progress. Ascribing cognitive symptoms to normal aging without an assessment for MCI may result in failure to assess for reversible causes of cognitive impairment or to provide patients and families with an accurate diagnosis that may affect life

choices, or both. Although subjective cognitive complaints alone are insufficient to diagnose MCI,^{e74} such complaints from either patients or their close contacts are core to most major MCI diagnostic criteria, as they may reflect a change in cognitive function.^{e75}

Recommendation

For patients for whom the patient or a close contact voices concern about memory or impaired cognition, clinicians should assess for MCI and not assume the concerns are related to normal aging (Level B).

2. Recommendation A2

Rationale

In the United States, the Medicare Annual Wellness Visit requires an assessment to detect cognitive impairment.^{e76} Subjective cognitive complaints alone can result in both over- and underdiagnosis of MCI and thus are insufficient to screen for MCI.^{e74} Clinicians assessing for cognitive impairment should use a brief, validated cognitive assessment instrument in addition to eliciting patient and informant history regarding cognitive concerns.

Recommendation

When performing a Medicare Annual Wellness Visit, clinicians should not rely on historical report of subjective memory concerns alone when assessing for cognitive impairment (Level B).

3. Recommendation A3

Rationale

When screening or assessing for MCI, validated assessment tools should be used. Various instruments have acceptable diagnostic accuracy for detecting MCI, with no instrument being superior to another.^{e77} Because brief cognitive assessment instruments are usually calibrated to maximize sensitivity rather than specificity, patients who test positive for MCI should then have further assessment (e.g., more in-depth cognitive testing, such as neuropsychological testing with interpretation based on appropriate normative data) to formally assess for this diagnosis. Diagnosis of MCI is based ultimately on a clinical evaluation determining cognitive function and functional status and not solely on a specific test score.

Recommendation

For patients for whom screening or assessing for MCI is appropriate, clinicians should use validated assessment tools to assess for cognitive impairment (Level B). For patients who test positive for MCI, clinicians should perform a more formal clinical assessment for diagnosis of MCI (Level B).

4. Recommendation A4

Rationale

In the presence of cognitive impairment, clinicians need to distinguish between a diagnosis of MCI and one of dementia, although the boundary is not always clear. Diagnosing dementia prematurely can lead to negative consequences for patients and families. Only a proportion of patients with MCI will proceed to dementia. In patients with cognitive impairment, clinicians must carefully assess for evidence of functional impairment limiting independence in daily activities (e.g., by taking a careful history from the patient and a close contact), a requirement for all dementia diagnoses, to help distinguish between MCI and dementia. With a specific inquiry about functional impairment, clinicians may also identify dementia in patients when patients and family are less forthcoming about functional problems.

Recommendation

For patients with MCI, clinicians should assess for the presence of functional impairment related to cognition before giving a diagnosis of dementia (Level B).

5. Recommendation A5

Rationale

Diagnoses of MCI and dementia have important implications for patients and families. Appropriate diagnosis is important for informing evaluation for underlying causes, counseling on long-term prognosis, and recommending therapeutic strategies. Clinicians in many disciplines can have experience in caring for individuals with cognitive impairment, including family practice, geriatrics, internal medicine, neurology, psychiatry, and psychology. When clinicians without experience in cognitive impairment identify patients for whom there is a concern of MCI, they should refer these patients to a specialist with experience in cognition for further evaluation.

Recommendation

For patients suspected to have MCI, clinicians who themselves lack the necessary experience should refer these patients to a specialist with experience in cognition (Level B).

6. Recommendation A6

Rationale

Although MCI is a high-risk state for progression to dementia, some patients with MCI remain stable and some improve. Some cases of MCI are associated with reversible causes of cognitive impairment, including medication AEs, sleep apnea, depression, and other medical conditions.^{e78} Patients with MCI should undergo a medical evaluation for MCI risk factors that may be treatable.

Recommendation

For patients diagnosed with MCI, clinicians should perform a medical evaluation for MCI risk factors that are potentially modifiable (Level B).

7. Recommendation A7

Rationale

Because patients with MCI can improve, remain stable, or progress cognitively, identifying biomarkers that can stratify risk is expected to be particularly important for prognosis. The use of biomarkers in patients with MCI is a rapidly evolving field,^{e79–e81} but to date, there are no biomarkers clearly shown to predict progression in patients with MCI.^{e82}

Recommendation A7a

For patients and families asking about biomarkers in MCI, clinicians should counsel that there are no accepted biomarkers available at this time (Level B).

Recommendation A7b

For interested patients, clinicians may discuss the option of biomarker research or refer patients or both, if feasible, to centers or organizations that can connect patients to this research (e.g., subspecialty centers, Trial Match, ClinicalTrials.gov) (Level C).

8. Recommendation A8

Rationale

Because patients with MCI can improve, remain stable, or progress cognitively over time, patients must be monitored serially for changes in status that could change diagnosis and thus management approach (e.g., treatment, counseling). Although MCI has no approved pharmacologic management, there are US Food and Drug Administration (FDA)–approved agents for treatment of Alzheimer dementia,^{e83–e87} further emphasizing the importance of assessing for a change in cognitive status over time.

Recommendation

For patients diagnosed with MCI, clinicians should perform serial assessments over time to monitor for changes in cognitive status (Level B).

Section B: Recommendations for management of MCI

9. Recommendation B1

Rationale

Some patients with MCI improve or remain stable rather than progress. In addition, some cases of MCI are associated with reversible causes of cognitive impairment, including medication side effects, general medical conditions, sleep disturbance, and depression.^{e78} Because these risk factors are treatable and have implications of their own, weaning patients from use of cognitively impairing medications where feasible and treating risk factors that may contribute to cognitive impairment should be the first steps in managing MCI, particularly because symptomatic treatment options are limited for impaired cognition.

Recommendation

For patients diagnosed with MCI, clinicians should wean patients from medications that can contribute to cognitive impairment (where feasible and medically appropriate) and treat modifiable risk factors that may be contributing (Level B).

10. Recommendation B2

Rationale

There are no FDA-approved medications for the treatment of MCI. Moreover, there are no high-quality, long-term studies identifying pharmacologic or dietary agents that either improve cognition or delay progression in patients with MCI.

Recommendation

For patients diagnosed with MCI, clinicians should counsel the patients and families that there are no pharmacologic or dietary agents currently shown to have symptomatic cognitive benefit in MCI and that no medications are FDA approved for this purpose (Level B).

11. Recommendation B3

Rationale

Studies of cholinesterase inhibitors showed no benefit on cognitive outcomes or reduction in progression from MCI to dementia, although some studies could not exclude an important effect. In addition to lacking efficacy, side effects of cholinesterase inhibitors are common, including gastrointestinal symptoms and cardiac concerns.^{e88}

Recommendation B3a

For patients diagnosed with MCI, clinicians may choose not to offer cholinesterase inhibitors (Level B).

Recommendation B3b

If clinicians choose to offer cholinesterase inhibitors, they must first discuss with patients the fact that this is an off-label prescription not currently backed by empirical evidence (Level A).

12. Recommendation B4

Rationale

Clinical trials provide an opportunity for interested patients to participate in identifying or testing new treatment options, which is of particular importance when no pharmacologic options are available.

Recommendation

For patients diagnosed with MCI who are interested in pharmacologic treatment, clinicians may inform these patients of centers or organizations that can connect patients to clinical trials (e.g., subspecialty centers, Trial Match, ClinicalTrials.gov) (Level C).

13. Recommendation B5

Rationale

Although long-term studies are unavailable, 6-month studies suggest a possible benefit of twice-weekly exercise for cognition in MCI. Exercise also has general health benefits and generally limited risk.

Recommendation

For patients diagnosed with MCI, clinicians should recommend regular exercise (twice/week) as part of an overall approach to management (Level B).

14. Recommendation B6

Rationale

Because the concept of MCI may be poorly understood or distressing to patients and families, it is important to educate patients and families regarding the diagnosis of MCI and how it may progress to dementia but also how individuals with MCI can remain stable or improve. Because MCI may progress to dementia, and particularly because of the lack of effective pharmacologic therapy or any proven methods to reduce the risk of progression of MCI to dementia, it is

particularly important to educate patients with MCI regarding their diagnosis and prognosis at the MCI stage while they can still understand the discussion and participate in planning, even though they may or may not progress. Because of the possibility of progression to a dementia state where patients may no longer be able to participate in decision making, patients with MCI should be encouraged to participate in long-term planning, including topics such as advance directives, living wills, power-of-attorney designations, and finances, which are important irrespective of progression.

Recommendation

For patients diagnosed with MCI, clinicians should discuss diagnosis and uncertainties regarding prognosis. Clinicians should counsel patients and families to discuss long-term planning topics such as advance directives, driving safety, finances, and estate planning (Level B).

15. Recommendation B7

Rationale

Although there are no treatments for cognitive symptoms in MCI, clinicians need to evaluate for and treat other symptoms that can contribute to quality of life in MCI. Behavioral/psychiatric symptoms are common in MCI^{e89–e91} and may be associated with greater functional impairment^{e92} and an increased risk of progression from MCI to dementia.^{e93,e94}

Recommendation

Clinicians should assess for behavioral and neuropsychiatric symptoms in MCI and treat with both pharmacologic and nonpharmacologic approaches when indicated (Level B).

16. Recommendation B8

Rationale

In patients with MCI, cognitive interventions may be beneficial in improving measures of cognitive function. It is good practice to offer non-medication approaches to care.

Recommendation

In patients with MCI, clinicians may recommend cognitive interventions (Level C).

SUGGESTIONS FOR FUTURE RESEARCH

The guideline panel recommends the following:

- The use of consistent diagnostic criteria for MCI and dementia in clinical trials, to improve the ability to apply and combine results
- The inclusion of patient cohorts with specific biomarker data in treatment studies targeted at specific pathologies (e.g., MCI due to AD)

- The use of outcome measures that are direct measures of clinically meaningful patient outcomes (i.e., development of dementia, reduction of ability to undertake ADLs or IADLs, patient or caregiver [or both] quality of life measures) or surrogate markers that have previously been shown to have a strong correlation with such measures
- Standardized reporting of trial design in publications using CONSORT criteria^{e95}
- Study of MCI thought to be secondary to AD and related to non-AD contexts (e.g., vascular MCI, MCI related to Lewy body pathology)
- Further study of early lifestyle and comorbidity modifications and the effects of such changes on the progression of MCI to different dementia subtypes

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CONFLICT OF INTEREST

The American Academy of Neurology (AAN) is committed to producing independent, critical, and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. The AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least 3 AAN committees, a network of neurologists, Neurology peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com. For complete information on this process, access the 2004 AAN process manual.^{e7}

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Appendix e-1. AAN GDDI mission

The mission of the GDDI is to develop, disseminate, and implement evidence-based systematic reviews and clinical practice guidelines related to the causation, diagnosis, treatment, and prognosis of neurologic disorders.

The GDDI is committed to using the most rigorous methods available within its budget, in collaboration with other available AAN resources, to most efficiently accomplish this mission.

Appendix e-2. AAN GDDI members 2015–2017

The AAN has structured its subcommittee overseeing guideline development in several ways in recent years. The GDDI was first formed in 2014; it existed under a previous name and structure when this guideline project was inaugurated. At the time this guideline was approved to advance beyond subcommittee development, the subcommittee was constituted as below.

Cynthia Harden, MD (Chair); Steven R. Messé, MD (Co-Vice-Chair); Sonja Potrebic, MD, PhD; (Co-Vice-Chair); Eric J. Ashman, MD; Stephen Ashwal, MD; Brian Callaghan, MD; Jane Chan, MD; Gregory S. Day, MD, MSc; Diane Donley, MD; Richard M. Dubinsky, MD, MPH; Gary S. Gronseth, MD; Jeffrey Fletcher, MD; Michael Haboubi, DO; John J. Halperin, MD; Yolanda Holler-Managan, MD; Annette M. Langer-Gould, MD, PhD; Nicole Licking, DO; David Michelson, MD; Pushpa Narayanaswami, MBBS, DM; Maryam Oskoui, MD; Alejandro A. Rabinstein, MD; Alexander Rae-Grant, MD; Kevin Sheth, MD; Kelly Sullivan, PhD; Jacqueline French, MD (Guideline Process Historian)

Appendix e-3. Complete search strategy

Mild cognitive impairment (performed December 2007)

MEDLINE

1. mild cognitive impairment.mp.
2. (exp cognition disorders/ or exp memory disorders/) and (mci or cind).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
3. ("no dementia" or "not demented").mp. [mp=title, original title, abstract, name of substance word, subject heading word]
4. (exp cognition disorders/ or exp memory disorders/) and 3
5. (mild\$ adj2 cognitive\$ adj2 impair\$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
6. 1 or 2 or 4 or 5
7. ..1/ 6 hu=y and yr=2000-2008
8. meta-analysis.pt. or meta-analysis.tw. or metaanalysis.tw.
9. (cochrane or embase or medline or cinahl or national library).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
10. handsearch\$.tw.
11. (search\$ and (hand or manual\$ or electronic or database\$ or bibliograph\$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
12. (review or guideline).pt. or consensus.ti. or guideline\$.ti. or literature\$.ti. or overview\$.ti. or review\$.ti.
13. (9 or 10 or 11) and 12
14. (synthesis or syntheses or overview or review or survey).ti.
15. (systematic\$ or critical or methodologic or quantitative or qualitative or literature or evidence).ti.
16. 14 and 15
17. (8 or 13 or 16) not ((case or report or editorial).ti. or editorial.pt. or comment.pt. or letter.pt.)
18. 7 and 17
19. exp Neuropsychological Tests/
20. disease progression/ or predictive value of tests/ or mental status schedule/
21. geriatric assessment/
22. (reproducibil\$ or transition\$ or baseline or "base-line").mp. [mp=title, original title, abstract, name of substance word, subject heading word]

23. preclinical\$.mp. or severity of illness index/ or activities of daily living/ [mp=title, original title, abstract, name of substance word, subject heading word]
24. 7 and 19
25. 7 and (20 or 21 or 22 or 23)
26. exp cognition disorders/di, ep or exp memory disorders/di,ep
27. 7 and 26
28. 24 or 25 or 27
29. 7 and diagnosis, differential/
30. 28 or 29
31. 7 and "sensitivity and specificity"/
32. 30 or 31
33. exp cohort studies/
34. 32 and 33
35. exp cognition disorders/di, ep, pa, co, cl or exp memory disorders/di,ep,pa,co,cl
36. 35 and 7
37. 32 or 36
38. 33 and 37
39. 37 and (reference values/ or risk factors/)
40. 38 or 39

CINAHL

1. mild cognitive impairment.mp.
2. ("no dementia" or "not demented").mp. [mp=abstract, title, author keywords, keywords plus]
3. (mild\$ adj2 cognitive\$ adj2 impair\$).mp. [mp=abstract, title, author keywords, keywords plus]
4. or/1-3
5. ..1/ 4 yr=2000-2008
6. (neuropsychological\$ or (mini adj mental) or assessment or (early adj3 (detect\$ or diagnos\$ or stage\$ or symptom\$ or recogni\$))).mp. [mp=abstract, title, author keywords, keywords plus]
7. 5 and 6
8. (preclinical\$ or prodrom\$ or decline or deteriorat\$ or degenerat\$ or progression or transition\$ or course or baseline or conversion).mp. [mp=abstract, title, author keywords, keywords plus]
9. 5 and 8

10. 7 or 9
11. 5 and criteri\$.mp. [mp=abstract, title, author keywords, keywords plus]
12. 10 or 11
13. 12 and (longitudin\$ or follow\$ or cohort\$ or population\$).mp. [mp=abstract, title, author keywords, keywords plus]
14. 1 or 3 or cind.mp. [mp=abstract, title, author keywords, keywords plus]
15. 13 and 14
16. (mild cognitive impairment or (mild\$ adj2 cognitive\$ adj2 impair\$) or cind).ti,kw,kp.
17. 15 and 16

EMBASE

1. mild cognitive impairment.mp.
2. (exp cognition disorders/ or exp memory disorders) and (mci or cind).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
3. ("no dementia" or "not demented").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
4. (exp cognition disorders/ or exp memory disorders) and 3
5. (mild\$ adj2 cognitive\$ adj2 impair\$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
6. 1 or 2 or 4 or 5
7. ..1/ 6 hu=y and yr=2000-2008
8. 7 and di.fs.
9. 6 and cognitive defect/
10. 6 or 9
11. 10 and (progression\$ or conversion or transition\$ or baseline or "base-line").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
12. prodrom\$.mp. and 10 [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
13. "prediction and forecasting"/ or exp prediction/ or exp prognosis/
14. exp Daily Life Activity/
15. Functional Assessment/ or Medical Assessment/ or Geriatric Assessment/
16. Scoring System/ or Disease Severity/
17. exp disease course/

18. Rating Scale/ or exp Validation Process/ or clinical validity.mp.
19. Risk Factor/
20. 10 and (12 or 13 or 14 or 15 or 16 or 17 or 18 or 19)
21. 11 or 12 or 20
22. ..1/ 21 hu=y and yr=2000-2008
23. clinical study/ or community trial/ or longitudinal study/ or major clinical study/ or prospective study/
24. 22 and 23
25. 22 and follow-up study/
26. 24 or 25
27. 26 not case report/

PsycInfo

1. mild cognitive impairment.mp.
2. (exp cognition disorders/ or exp memory disorders/) and (mci or cind).mp. [mp=title, abstract, heading word, table of contents, key concepts]
3. ("no dementia" or "not demented").mp. [mp=title, abstract, heading word, table of contents, key concepts]
4. (exp cognition disorders/ or exp memory disorders/) and 3
5. (mild\$ adj2 cognitive\$ adj2 impair\$).mp. [mp=title, abstract, heading word, table of contents, key concepts]
6. 1 or 2 or 4 or 5
7. ..1/ 6 hu=y and yr=2000-2008
8. 1 or 3 or 5
9. ..1/ 8 hu=y and yr=2000-2008
10. 9 and (cognitive assessment/ or diagnosis/)
11. 9 and (prevalence or epidemiol\$ or incidence\$).mp. [mp=title, abstract, heading word, table of contents, key concepts]
12. 9 and (transition\$ or progression\$).mp. [mp=title, abstract, heading word, table of contents, key concepts]
13. 9 and (severity\$ or predict\$ or baseline or "base-line").mp. [mp=title, abstract, heading word, table of contents, key concepts]
14. or/10-13
15. 9 and (longitudinal\$ or longterm\$ or follow-up\$ or followup\$).mp. [mp=title, abstract, heading word, table of contents, key concepts]
16. exp Neuropsychological Assessment/ or exp Rating Scales/ or exp Test Validity/ or exp Differential Diagnosis/ or exp Test Reliability/ or "mini mental"
17. 9 and 16

18. 14 and empirical\$.mp. [mp=title, abstract, heading word, table of contents, key concepts]
19. "Followup Study".md.
20. 14 and 19
21. 15 or 17 or 18 or 20
22. 21 not dissertation\$.pt.
23. 14 and population\$.mp. [mp=title, abstract, heading word, table of contents, key concepts]
24. 21 or 23
25. 24 not dissertation\$.pt.
26. limit 25 to (journal article or reviews)

Updated literature search (performed April 2014)

AAN MCI MEDLINE

1. mild cognitive impairment.mp.
2. exp cognition disorders/ and (mci or cind).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
3. ("no dementia" or "not demented").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
4. exp cognition disorders/ and 3
5. (mild\$ adj2 cognitive\$ adj2 impair\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
6. 1 or 2 or 4 or 5
7. meta-analysis.pt. or meta-analysis.tw. or metaanalysis.tw.
8. (cochrane or embase or medline or cinahl or national library).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
9. handsearch\$.tw.
10. (search\$ and (hand or manual\$ or electronic or database\$ or bibliograph\$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
11. (review or guideline).pt. or consensus.ti. or guideline\$.ti. or literature\$.ti. or overview\$.ti. or review\$.ti.
12. (synthesis or syntheses or overview or review or survey).ti.

13. (systematic\$ or critical or methodologic or quantitative or qualitative or literature or evidence).ti.
14. or/7-13
15. 6 and 14
16. exp cognition disorders/dh, dt, pc, px, th, rh or exp memory disorders/dh, dt, pc, px, th, rh
17. 6 and 16
18. limit 17 to (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 comparative study or controlled clinical trial or evaluation studies or meta analysis or multicenter study or pragmatic clinical trial or practice guideline or randomized controlled trial)
19. exp clinical trials as topic/ or exp intervention studies/
20. 17 and 19
21. 15 or 18 or 20
22. 17 and tu.fs.
23. 17 and treatment outcome/
24. 21 or 22 or 23
25. ..1/ 24 yr=2008-2014
26. (exp *cognition disorders/dh, dt, pc, px, th, rh or exp *memory disorders/dh, dt, pc, px, th, rh) and 25
27. exercise.mp. or exercise therapy/ or resistance training/ or physical fitness/ or aerobic*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
28. exp Dietary Supplements/ or exp Vitamins/
29. exp Diet/
30. exp Anti-Inflammatory Agents, Non-Steroidal/
31. exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ or exp Anticholesteremic Agents/
32. exp Behavior Therapy/
33. exp psychotherapy/
34. (counseling/ or 27 or 28 or 29 or 30 or 31 or 32 or 33) and 25
35. 25 and tu.fs.
36. 26 or 34 or 35
37. 36 not (letter or news or editorial).pt.
38. remove duplicates from 37

AAN MCI treatment EMBASE

1. mild cognitive impairment.mp.
2. exp cognition disorders/ and (mci or cind).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
3. ("no dementia" or "not demented").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
4. exp cognition disorders/ and 3
5. (mild\$ adj2 cognitive\$ adj2 impair\$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
6. 1 or 2 or 4 or 5
7. meta-analysis.pt. or meta-analysis.tw. or metaanalysis.tw.
8. (cochrane or embase or medline or cinahl or national library).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
9. handsearch\$.tw.
10. (search\$ and (hand or manual\$ or electronic or database\$ or bibliograph\$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
11. (review or guideline).pt. or consensus.ti. or guideline\$.ti. or literature\$.ti. or overview\$.ti. or review\$.ti.
12. (synthesis or syntheses or overview or review or survey).ti.
13. (systematic\$ or critical or methodologic or quantitative or qualitative or literature or evidence).ti.
14. or/7-13
15. 6 and 14
16. exp clinical trials as topic/ or exp intervention studies/
17. exercise.mp. or exercise therapy/ or resistance training/ or physical fitness/ or aerobic*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
18. exp Dietary Supplements/ or exp Vitamins/
19. exp Diet/
20. exp Anti-Inflammatory Agents, Non-Steroidal/
21. exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ or exp Anticholesteremic Agents/
22. exp Behavior Therapy/
23. exp psychotherapy/
24. exp cognitive defect/ or exp memory disorder/ or exp mild cognitive impairment/
25. exp cognitive defect/dm, dt, pc, rh, th or exp memory disorder/dm, dt, pc, rh, th or exp mild cognitive impairment/dm, dt, pc, rh, th

26. 6 and 25
27. or/16-23
28. 24 and 27
29. 6 and 28
30. 15 or 26 or 29
31. exp case control study/ or exp clinical trial/ or exp "clinical trial (topic)"/ or exp intervention study/ or exp longitudinal study/ or exp major clinical study/ or exp prospective study/ or exp retrospective study/
32. exp cohort analysis/ or exp control group/ or exp cross-sectional study/ or exp evidence based practice/ or exp practice guideline/
33. 25 and 30 and (31 or 32)
34. 6 and dt.fs.
35. 34 and (31 or 32)
36. 33 or 35
37. ..1/ 36 hu=y and yr=2008-2014
38. 37 not (case report/ or letter.pt. or note.pt. or short survey.pt.)

AAN MCI treatment PsycInfo

1. mild cognitive impairment.mp.
2. ("no dementia" or "not demented").mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
3. (mild\$ adj2 cognitive\$ adj2 impair\$).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
4. meta-analysis.pt. or meta-analysis.tw. or metaanalysis.tw.
5. (cochrane or embase or medline or cinahl or national library).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
6. handsearch\$.tw.
7. (search\$ and (hand or manual\$ or electronic or database\$ or bibliograph\$)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
8. (review or guideline).pt. or consensus.ti. or guideline\$.ti. or literature\$.ti. or overview\$.ti. or review\$.ti.
9. (synthesis or syntheses or overview or review or survey).ti.
10. (systematic\$ or critical or methodologic or quantitative or qualitative or literature or evidence).ti.
11. or/4-10

12. exercise.mp. or exercise therapy/ or resistance training/ or physical fitness/ or aerobic*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
13. exp Dietary Supplements/ or exp Vitamins/
14. exp Anti-Inflammatory Agents, Non-Steroidal/
15. exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ or exp Anticholesteremic Agents/
16. exp Behavior Therapy/
17. exp psychotherapy/
18. exp cognitive defect/ or exp memory disorder/ or exp mild cognitive impairment/
19. exp case control study/ or exp clinical trial/ or exp "clinical trial (topic)"/ or exp intervention study/ or exp longitudinal study/ or exp major clinical study/ or exp prospective study/ or exp retrospective study/
20. exp cohort analysis/ or exp control group/ or exp cross-sectional study/ or exp evidence based practice/ or exp practice guideline/
21. 1 or 2 or 3
22. or/11-17
23. 21 and 22
24. physical treatment methods/ or treatment/ or drug therapy/ or immunotherapy/ or transcranial magnetic stimulation/
25. 21 and 24
26. 23 or 25
27. limit 26 to (all journals and yr="2008 - 2015")
28. limit 27 to human

Updated literature search (performed October of 2015)

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

- 1 exp cognition disorders/ and (mci or cind or (mild* adj2 cognit*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
- 2 exp cognition disorders/ and ("no dementia" or "not demented" or (without adj2 dement*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
- 3 (mild\$ adj2 cognitive* adj2 impair*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

4 (cognit* adj3 (prodrom* or declin*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
5 mild cognitive impairment/
6 or/1-5
7 6 and (incidence or prevalence or epidemiol* or population*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
8 mild cognitive impairment/ep
9 exp epidemiologic studies/
10 6 and 9
11 7 or 8 or 10
12 ..1/ 11 yr=2011-2015
13 limit 12 to (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 comparative study or controlled clinical trial or multicenter study or pragmatic clinical trial or randomized controlled trial)
14 12 and (longitudinal* or cohort* or "cross-section*" or "follow up" or followup* or prospective* or retrospective*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
15 (1 or 2 or 3 or *mild cognitive impairment/) and 14
16 13 or 15
17 remove duplicates from 16
18 17 not (letter or editorial or note or comment*).pt.
CENTRAL – same strategy = 224

Embase 1988 to 2015 Week 47

Searches

1 exp cognition disorders/ and (mci or cind or (mild* adj2 cognit*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
2 exp cognition disorders/ and ("no dementia" or "not demented" or (without adj2 dement*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
3 (mild\$ adj2 cognitive* adj2 impair*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

4 (cognit* adj3 (prodrom* or declin*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
5 mild cognitive impairment/
6 or/1-5
7 6 and (incidence or prevalence or epidemiol* or population*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
8 mild cognitive impairment/ep
9 exp epidemiology/
10 6 and 9
11 5 and 7
12 8 or 10 or 11
13 ..1/ 12 hu=y and yr=2011-2015
14 clinical study/ or exp case control study/ or exp clinical trial/ or exp "clinical trial (topic)"/ or exp longitudinal study/ or exp major clinical study/ or exp prospective study/ or exp retrospective study/
15 13 and 14
16 13 and cohort*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
17 15 or 16
18 remove duplicates from 17
19 limit 18 to (adult <18 to 64 years> or aged <65+ years>)

CINAHL

#	Query
S12	S10 AND S11
S11	TX trial* OR cohort* OR longitudinal* OR population* OR "case control"
S10	S6 OR S8
S9	S6 OR S8
S8	S5 AND S7
S7	(MH "Incidence") OR (MH "Prevalence") OR (MH "Epidemiology+")
S6	S5 AND (S4 OR S3)
S5	S1 OR S2
S4	(MH "Cognition Disorders+/EP")

S3 (MH "Dementia+/EP")
 S2 TX "mild* cognitive* impair*"
 S1 TX "mild cognitive impairment"

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

Searches

1 exp cognition disorders/ and (mci or cind or (mild* adj2 cognit*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
 2 exp cognition disorders/ and ("no dementia" or "not demented" or (without adj2 dement*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
 3 (mild\$ adj2 cognitive* adj2 impair*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
 4 (cognit* adj3 (prodrom* or declin*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
 5 mild cognitive impairment/
 6 or/1-5
 7 6 and (predict* or prognos* or trajector* or baseline*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
 8 disease progression/ or ((clinical or natural or disease) adj2 (course or history or progression)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
 9 (risk adj2 (assess* or high or stratif*)).mp. or risk factors/ [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
 10 (conversion or convert* or transition*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
 11 (first adj2 episode*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
 12 6 and (8 or 9 or 10 or 11)

13 7 or 12
 14 ((geriatric or functional) adj2 assess*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
 15 13 and 14
 16 (adl.mp. or activities of daily living/) and 13 [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
 17 (iadi or "daily living").mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
 18 13 and 17
 19 13 and (symptom* or severity or scoring or score or scale*).mp.
 20 15 or 16 or 18 or 19
 21 20 and (follow up studies/ or longitudinal studies/ or cohort*.mp. or prospective*.mp. or retrospective*.mp. or outcome*.mp.) [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
 22 20 and randomized controlled trial.pt.
 23 20 and random*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
 24 21 or 22 or 23
 25 ..1/ 24 yr=2011-2015
 26 remove duplicates from 25
 CENTRAL – 310

Embase 1988 to 2015 Week 47

Searches

1 exp cognition disorders/ and (mci or cind or (mild* adj2 cognit*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
 2 exp cognition disorders/ and ("no dementia" or "not demented" or (without adj2 dement*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
 3 (mild\$ adj2 cognitive* adj2 impair*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
 4 mild cognitive impairment/

5 disease progression/ or ((clinical or natural or disease) adj2 (course or history or progression)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

6 (risk adj2 (assess* or high or stratif*)).mp. or risk factors/ [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

7 (conversion or convert* or transition*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

8 (first adj2 episode*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

9 ((geriatric or functional) adj2 assess*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

10 (iadi or "daily living").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

11 (predict* or prognos* or trajector* or baseline or "base line").mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

12 (first adj2 episode*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

13 "evaluation and follow up"/ or exp adl disability/ or exp clinical assessment/ or exp course evaluation/ or exp follow up/ or exp functional assessment/ or exp functional assessment inventory/ or exp geriatric assessment/ or exp outcome assessment/

14 4 and (5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13)

15 4 and (symptom* or severity or scoring or score or scale*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

16 14 or 15

17 ..1/ 16 hu=y and yr=2011-2015

18 exp controlled clinical trial/

19 exp "controlled clinical trial (topic)"/

20 prospective study/ or retrospective study/

21 longitudinal study/

22 cohort analysis/ or cross-sectional study/

23 or/18-22

24 17 and 23

25 24 not (letter or editorial or comment or note).pt.

26 remove duplicates from 25

Searches

- 1 disease progression/ or ((clinical or natural or disease) adj2 (course or history or progression)).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
- 2 (risk adj2 (assess* or high or stratif*)).mp. or risk factors/ [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
- 3 (conversion or convert* or transition*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
- 4 (first adj2 episode*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
- 5 ((geriatric or functional) adj2 assess*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
- 6 (iadi or "daily living").mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
- 7 (predict* or prognos* or trajector* or baseline or "base line").mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
- 8 (first adj2 episode*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
- 9 ((functional or clinical or course or geriatric) adj2 assess*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
- 10 (mild\$ adj2 cognitive* adj2 impair*).mp.
- 11 or/1-9
- 12 *cognitive impairment/ or exp cognitive ability/ or exp dementia/ or exp memory disorders/
- 13 12 and (mci or mild*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
- 14 10 or 13
- 15 14 and 11
- 16 14 and (predict* or prognos* or followup* or severity or score* or scoring or scale* or symptom*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
- 17 15 or 16
- 18 limit 17 to (all journals and yr="2011 - 2015")
- 19 limit 18 to ("0450 longitudinal study" or "0451 prospective study" or "0453 retrospective study" or "2000 treatment outcome/clinical trial")
- 20 18 and (population* or cohort* or prospective* or retrospective*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
- 21 19 or 20

22 10 and 21
 23 21 and mci.tw.
 24 22 or 23
 25 remove duplicates from 24

S18 S14 AND S17
 S17 S15 OR S16
 S16 (MH "Prospective Studies+") OR (MH "Concurrent Prospective Studies") OR (MH "Nonconcurrent Prospective Studies") OR
 "cohort"
 S15 (MH "Randomized Controlled Trials") OR (MH "Clinical Trials+")
 S14 S8 OR S13
 S13 S3 AND S12
 S12 S9 OR S10 OR S11
 S11 (MH "Geriatric Assessment+") OR (MH "Geriatric Functional Assessment") OR (MH "Functional Assessment+") OR (MH
 "Clinical Assessment Tools+")
 S10 TX baseline OR TX trajectory* OR TX predict*
 S9 (MH "Disease Progression")
 S8 S3 AND S7
 S7 S4 OR S5 OR S6
 S6 (MH "Cognition Disorders+/PR")
 S5 (MH "Dementia+/PR")
 S4 (MH "Prognosis+") OR "prognosis" OR (MH "Clinical Assessment Tools+")
 S3 S1 OR S2
 S2 ""mild* cognitive* impair*""
 S1 ""mild cognitive impairment""

Appendix e-4. AAN rules for classification of evidence for risk of bias

Screening scheme

Class I

A statistical, population-based sample of patients studied at a uniform point in time (usually early) during the course of the condition. All patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation that is masked to the patients' clinical presentations.

Class II

A statistical, non-referral-clinic-based sample of patients studied at a uniform point in time (usually early) during the course of the condition. Most patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation that is masked to the patients' clinical presentations.

Class III

A sample of patients studied during the course of the condition. Some patients undergo the intervention of interest. The outcome, if not objective, is determined in an evaluation by someone other than the treating physician.

Class IV

Studies not meeting Class I, II, or III criteria, including consensus, expert opinion, or a case report.

Prognostic accuracy scheme

Class I

A cohort study of a broad spectrum of persons at risk for developing the outcome (e.g., target disease, work status). The outcome is defined by an acceptable reference standard for case definition. The outcome is objective or measured by an observer who is masked to the presence of the risk factor. Study results allow calculation of measures of prognostic accuracy.

Class II

A case-control study of a broad spectrum of persons with the condition compared with a broad spectrum of controls, or a cohort study of a broad spectrum of persons at risk for the outcome (e.g., target disease, work status) where the data were collected retrospectively. The outcome is defined by an acceptable reference standard for case definition. The outcome is objective or measured by an observer who is masked to the presence of the risk factor. Study results allow calculation of measures of prognostic accuracy.

Class III

A case-control study or a cohort study where either the persons with the condition or the controls are of a narrow spectrum where the data were collected retrospectively. The outcome is defined by an acceptable reference standard for case definition. The outcome is objective or measured by an observer who did not determine the presence of the risk factor. Study results allow calculation of measures of a prognostic accuracy.

Class IV

Studies not meeting Class I, II, or III criteria, including consensus, expert opinion, or a case report.

Therapeutic scheme

Class I

A randomized controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent between treatment groups, or there is appropriate statistical adjustment for differences.

The following are also required:

- a. concealed allocation
- b. no more than 2 primary outcomes specified
- c. exclusion/inclusion criteria clearly defined
- d. adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias.
- e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*:
 - i. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority.

- ii. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective).
 - iii. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.
 - iv. The interpretation of the study results is based upon a per-protocol analysis that accounts for dropouts or crossovers.
- f. For crossover trials, both period and carryover effects examined and statistical adjustments performed, if appropriate

Class II

An RCT of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e above (see Class I) or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e above (see Class I). (Alternatively, a randomized crossover trial missing 1 of the following 2 characteristics: period and carryover effects described or baseline characteristics of treatment order groups presented.) All relevant baseline characteristics are presented and substantially equivalent among treatment groups, or there is appropriate statistical adjustment for differences.

Class III

All other controlled trials (including studies with external controls such as well-defined natural history controls). (Alternatively, a crossover trial missing both of the following 2 criteria: period and carryover effects described or baseline characteristics of treatment order groups presented.) A description of major confounding differences between treatment groups that could affect outcome.** Outcome assessment is masked, objective, or performed by someone who is not a member of the treatment team.

Class IV

Studies that (1) did not include patients with the disease, (2) did not include patients receiving different interventions, (3) had undefined or unaccepted interventions or outcomes measures, or (4) had no measures of effectiveness or statistical precision presented or calculable.

* Note that numbers 1–3 in Class Ie are required for Class II in equivalence trials. If any 1 of the 3 is missing, the class is automatically downgraded to Class III.

**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

Appendix e-5. Rules for determining confidence in evidence

- Modal modifiers used to indicate the final confidence in evidence in the conclusions
 - High confidence: highly likely or highly probable
 - Moderate confidence: likely or probable
 - Low confidence: possibly
 - Very low confidence: insufficient evidence
- Initial rating of confidence in the evidence for each intervention outcome pair
 - High: requires 2 or more Class I studies
 - Moderate: requires 1 Class I study or 2 or more Class II studies
 - Low: requires 1 Class II study or 2 or more Class III studies
 - Very low: requires only 1 Class III study or 1 or more Class IV studies
- Factors that could result in downgrading confidence by 1 or more levels
 - Consistency
 - Precision
 - Directness
 - Publication bias
 - Biological plausibility
- Factors that could result in downgrading confidence by 1 or more levels or upgrading confidence by 1 level
 - Magnitude of effect
 - Dose response relationship
 - Direction of bias

Appendix e-6. Evidence synthesis tables

Evidence profile: Frequency/Screening

Study (first author, y)	Outcome (MCI, subtype, CIND)	Criteria used to determine MCI vs CIND	Narrow or broad MCI criteria	Population/ Geographic area	Ages included (baseline)	Ages older vs younger	Sex (% female)	Education	Number & class of studies	Effect (e.g., frequency, prevalence)	Precision	Consistency	Directness	Plausibility	Magnitude of effect	Dose response	Comment	Confidence in Evidence
Anstey, 2008 ^{e12}	MCI (Jack, 1999 ^{e102})	NA	Narrow	White Australian	60–64		49%	13.98	Class I	2.10%							43 MCI cases among 2,073 interviewed, used for meta-analysis	
Di Carlo, 2007 ^{e13}	MCI and CIND	MCI (Petersen, 1999 ^{e3} ; Winblad, 2004 ^{e1}); CIND (Palmer, 2002 ^{e99})	Broad	Italian	≥65; 73.7(5.6)		46.40%	6.4	Class I	CIND 9.5%, MCI 16.1%								
Fei, 2009 ^{e10}	CIND (operational)	Operationalized definition of CIND	Narrow	Chinese urban	>65 (mean age 73.31(2.17))		70.60%	6.53	Class I	9.70%								

Hanninen, 2002^{e14}	MCI (Petersen, 1995 ^{e100})	NA	Narrow	Finnish urban	60–79;68.1 (4.5)		60.50 %	9.1	Class I	5.30%								
Louis, 2005^{e15}	aMCI (Petersen, 1999 ^{e3}) and nMCI	NA	Broad	US urban	≥65 (aMCI 78.1(7.0); no memory deficit MCI 77.1(6.6))		65.5% aMCI,	aMCI 10.2; nMCI 9.6; no cog 10.5	Class I	27.3% (aMCI and nMCI)								
Purser, 2006^{e16}	MCI (Petersen, 1999 ^{e3})	NA	Narrow	US rural	≥65; 74.6(6.3)		59.96 %	10.2	Class I	25.00 %								
Schonknecht, 2005^{e17}	AACD (Levy, 1994 ^{e103})	NA	Broad	German urban	62.4(2.4)		49.90 %	Not reported	Class I	13.40 %								
Artero, 2008^{e18}	Revised MCI (Winblad, 2004 ^{e1})	NA	Broad	White French	>60; (75.7[7.8])		70%	Not reported	Class I	42.00 %								
Boyle, 2006^{e19}	MCI (Bennett, 2002 ^{e98})	NA	Broad	US urban white	78.6 (6.8) MCI;74.3 (6.5) no cognitive impairment (range not reported)		69.2% (MCI), 64.4% no cog impairment	17.9 MCI, 18.3 no cog impairment	Class I	28.10 %								

Busse, 2006^{e20}	MCI (Petersen, 2004 ^{e2})	NA	Narrow	German	≥75; 81.5(4.8)		75%	Low 22.4% , middle 63.7% , high 13.8% ; not further defined	Class I	19.30%								
Das, 2007^{e21}	MCI (Petersen, 2001 ^{e5})	NA	Narrow	Indian urban	66.75 (9.96)		50.30%	7.71 (5.48)	Class I	aMCI 6.04%; nMCI 8.85%								
Lobo, 2008^{e22}	MCI (Petersen, 1999, ^{e3} operationalized)	NA	Narrow	Spanish urban	<64 1,080; 65–79 2,319; >80 1,396		57.70%	7.93 (3.58)	Class I	20.80%								
Lopez, 2007^{e23}	Operational	NA	Broad	US urban White (Pittsburgh cohort)	77.7(3.8) normal; 78.0 (3.5) MCI		60%	62% > high school education	Class I	21.70%								
Petersen, 2010^{e24}	Petersen, 2004 ^{e2}	NA	Narrow	US single county	70–89		49.90%	53.3% >12 y education	Class I	16.00%								
Wilson, 2007^{e25}	MCI (Bennett, 2002 ^{e98})	NA	Broad	US urban	MCI 81.7(6.7), no cognitive impairment 79.2(6.8)		MCI 71.2, no cognitive impairment 79.2	MCI 14.8, no cognitive impairment 14.5	Class I	24.30%								

Ganguli, 2004^{e9}	aMCI (Petersen, 1999 ^{e3}) operationalized	NA	Narrow	US rural	≥65; 74.6(5.3)		60.70 %	“mean education level high school graduate”	Class I	3.20%							
Lopez, 2003^{e27}	aMCI and MCI multiple cognitive domains, Lopez, 2003 ^{e27}	NA	Broad	US multisite	≥65; broken down by MCI and healthy and by age range		60.90 %	1,274 < high school, 1,192 ≥ high school	Class I	18.80 %							
Ganguli, 2010^{e26}	MCI (Petersen, 1999, ^{e3} Winblad, 2004 ^{e1})			Western Pennsylvania	≥65 y		61.1%	< high school : 13.8% ; high school : 45.1% ; > high school : 41.1%	Class I	aMCI: 2.27%; expanded MCI: 17.6%							
Shi, 2013^{e28}	CIND	Mild cognitive / functional impairment not meeting criteria for	Broad	Rural China	≥80 y		54%		Class I	47.4% CIND							

		dementia or performance on NP/functional measures below expectations and ≥ 65 0.5 SD below published norms on any test																
Guaita, 2015^{e29}	CIND	MCI	Narrow	Residents of Abbiatgrosso, Italy	70–75 y		54%	NA	Class I	5% MCI								
Overall									20 Class I and 14 Class II (only Class I listed here because of their	See meta-analysis; evaluating age, education, MCI criteria, sex	N	N	N	N	N	N	MCI is common in older populations, and its prevalence increases with age (high confidence, multiple Class	High

									volu me and least risk of bias)								I studies, consist ent meta- analysi s).	
--	--	--	--	--	--	--	--	--	---	--	--	--	--	--	--	--	--	--

Abbreviations: AACD = age-associated cognitive disorder; aMCI = amnesic mild cognitive impairment; CIND = cognitively impaired no dementia; D = downgrade (all); MCI = mild cognitive impairment; N = neutral; nMCI = nonamnesic mild cognitive impairment; U = upgrade (only for magnitude of effect and dose response).

Evidence profile: Prognosis

Risk factor	Study (first author, y)	Outcomes	Age of patients	Time frame	Number & class of studies	Effect (e.g., risk ratio, odds ratio, risk difference)	Precision	Consistency	Directness	Plausibility	Magnitude of effect	Dose response	Comments	Confidence in evidence	Conclusion
MCI	Boyle, 2006 ^{e19}	AD	55–100 y (ave 80.5 SD 6.9)	2.5 y	Class I	RR 6.75 (95% CI 4.11–11.09)									
	Di Carlo, 2007 ^{e13}	Dementia	65–84 y	3.9 y (0.7)	Class I	HR 2.90 (95% CI 1.59–5.31)									
	Ganguli, 2004 ^{e9}	Dementia	65+ y	10 y	Class I	HR 3.9 (95% CI 2.1–7.2)									
	(Lopez, 2003 ^{e27} ; Lopez, 2007 ^{e23})	Dementia	75+ y	5–10 y	Class I	Dementia 38/1,000 person-years in “normal” (CI 29.9–48.2), 147/1,000 in MCI (CI 113.3–189.6)									
	Monastero, 2007 ^{e46}	AD	75+ y	6 y	Class I	Mild CIND RR 1.7 (95% CI 1.3–2.2), moderate CIND 1.5 (1.0–2.1), severe CIND									

					1.8 (1.2–2.7)										
Saxton, 2009 ^{e42}	Dementia	75+ y	Medi an follo w-up 6.1 y	Class I	7.4% of pts with normal neuropsychol ogy progressed to dementia vs 41.5% of pts with MCI on NP testing.										
Tschant z, 2006 ^{e47}	Dementia	65+ y	3+ y	Class I	At follow-up 3.3% of neurologically intact, 39.1% with cognitive symptoms, and 54.9% with prodromal AD had dementia.										
Roberts , 2014 ^{e45}	Dementia	≥70 y	Medi an follo w-up: 5.1 y	Class I	153 of 534 participants (28.7%) with prevalent or incident MCI progressed to dementia; cumulative dementia incidence: 5.4% at 1 y, 16.1% at 2 y, 23.4% at 3 y, 31.1% at 4 y, 42.5% at 5 y										

						11.7% with CIND progressed to dementia annually; those with prodromal AD and stroke progressed to 17%–20% annually. Annual death rate = 8% among those with CIND and ~15% among those with cognitive impairment due to medical conditions.									
	Plasma n, 2008 ^{e44}	Dementia , AD	≥71 y	3.5 y	Class I										
Overall: MCI					9 Class I articles		N	N	N	N	N	N	Pts with MCI are at higher risk of progressing to dementia than age-matched controls.	High	
Sex															
Age at diagnosis															
Other															

Abbreviations: AD = Alzheimer disease; CIND = cognitively impaired no dementia; HR = hazard ratio; MCI = mild cognitive impairment; N = neutral; NP = neuropsychological; RR = relative risk.

Evidence profile: Therapeutic – pharmacologic

Intervention	Study	Outcome	Time frame	Number & class of studies	Effect	Precision	Consistency	Directness	Plausibility	Magnitude of effect	Dose response	Comment	Confidence in evidence	Conclusion
Donepezil (10 mg)	Petersen, 2005 ^{e53}	Progression to AD	3 y	Class II	HR for time to AD 0.80 (95% CI 0.57–1.13) with donepezil									
Donepezil summary: progression to AD				1 Class II study ^{e52} (anchor: low)	HR for time to AD 0.80 (95% CI 0.57–1.13) with donepezil	-	-	-	-	-	N A		Low	In pts with MCI, donepezil use over 3 y is possibly ineffective for reducing progression to possible or probable AD (1 Class II study).
Donepezil (10 mg)	Doody, 2009 ^{e54}	Change from baseline in modified ADAS-Cog (dual primary outcomes)	48 wk	Class II	Difference between tx groups at endpoint: -0.90 (95% CI -1.63 to -0.17)							Change is statistically significant but not clinically meaningful; used an LOCF approach, but discontinuations much	Low	In pts with MCI, donepezil use is possibly ineffective for improving modified ADAS-Cog

												higher in donepezil group (165) than placebo group (114)		measures.
		Change in baseline in CDR-SB (dual primary outcomes)			Difference in mean change between tx groups: -0.1 (95% CI - 0.38 to 0.18), calculated from table 2 in article, assuming +/- SE									
Donepezil (10 mg)	Salloway , 2004 ^{e55}	NYU Paragraph Delayed Recall Test	24 wk	Class II	ITT-LOCF: difference in mean change between groups 0.3 (95% CI - 0.85 to 1.45); ITT-OC: difference in mean change between groups 0.5 (95% CI - 0.33 to 1.33)									

		ADCS CGIC-MCI			<p>Not enough information for CIs: "In measures of global function, the least squares mean CGIC-MCI scores were better for donepezil-treated than placebo-treated subjects at end point, but the differences were not significant in the ITT or FE populations. In the ITT-OC population, 32.6% of donepezil-treated subjects showed minimal or moderate improvement, compared with 24.3% of placebo-</p>												
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					treated subjects; 51.7% of donepezil treated and 60.4% of placebo-treated subjects showed no change. These proportions were similar in the FE population."									
Donepezil summary cognitive measures				2 Class II ^{e54,e55} (anchor: moderate)	(See above)	D	D?	D	-	D	N A	Downgraded for precision (Salloway CIs could not exclude important effect), downgraded for magnitude of effect (ADAS-Cog change statistically significant but not clinically meaningful); downgraded because of indirect	Very low	It is unknown whether donepezil slows progression on various cognitive scales (2 Class II studies downgraded for precision and low magnitude of effect).

												relationship of ADAS- Cog with ADL		
Galantamine	Winblad, 2008 ^{e56}	Conversion from MCI to dementia at mo 24	24 mo	2 Class II studies reported in same article (anchor: moderate)	There were no differences between galantamine and placebo in 24-mo conversion rates (study 1: 22.9% [galantamine] vs 22.6% [placebo], p = 0.146; study 2: 25.4% [galantamine] vs 31.2% [placebo], p = 0.619).	-	-	-	-	-	-		Moderate	In pts with MCI, galantamine use over 24 mo is probably ineffective for reducing progression to possible or probable AD (2 Class II studies).
Rivastigmine	Feldman, 2007 ^{e57}	Time to AD and rate of cog decline (different in cumulative z score on NP battery)	Up to 48 mo	1 Class II (anchor: low)	HR for progression to AD 0.85 (95% CI 0.64–1.12); mean change z score	-	N A	-	-	-	N A		Low	In pts with MCI, rivastigmine use over up to 48 mo is possibly ineffective for reducing

					between groups - 0.10 (95% CI -0.63 to 0.44)									to progression to possible or probable AD (1 Class II study).
Flavonoid drink	Desideri, 2012 ^{e58}	Composite cognitive z score at 8 wk; MMSE, TMT-A, TMT-B, verbal fluency	8 wk	1 Class II (anchor: low)	Composite cognitive z score significantly changed during the study period ($p < 0.0001$), with HF (0.693 ± 0.223 ; $p < 0.0001$) and IF (0.404 ± 0.141 ; $p < 0.0001$) groups demonstrating significant improvement; no change was observed in the LF group (0.072 ± 0.383 ; $p = 0.31$; table 1 and figure S2 in the article). Composite cognitive z	D	N A	-	-	-	-	Downgraded for no description of allocation concealment and no primary outcome; downgraded for precision (CIs include unimportant effects)	Low	In pts with MCI, a drink with high- (about 990 mg) or intermediate-dose (about 520 mg) flavonoids might improve on integrated measure (cognitive z score) of overall cognitive function at 8 wk (1 Class II study). The long-term implications of this approach are unknown.

					score at the end of follow-up was significantly ($p < 0.05$) better in pts assigned to HF compared with those assigned to LF									
B vitamins	Smith, 2010 ^{e59}	Atrophy change per y (neuropsychological secondary outcomes)	24 mo	1 Class II (anchor: low)	The mean rate of brain atrophy per y was 0.76% [95% CI 0.63–0.90] in the active treatment group and 1.08% [95% CI 0.94–1.22] in the placebo group ($p = 0.001$).	-	N A	D	-	-	N A	Downgraded for directness (the clinical relevance of annual atrophy change in unknown)	Very low	In pts with MCI, homocysteine-lowering B vitamin therapy over 24 mo is possibly effective for reducing the rate of annual brain volume atrophy (1 Class II study); however, the clinical relevance of this is unknown.

Nicotine patch	Newhouse, 2012 ^{e60}	CPT (primary)	26 wk 6 mo	1 Class I (anchor: moderate)	Hit RT standard error over interstimulus interval (the primary outcome measure) showed a significant ($F_{1,57} = 4.89, p = 0.031$) main effect of nicotine treatment, with the variability in RT over the varying interstimulus intervals being significantly improved (reduced) on nicotine treatment compared with placebo (figure 2A in article) by d 91 and d 182 ($p = 0.005$). There was no statistical difference between	-	NA	D	-	-	NA	Downgraded for directness (the clinical relevance of hit RT is unknown)	Low	Six mo of transdermal nicotine (15 mg/d) possibly improves cognitive test performance but not CGIC in pts with aMCI who do not smoke (1 Class I study downgraded for directness).
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					treatment groups in the distribution of pts rated improved or not improved ($p = 0.13$).									
Piribedil	Nagaraga, 2001 ^{e61}	MMSE	90 d	1 Class III (anchor: very low)	After 1 mo, no. of pts who responded to tx with an improvement in MMSE score to ≥ 26 was 14 (46.7%) for piribedil and 8 (26.7%) for placebo ($\chi^2 = 1.76$, $df = 1$, $p < 0.50$). After 2 mos, the nos. were 17 (56.7%) vs 9 (30.0%)	-	N A	-	-	-	N A		Very low	Data are insufficient to support or refute an effect of piribedil on cognitive measures in MCI (1 Class III study).

					($\chi^2 = 3.32$, $df = 1$, $p < 0.07$); after 3 mo, 19 (63.3%) vs 8 (26.7%) ($\chi^2 = 6.73$, $df = 1$, $p < 0.01$). Increase in mean MMSE score between baseline and 90 d was 1.23 for the pts who received piribedil, which was significantly greater than the increase for placebo group (figure 1 in article, $p < 0.01$).									
Rofecoxib	Thal, 2005 ^{e62}	Development of AD	Up to 4 y	1 Class II (anchor: low)	HR 1.46 [95% CI 1.09–1.94] in favor of placebo	-	N A	-	-	-	-		Low	Rofecoxib possibly increases the risk of progression to AD in pts with MCI (1 Class II study).

GHRH (tesamorelin)	Baker, 2012 ^{e64}	Primary cognitive outcomes = 3 composites reflecting executive function, verbal memory, visual memory	20 wk	1 Class II (anchor: low)	The 3 composite scores indicated favorable effects on cognitive function at wk 20 over baseline for adults allocated to receive GHRH vs adults given placebo ($F_{3,133} = 3.11, p = 0.03$).	-	N A	-	-	-	-		Low	In pts with MCI, tesamorelin injections over 20 wk are possibly effective to improve various cognitive measures (1 Class II study).
V0191 (procholinergic drug)	Dubois, 2012 ^{e65}	ADAS-Cog, responder rate	24 wk	1 Class III (anchor: very low)	Responder rate (decrease of ≥ 4 points on ADAS-Cog) OR 0.63 (95% CI 0.22–1.81), $p = 0.368$	-	N A	-	-	-	-		Very low	Data are insufficient to support or refute an effect of V0191 on ADAS-Cog responder rates in pts with MCI.
Vitamin E	Petersen, 2005 ^{e53}	Progression to AD	3 y	1 Class II (anchor: low)	HR 1.02 (95% CI 0.74–1.41)	-	N A	-	-	-	-		Low	In pts with MCI, vitamin E 2,000 IU daily is possibly ineffective for reducing progression to possible or probable

															AD (1 Class II study).
Vitamins C and E	Naeini, 2014 ^{e66}	MMSE	1 y	1 Class III	Tx group MMSE score at 1 y 26.8±0.17; control group MMSE score at 1 y 26.5±0.18										

Abbreviations: AD = Alzheimer disease; ADAS-Cog = Alzheimer's Disease Assessment Scale–Cognitive Subscale; ADCS = Alzheimer's Disease Cooperative Study; ADL = activities of daily living; aMCI = amnesic mild cognitive impairment; CDR-SB = Clinical Dementia Rating scale Sum of Boxes; CGIC = Clinical Global Impression of Change; CGIC-MCI = Clinical Global Impression of Change–Mild Cognitive Impairment; CPT = Connors Continuous Performance Test; FE = fully evaluable; HF = high flavanol; HR = hazard ratio; IF = intermediate flavanol; ITT-LOCF = intention to treat–last observation carried forward; ITT-OC = intention to treat–observation carried; LF = low flavanol; LOCF = last observation carried forward; MMSE = Mini-Mental State Examination; NP = neuropsychological; NYU = New York University; OR = odds ratio; RT = reaction time; TMT-A = Trail Making Test A; TMT-B = Trail Making Test B.

Evidence profile: Therapeutic – Nonpharmacologic (exercise)

Intervention	Study (first author, y)	Outcome	Time frame	Number & class of studies	Effect	Precision	Consistency	Directness	Plausibility	Magnitude of effect	Dose response	Comment	Confidence in evidence	Conclusion
Twice-weekly resistance training	Nagamatsu, 2012 ^{e67}	Stroop test performance/secondary effects Trail Making Tests, verbal digits test	6 mo	1 Class II	Resistance-training group improved performance on Stroop test and associative memory task ($p = 0.03$)									
Multicomponent exercise	Suzuki, 2013 ^{e68}	MMSE, ADAS-Cog	6 mo	1 Class II	Significant group effect for MMSE (ANOVA, $p = 0.03$)									
						N	N	N	N	N	N		Moderate (2 Class II studies)	In pts with MCI, exercise training for 6 mo is likely to improve cognitive measures, including MMSE, Stroop test,

														and an associative task.
Memory intervention	Kinsella, 2009 ^{e69}	Everyday memory task	4 mo	1 Class II	Significant medium-size group $F_{(1,36)} = 5.98, p = 0.020, \eta^2 = 0.14$	N	N A	N	N	N A	N A		Low	In pts with MCI, a 4-mo memory intervention possibly improves measures of everyday memory.
Multidimensional therapy	Tsolaki, 2011 ^{e72}	NP battery	6 mo	1 Class III	Significantly better NP measures in intervention group	N	N A	N	N	N A	N A		Very low	In pts with MCI, there is insufficient evidence to determine if multidimensional therapy has an effect.

Abbreviations: ADAS-Cog = Alzheimer's Disease Assessment Scale–Cognitive Subscale; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; N = neutral; NP = neuropsychological.

Evidence profile: Therapeutic – Nonpharmacologic (cognitive training)

Intervention	Outcome	Number & class of studies	Effect	Precision	Consistency	Directness	Plausibility	Magnitude of effect	Dose response	Comment	Confidence in evidence
Memory intervention	Various	1 Class II (Kinsella, 2009 ^{e69}), 1 Class III (Kinsella, 2016 ^{e70})	Class II: All nonsignificant (likely insufficient precision due to small sample size); Class III: improvements in strategy knowledge, internal strategy use, and well-being but not external strategy or memory	D	NC	NC	NC	NC	NA		Very low
Multidimensional	Various	1 Class III (Tsolaki, 2011 ^{e71})	Improved MMSE, MoCA, delayed recall, etc.	NC	NA	NC	NC	NC	NA		Very low
Cognitive intervention vs physical vs reminiscence	Various, MMSE	1 Class III (Nakatsuka, 2015 ^{e72})	Improved MMSE with cognitive and physical but limitations	NC	NA	NC	NC	NC	NA		Very low

Cognitive vs physical vs integrated vs social	Various	1 Class III (Lam, 2015 ^{e73})	No differences when considering full MCI group; single-domain group with integrated intervention on ADAS-Cog, CVFT, and recall; multidomain on CVFT	NC	NA	NC	NC	NC	NA		Very low
All cognitive interventions		1 Class II with limited precision, ^{e69} 4 Class III ^{e70–e73}		NC	NC	NC	NC	NC	NA		Low

Abbreviations: ADAS-Cog = Alzheimer’s Disease Assessment Scale–Cognitive Subscale; CVFT = Category Verbal Fluency Test ; MCI = mild cognitive impairment MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment.

Appendix e-7: Steps and rules for formulating recommendations

Constructing the recommendation and its rationale

Rationale for recommendation summarized in the rationale includes 3 categories of premises

- Evidence-based conclusions for the systematic review
- Stipulated axiomatic principles of care
- Strong evidence from related conditions not systematically reviewed

Actionable recommendations include the following mandatory elements

- The patient population that is the subject of the recommendation
- The person performing the action of the recommendation statement
- The specific action to be performed
- The expected outcome to be attained

Assigning a level of obligation

Modal modifiers used to indicate the final level of obligation (LOO)

- Level A: *Must*
- Level B: *Should*
- Level C: *May*
- Level U: No recommendation supported

LOO assigned by eliciting panel members' judgments regarding multiple domains, using a modified Delphi process. Goal is to attain consensus after a maximum of 3 rounds of voting. Consensus is defined by:

- $\geq 80\%$ agreement on dichotomous judgments
- $\geq 80\%$ agreement, within 1 point for ordinal judgments
- If consensus obtained, LOO assigned at the median. If not obtained, LOO assigned at the 10th percentile

Three steps used to assign final LOO

1. Initial LOO determined by the cogency of the deductive inference supporting the recommendation on the basis of ratings within 4 domains. Initial LOO anchored to lowest LOO supported by any domain.
 - Confidence in evidence. LOO anchored to confidence in evidence determined by modified form of the Grading of Recommendations Assessment, Development and Evaluation process
 - Level A: High confidence
 - Level B: Moderate confidence
 - Level C: Low confidence
 - Level U: Very low confidence

- Soundness of inference assuming all premises are true. LOO anchored to proportion of panel members convinced of soundness of the inference
 - Level A: 100%
 - Level B: $\geq 80\%$ to $< 100\%$
 - Level C: $\geq 50\%$ to $< 80\%$
 - Level U or R: $< 50\%$
 - Acceptance of axiomatic principles: LOO anchored to proportion of panel members who accept principles
 - Level A: 100%
 - Level B: $\geq 80\%$ to $< 100\%$
 - Level C: $\geq 50\%$ to $< 80\%$
 - Level U or R: $< 50\%$
 - Belief that evidence cited from related conditions is strong: LOO anchored to proportion of panel members who believe the related evidence is strong
 - Level B: $\geq 80\%$ to 100% (recommendations dependent on inferences from nonsystematically reviewed evidence cannot be anchored to a Level A LOO)
 - Level C: $\geq 50\%$ to $< 80\%$
 - Level U or R: $< 50\%$
- 2. LOO is modified mandatorily on the basis of the judged magnitude of benefit relative to harm expected to be derived from complying with the recommendation
 - Magnitude relative to harm rated on 4-point ordinal scale
 - Large benefit relative to harm: benefit judged large, harm judged none
 - Moderate benefit relative to harm: benefit judged large, harm judged minimal; or benefit judged moderate, harm judged none
 - Small benefit relative to harm: benefit judged large, harm judged moderate; or benefit judged moderate, harm judged minimal; or benefit judged small, harm judged none
 - Benefit to harm judged too close to call: benefit and harm judged to be substantially similar
 - Regardless of cogency of the recommendation the LOO can be no higher than that supported by the rating of the magnitude of benefit relative to harm
 - Level A: large benefit relative to harm
 - Level B: moderate benefit relative to harm
 - Level C: small benefit relative to harm
 - Level U: too close to call
 - LOO can be increased by one grade if LOO corresponding to benefit relative to harm greater than LOO corresponding to the cogency of the recommendation
- 3. LOO optionally downgraded on the basis of the following domains

- Importance of the outcome: critical, important, mildly important, not important
- Expected variation in patient preferences: none, minimal, moderate, large
- Financial burden relative to benefit expected: none, minimal, moderate, large
- Availability of intervention: universal, usually, sometimes, limited

The rationale profiles shown in appendix e-8 summarize the results of panel ratings for each domain described above. The profiles also indicate the corresponding assigned LOOs. The last column in each indicates whether consensus was obtained for that domain.

Appendix e-8: Rationale of factors considered in developing the practice recommendations

In this appendix, *EVID* refers to evidence systematically reviewed; *RELA* to strong evidence derived from related conditions; *PRIN* to axiomatic principles of care; and *INFER* to inferences made from one or more statements in the recommendation rationale.

In the tables that follow, consensus is considered to have been reached if 80% or more of the guideline panel agree on the strength of a given domain. For nonpremise domains, intensity of shading corresponds to the number of panel members who were in agreement (shading of greater intensity indicates a larger number of panel members who reached agreement). The strength of the recommendation is anchored to the strength of the inference. The recommendation strength can be downgraded for any modifier; it can be upgraded only by one level for a moderate to large benefit relative to harm. In addition, domains include the premises and factors on which the recommendations are based. Please see appendix e-7 for the steps and rules for formulating recommendation strength.

PRACTICE RECOMMENDATIONS

1. Recommendation A1

Rationale

Appropriate diagnosis of MCI is important because MCI becomes increasingly common as individuals age (*EVID*) and is associated with an increased risk of progression to dementia (*EVID*), suggesting that this condition reflects a pathologic disease state rather than normal cognitive aging (*INFER*). Appropriate diagnosis of MCI is important in order to assess for reversible causes of cognitive impairment, to help patients and families understand the cause of their cognitive concerns, and to discuss the prognostic possibilities with the provider so they can plan accordingly (*PRIN*), although sharing the diagnosis must be balanced with the potential harm of anxieties from diagnosing a patient with a condition that may not progress (*PRIN*, *EVID*). Ascribing cognitive symptoms to normal aging without an assessment for MCI may result in failure to assess for reversible causes of cognitive impairment or to provide patients and families with an accurate diagnosis that may affect life choices, or both (*INFER*). Although subjective cognitive complaints alone are insufficient to diagnose MCI (*RELA*),^{e74} such complaints from either patients or their close contacts are core to most major MCI diagnostic criteria, as they may reflect a change in cognitive function (*RELA*).^{e75}

Recommendation

For patients for whom the patient or a close contact voices concern about memory or impaired cognition, clinicians should assess for MCI and not assume the concerns are related to normal aging (Level B).

Rationale profile

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate	High	10
Benefit relative to Harm	Harm \geq Benefit 0	Benefit > Harm 0	Benefit >> Harm 3	Benefit >>> Harm 6	Yes
Importance of outcomes	Not Important or Unknown 0	Mildly Important 0	Very Important 6	Critically Important 3	Yes
Variation in preferences	Large 0	Moderate 1	Modest 4	Minimal 4	Yes
Feasibility	Rarely 0	Occasionally 1	Usually 1	Always 7	Yes
Cost relative to net benefit	Very Large 0	Large 0	Moderate 4	Small 5	Yes
Strength of recommendation	R/U	C	B	A	

2. Recommendation A2

Rationale

In the United States, the Medicare Annual Wellness Visit requires an assessment to detect cognitive impairment (RELA).^{e76} Subjective cognitive complaints alone can result in both over- and underdiagnosis of MCI and thus are insufficient to screen for MCI (RELA).^{e74} Clinicians assessing for cognitive impairment should use a brief, validated cognitive assessment instrument in addition to eliciting patient and informant history regarding cognitive concerns (INFER, PRIN).

Recommendation

When performing a Medicare Annual Wellness Visit, clinicians should not rely on historical report of subjective memory concerns alone when assessing for cognitive impairment (Level B).

Rationale profile

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference	Very low	Low	Moderate	High	10
Benefit relative to Harm	Harm \geq Benefit 0	Benefit > Harm 0	Benefit >> Harm 3	Benefit >>> Harm 4	Yes
Importance of outcomes	Not Important or 0	Mildly 0	Very 6	Critically Important 1	Yes
Variation in preferences	Large 0	Moderate 0	Modest 1	Minimal 6	Yes
Feasible	Rarely 0	Occasionally 0	Usually 1	Always 6	Yes
Cost relative to net benefit	Very Large 0	Large 0	Moderate 5	Small 2	Yes
Strength of recommendation	R/U	C	B	A	

3. Recommendation A3

Rationale

When screening or assessing for MCI, validated assessment tools should be used (PRIN). Various instruments have acceptable diagnostic accuracy for detecting MCI, with no instrument being superior to another (RELA).^{e77} Because brief cognitive assessment instruments are usually calibrated to maximize sensitivity rather than specificity (PRIN), patients who test positive for MCI should then have further assessment (e.g., more in-depth cognitive testing, such as neuropsychological testing with interpretation based on appropriate normative data) to formally assess for this diagnosis (INFER). Diagnosis of MCI is based ultimately on a clinical evaluation determining cognitive function and functional status and not solely on a specific test score (PRIN).

Recommendation

For patients for whom screening or assessing for MCI is appropriate, clinicians should use validated assessment tools to assess for cognitive impairment (Level B). For patients who test positive for MCI, clinicians should perform a more formal clinical assessment for diagnosis of MCI (Level B).

Rationale profile

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate	High	
Benefit relative to Harm	Harm \geq Benefit 0	Benefit > Harm 0	Benefit >> Harm 2	Benefit >>> Harm 8	Yes
Importance of outcomes	Not Important or Unknown 0	Mildly Important 0	Very Important 6	Critically Important 4	Yes
Variation in preferences	Large 0	Moderate 1	Modest 7	Minimal 2	Yes
Feasibility	Rarely 0	Occasionally 0	Usually 5	Always 5	Yes
Cost relative to net benefit	Very Large 0	Large 0	Moderate 6	Small 4	Yes
Strength of recommendation	R/U	C	B	A	

4. Recommendation A4

Rationale

In the presence of cognitive impairment, clinicians need to distinguish between a diagnosis of MCI and one of dementia (PRIN), although the boundary is not always clear. Diagnosing dementia prematurely can lead to negative consequences for patients and families (PRIN). Only a proportion of patients with MCI will proceed to dementia (EVID). In patients with cognitive impairment, clinicians must carefully assess for evidence of functional impairment limiting independence in daily activities (e.g., by taking a careful history from the patient and a close contact), a requirement for all dementia diagnoses, to help distinguish between MCI and dementia. With a specific inquiry about functional impairment, clinicians may also identify dementia in patients when patients and family are less forthcoming about functional problems (INFER).

Recommendation

For patients with MCI, clinicians should assess for the presence of functional impairment related to cognition before giving a diagnosis of dementia (Level B).

Rationale profile

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate ¹⁰	High	
Benefit relative to Harm	Harm ≥ Benefit ⁰	Benefit > Harm ⁰	Benefit >> Harm ¹	Benefit >>> Harm ⁸	Yes
Importance of outcomes	Not Important or Unknown ⁰	Mildly Important ⁰	Very Important ⁵	Critically Important ⁴	Yes
Variation in preferences	Large ⁰	Moderate ⁰	Modest ³	Minimal ⁶	Yes
Feasibility	Rarely ⁰	Occasionally ⁰	Usually ²	Always ⁶	Yes
Cost relative to net benefit	Very Large ⁰	Large ⁰	Moderate ⁵	Small ⁴	Yes
Strength of recommendation	R/U	C	B	A	

5. Recommendation A5

Rationale

Diagnoses of MCI and dementia have important implications for patients and families (PRIN). Appropriate diagnosis is important for informing evaluation for underlying causes, counseling on long-term prognosis, and recommending therapeutic strategies (PRIN). Clinicians in many disciplines can have experience in caring for individuals with cognitive impairment, including family practice, geriatrics, internal medicine, neurology, psychiatry, and psychology (PRIN). When clinicians without experience in cognitive impairment identify patients for whom there is a concern of MCI, they should refer these patients to a specialist with experience in cognition for further evaluation (INFER).

Recommendation

For patients suspected to have MCI, clinicians who themselves lack the necessary experience should refer these patients to a specialist with experience in cognition (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate	High	10
Benefit relative to Harm	Harm \geq Benefit 0	Benefit > Harm 0	Benefit >> Harm 0	Benefit >>> Harm 7	Yes
Importance of outcomes	Not Important or 0	Mildly 0	Very 6	Critically Important 1	Yes
Variation in preferences	Large 0	Moderate 0	Modest 7	Minimal 0	Yes
Feasible	Rarely 0	Occasionally 0	Usually 6	Always 1	Yes
Cost relative to net benefit	Very Large 0	Large 1	Moderate 5	Small 1	Yes
Strength of recommendation	R/U	C	B	A	

6. Recommendation A6

Rationale

Although MCI is a high-risk state for progression to dementia (EVID), some patients with MCI remain stable and some improve (EVID). Some cases of MCI are associated with reversible causes of cognitive impairment, including medication AEs, sleep apnea, depression, and other medical conditions (RELA).^{e78} Patients with MCI should undergo a medical evaluation for MCI risk factors that may be treatable (INFER).

Recommendation

For patients diagnosed with MCI, clinicians should perform a medical evaluation for MCI risk factors that are potentially modifiable (Level B).

Rationale profile

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate	High	
Benefit relative to Harm	Harm \geq Benefit 0	Benefit > Harm 0	Benefit >> Harm 1	Benefit >>> Harm 8	Yes
Importance of outcomes	Not Important or Unknown 0	Mildly Important 0	Very Important 1	Critically Important 8	Yes
Variation in preferences	Large 0	Moderate 1	Modest 1	Minimal 7	Yes
Feasibility	Rarely 0	Occasionally 0	Usually 4	Always 5	Yes
Cost relative to net benefit	Very Large 0	Large 0	Moderate 4	Small 5	Yes
Strength of recommendation	R/U	C	B	A	

7. Recommendation A7

Rationale A7

Because patients with MCI can improve, remain stable, or progress cognitively (EVID), identifying biomarkers that can stratify risk is expected to be particularly important for prognosis (INFER). The use of biomarkers in patients with MCI is a rapidly evolving field (RELA),^{e79–e81} but to date, there are no biomarkers clearly shown to predict progression in patients with MCI (RELA).^{e82}

Recommendation A7a

For patients and families asking about biomarkers in MCI, clinicians should counsel that there are no accepted biomarkers available at this time (Level B).

Rationale profile

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate	High	10
Benefit relative to Harm	Harm \geq Benefit 0	Benefit > Harm 0	Benefit >> Harm 3	Benefit >>> Harm 5	Yes
Importance of outcomes	Not Important or 0	Mildly 1	Very 5	Critically Important 2	Yes
Variation in preferences	Large 0	Moderate 1	Modest 1	Minimal 6	Yes
Feasible	Rarely 0	Occasionally 0	Usually 2	Always 6	Yes
Cost relative to net benefit	Very Large 0	Large 2	Moderate 2	Small 4	No
Strength of recommendation	R/U	C	B	A	

Recommendation A7b

For interested patients, clinicians may discuss the option of biomarker research or refer patients or both, if feasible, to centers or organizations that can connect patients to this research (e.g., subspecialty centers, Trial Match, ClinicalTrials.gov) (Level C).

Rationale profile

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate	High	10
Benefit relative to Harm	Harm \geq Benefit 0	Benefit > Harm 0	Benefit >> Harm 3	Benefit >>> Harm 5	Yes
Importance of outcomes	Not Important or 0	Mildly 3	Very 4	Critically Important 1	Yes
Variation in preferences	Large 0	Moderate 4	Modest 2	Minimal 2	No
Feasible	Rarely 0	Occasionally 1	Usually 3	Always 4	Yes
Cost relative to net benefit	Very Large 1	Large 2	Moderate 2	Small 3	No
Strength of recommendation	R/U	C	B	A	

8. Recommendation A8

Rationale

Because patients with MCI can improve, remain stable, or progress cognitively over time (EVID), patients must be monitored serially for changes in status that could change diagnosis and thus management approach (e.g., treatment, counseling) (INFER). Although MCI has no approved pharmacologic management (EVID), there are US Food and Drug Administration (FDA)–approved agents for treatment of Alzheimer dementia (RELA),^{e83–e87} further emphasizing the importance of assessing for a change in cognitive status over time (INFER).

Recommendation

For patients diagnosed with MCI, clinicians should perform serial assessments over time to monitor for changes in cognitive status (Level B).

Rationale profile

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate	High	
Benefit relative to Harm	Harm \geq Benefit 0	Benefit > Harm 0	Benefit >> Harm 2	Benefit >>> Harm 7	Yes
Importance of outcomes	Not Important or Unknown 0	Mildly Important 0	Very Important 5	Critically Important 4	Yes
Variation in preferences	Large 0	Moderate 0	Modest 6	Minimal 3	Yes
Feasibility	Rarely 0	Occasionally 0	Usually 4	Always 5	Yes
Cost relative to net benefit	Very Large 0	Large 0	Moderate 6	Small 3	Yes
Strength of recommendation	R/U	C	B	A	

9. Recommendation B1

Rationale

Some patients with MCI improve or remain stable rather than progress (EVID). In addition, some cases of MCI are associated with reversible causes of cognitive impairment, including medication side effects, general medical conditions, sleep disturbance, and depression (RELA).^{e78} Because these risk factors are treatable and have implications of their own, weaning patients from use of cognitively impairing medications where feasible and treating risk factors that may contribute to cognitive impairment should be the first steps in managing MCI (INFER), particularly because symptomatic treatment options are limited for impaired cognition (EVID).

Recommendation

For patients diagnosed with MCI, clinicians should wean patients from medications that can contribute to cognitive impairment (where feasible and medically appropriate) and treat modifiable risk factors that may be contributing (Level B).

Rationale profile

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate	High	
Benefit relative to Harm	Harm \geq Benefit 0	Benefit > Harm 0	Benefit >> Harm 4	Benefit >>> Harm 5	Yes
Importance of outcomes	Not Important or Unknown 0	Mildly Important 0	Very Important 4	Critically Important 5	Yes
Variation in preferences	Large 0	Moderate 1	Modest 4	Minimal 4	Yes
Feasibility	Rarely 0	Occasionally 0	Usually 0	Always 9	Yes
Cost relative to net benefit	Very Large 0	Large 0	Moderate 4	Small 5	Yes
Strength of recommendation	R/U	C	B	A	

10. Recommendation B2

Rationale

There are no FDA-approved medications for the treatment of MCI (PRIN). Moreover, there are no high-quality, long-term studies identifying pharmacologic or dietary agents that either improve cognition or delay progression in patients with MCI (EVID).

Recommendation

For patients diagnosed with MCI, clinicians should counsel the patients and families that there are no pharmacologic or dietary agents currently shown to have symptomatic cognitive benefit in MCI and that no medications are FDA approved for this purpose (Level B).

Rationale profile

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate	High	
Benefit relative to Harm	Harm \geq Benefit 0	Benefit > Harm 2	Benefit >> Harm 5	Benefit >>> Harm 4	Yes
Importance of outcomes	Not Important or Unknown 0	Mildly Important 3	Very Important 6	Critically Important 2	Yes
Variation in preferences	Large 1	Moderate 0	Modest 6	Minimal 4	Yes
Feasibility	Rarely 0	Occasionally 1	Usually 0	Always 10	Yes
Cost relative to net benefit	Very Large 0	Large 0	Moderate 2	Small 9	Yes
Strength of recommendation	R/U	C	B	A	

11. Recommendation B3

Rationale

Studies of cholinesterase inhibitors showed no benefit on cognitive outcomes or reduction in progression from MCI to dementia (EVID), although some studies could not exclude an important effect (EVID). In addition to lacking efficacy, side effects of cholinesterase inhibitors are common, including gastrointestinal symptoms and cardiac concerns (RELA).^{e88}

Recommendation B3a

For patients diagnosed with MCI, clinicians may choose not to offer cholinesterase inhibitors (Level B).

Rationale profile

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate	High	10
Benefit relative to Harm	Harm \geq Benefit 0	Benefit > Harm 0	Benefit >> Harm 4	Benefit >>> Harm 4	Yes
Importance of outcomes	Not Important or 0	Mildly 0	Very 6	Critically Important 2	Yes
Variation in preferences	Large 0	Moderate 0	Modest 1	Minimal 7	Yes
Feasible	Rarely 0	Occasionally 0	Usually 1	Always 7	Yes
Cost relative to net benefit	Very Large 0	Large 2	Moderate 4	Small 2	No
Strength of recommendation	R/U	C	B	A	

Recommendation B3b

If clinicians choose to offer cholinesterase inhibitors, they must first discuss with patients the fact that this is an off-label prescription not currently backed by empirical evidence (Level A).

*Rationale profile **

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate	High	10
Benefit relative to Harm	Harm \geq Benefit 0	Benefit > Harm 0	Benefit >> Harm 0	Benefit >>> Harm 8	Yes
Importance of outcomes	Not Important or 0	Mildly 0	Very 4	Critically Important 4	Yes
Variation in preferences	Large 0	Moderate 0	Modest 0	Minimal 8	Yes
Feasible	Rarely 0	Occasionally 0	Usually 2	Always 6	Yes
Cost relative to net benefit	Very Large 0	Large 1	Moderate 4	Small 3	Yes
Strength of recommendation	R/U	C	B	A	

*On the basis of the confidence in the inference and the benefit relative to harm, the level of obligation for this recommendation is Level A. Although according to AAN methodology the guideline panel can choose to downgrade for the 4 modifiers, the panel chose not to downgrade for cost relative to net benefit (pointing to a Level B recommendation) because there is no cost to the patient associated with counseling.

12. Recommendation B4

Rationale

Clinical trials provide an opportunity for interested patients to participate in identifying or testing new treatment options, which is of particular importance when no pharmacologic options are available (PRIN).

Recommendation

For patients diagnosed with MCI who are interested in pharmacologic treatment, clinicians may inform these patients of centers or organizations that can connect patients to clinical trials (e.g. subspecialty centers, Trial Match, ClinicalTrials.gov) (Level C).

Rationale profile

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate	High	10
Benefit relative to Harm	Harm \geq Benefit 0	Benefit > Harm 3	Benefit >> Harm 2	Benefit >>> Harm 2	No
Importance of outcomes	Not Important or 0	Mildly 1	Very 5	Critically Important 1	Yes
Variation in preferences	Large 0	Moderate 5	Modest 2	Minimal 0	Yes
Feasible	Rarely 0	Occasionally 1	Usually 4	Always 2	Yes
Cost relative to net benefit	Very Large 1	Large 3	Moderate 3	Small 0	Yes
Strength of recommendation	R/U	C	B	A	

13. Recommendation B5

Rationale

Although long-term studies are unavailable, 6-month studies suggest a possible benefit of twice-weekly exercise for cognition in MCI (EVID). Exercise also has general health benefits and generally limited risk (PRIN).

Recommendation

For patients diagnosed with MCI, clinicians should recommend regular exercise (twice/week) as part of an overall approach to management (Level B).

Rationale profile

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate	High	10
Benefit relative to Harm	Harm \geq Benefit 0	Benefit > Harm 0	Benefit >> Harm 1	Benefit >>> Harm 6	Yes
Importance of outcomes	Not Important or 0	Mildly 1	Very 6	Critically Important 0	Yes
Variation in preferences	Large 0	Moderate 0	Modest 0	Minimal 7	Yes
Feasible	Rarely 0	Occasionally 0	Usually 2	Always 5	Yes
Cost relative to net benefit	Very Large 1	Large 1	Moderate 4	Small 1	No
Strength of recommendation	R/U	C	B	A	

14. Recommendation B6

Rationale

Because the concept of MCI may be poorly understood or distressing to patients and families (PRIN), it is important to educate patients and families regarding the diagnosis of MCI and how it may progress to dementia (EVID) but also how individuals with MCI can remain stable or improve (EVID). Because MCI may progress to dementia (EVID), and particularly because of the lack of effective pharmacologic therapy or any proven methods to reduce the risk of progression of MCI to dementia (EVID), it is particularly important to educate patients with MCI regarding their diagnosis and prognosis at the MCI stage while they can still understand the discussion and participate in planning (PRIN), even though they may or may not progress. Because of the possibility of progression to a dementia state where patients may no longer be able to participate in decision making (EVID), patients with MCI should be encouraged to participate in long-term planning, including topics such as advance directives, living wills, power-of-attorney designations, and finances, which are important irrespective of progression (PRIN).

Recommendation

For patients diagnosed with MCI, clinicians should discuss diagnosis and uncertainties regarding prognosis. Clinicians should counsel patients and families to discuss long-term planning topics such as advance directives, driving safety, finances, and estate planning (Level B).

Rationale profile

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate	High	
Benefit relative to Harm	Harm \geq Benefit 0	Benefit > Harm 1	Benefit >> Harm 2	Benefit >>> Harm 4	Yes
Importance of outcomes	Not Important or 0	Mildly 0	Very 3	Critically Important 4	Yes
Variation in preferences	Large 0	Moderate 0	Modest 1	Minimal 6	Yes
Feasible	Rarely 0	Occasionally 0	Usually 3	Always 4	Yes
Cost relative to net benefit	Very Large 0	Large 1	Moderate 4	Small 2	Yes
Strength of recommendation	R/U	C	B	A	

15. Recommendation B7

Rationale

Although there are no treatments for cognitive symptoms in MCI (EVID), clinicians need to evaluate for and treat other symptoms that can contribute to quality of life in MCI (PRIN).

Behavioral/psychiatric symptoms are common in MCI (RELA)^{e89–e91} and may be associated with greater functional impairment^{e92} and an increased risk of progression from MCI to dementia (RELA).^{e93,e94}

Recommendation

Clinicians should assess for behavioral and neuropsychiatric symptoms in MCI and treat with both pharmacologic and nonpharmacologic approaches when indicated (Level B).

Rationale profile

Strength of inference and strength of recommendation

4

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in Inference	Very low	Low	Moderate	High	10
Benefit relative to Harm	Harm \geq Benefit 0	Benefit > Harm 1	Benefit >> Harm 1	Benefit >>> Harm 5	Yes
Importance of outcomes	Not Important or 0	Mildly 0	Very 2	Critically Important 5	Yes
Variation in preferences	Large 0	Moderate 0	Modest 2	Minimal 5	Yes
Feasible	Rarely 0	Occasionally 0	Usually 5	Always 2	Yes
Cost relative to net benefit	Very Large 1	Large 1	Moderate 1	Small 4	No
Strength of recommendation	R/U	C	B	A	

16. Recommendation B8

Rationale

In patients with MCI, cognitive interventions may be beneficial in improving measures of cognitive function (EVID). It is good practice to offer non-medication approaches to care (PRIN).

Recommendation

In patients with MCI, clinicians may recommend cognitive interventions (Level C).

Rationale profile

Strength of inference and strength of recommendation

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence strong & applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in Inference	Very low	Low	Moderate	High ₁₀	
Benefit relative to Harm	Harm \geq Benefit ₀	Benefit > Harm ₁	Benefit >> Harm ₅	Benefit >>> Harm ₁	Yes
Importance of outcomes	Not Important or ₀	Mildly ₃	Very ₄	Critically Important ₀	Yes
Variation in preferences	Large ₀	Moderate ₂	Modest ₅	Minimal ₀	Yes
Feasible	Rarely ₀	Occasionally ₅	Usually ₂	Always ₀	Yes
Cost relative to net benefit	Very Large ₀	Large ₂	Moderate ₅	Small ₀	Yes
Strength of recommendation	R/U	C	B	A	

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