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GERIATRIC DISORDERS (W MCDONALD, SECTION EDITOR)

Mild Cognitive Impairment: Diagnosis, Longitudinal Course, and Emerging Treatments

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Abstract Mild cognitive impairment (MCI) is widely regarded as the intermediate stage of cognitive impairment between the changes seen in normal cognitive aging and those associated with dementia. Elderly patients with MCI constitute a high-risk population for developing dementia, in particular Alzheimer's disease (AD). Although the core clinical criteria for MCI have remained largely unchanged, the operational definition of MCI has undergone several revisions over the course of the last decade and remains an evolving diagnosis. Prognostic implications of this diagnosis are becoming clearer with regard to the risk of progressive cognitive deterioration. Although patients with MCI may represent an optimal target population for pharmacological and non-pharmacological interventions, results from clinical trials have been mixed and an effective treatment remains elusive. This article provides a brief overview of the evolution of the concept of MCI and reviews current diagnostic criteria, the longitudinal course of the disorder, and current and emerging treatments for MCI.

Keywords Mild cognitive impairment · Mild neurocognitive disorder · Cognitive decline · Treatments

Introduction

Mild cognitive impairment (MCI) is a syndrome defined as a subjective and objective decline in cognition and function greater than expected for an individual's age and education level that does not meet criteria for a diagnosis of dementia [1–3]. Elderly patients with MCI constitute a high-risk population for developing dementia, in particular Alzheimer's disease (AD) [2, 4–6]. The concept of MCI originally evolved out of the effort to characterize the pre-dementia phase of cognitive impairment for which, at the time, there was no clinical definition. The need for a clinical definition of this pre-dementia syndrome was further strengthened by the hypothesis that therapeutic interventions may have greater efficacy in the earliest stages of the disease [1]. Although the core clinical criteria for MCI have remained largely unchanged, the operational definition of MCI has undergone several revisions over the course of the last decade and remains an evolving diagnosis. The aim of this review is to first provide a brief overview of the evolution of the concept of MCI and longitudinal course of the disorder. We will then discuss various issues to consider when making a clinical diagnosis of MCI and review current and emerging treatments for MCI.

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Evolution of the Concept of MCI

Reisberg and colleagues introduced the term MCI in the late 1980s to characterize patients who were in an intermediate stage of cognitive impairment between the changes seen in normal cognitive aging and those associated with dementia [7]. The first clinical criteria for MCI, developed by Petersen et al. [1] (referred to as original Mayo Clinic criteria), focused primarily on episodic memory impairment (i.e., the ability to learn and retain new information) problems. The emphasis of the original Mayo Clinic [1] classification was directed specifically toward the detection of underlying AD. Deficits in non-memory cognitive domains (e.g., executive control, language or visuospatial abilities) were allowed, but deficits found solely in non-memory domains were not considered. However, as research on MCI progressed, it became clear that

several clinical subtypes of MCI exist. Therefore, these criteria were further revised at an international consensus conference in 2003 (referred to as revised Mayo Clinic criteria), which led to the publication of international criteria for MCI that expanded the construct of MCI to a broader clinical syndrome with multiple subtypes, each, presumably, with different underlying etiologies [2, 3]. According to the revised Mayo Clinic criteria (see Table 1) [2, 3], patients with MCI were classified as amnestic MCI (a-MCI) if patients exhibited performance deficits on neuropsychological tests of episodic memory, or non-amnestic MCI (na-MCI) if patients exhibited performance deficits on neuropsychological tests of non-memory domains of cognition. Impairment could be limited to one cognitive domain (MCI single domain) or to multiple domains (MCI multiple domains). Therefore, patients could be classified as one of four possible clinical subtypes: 1) a-MCI single domain, 2) a-MCI multiple domain, 3) na-MCI single domain or 4) na-MCI multiple domain. The combination of clinical subtype and the presumed etiology (degenerative, vascular, psychiatric, trauma) could then be used to predict the type of dementia that the patient with MCI would most likely develop (AD, vascular dementia, frontotemporal dementia (FTD), dementia with Lewy bodies (DLB), etc) [2, 3].

Table 1 Currently used diagnostic criteria for mild cognitive impairment (MCI)

Revised Mayo Clinic criteria (2003) [2, 3]

Clinical criteria:

- Subjective (self or informant) cognitive complaint
- Objective cognitive impairment
- Preserved independence in functional abilities
- No dementia

Further characterization:

	Yes	**No**
Memory Impairment	Amnestic MCI	Non-amnestic MCI
Single domain	Amnestic MCI single domain	Non-amnestic MCI single domain
Multiple domain	Amnestic MCI Multiple Domain	Non-amnestic MCI multiple domain

NIA-AA criteria for MCI due to AD (2011) [8]

Clinical criteria:

- Concern regarding a change in cognition (self/informant/clinician report)
- Objective evidence of impairment in one or more cognitive domains, typically including memory
- Preservation of independence in functional abilities
- Not demented

Further characterization (for purposes of research and/or clinical trials):

Diagnostic category	**Biomarkers of Aβ deposition (PET or CSF Aβ)**	**Biomarkers of neuronal injury (tau, FDG PET, MRI)**
MCI core clinical criteria	Conflicting/untested	Conflicting/untested
MCI due to AD: intermediate likelihood	Positive/untested	Positive/untested
MCI due to AD: high likelihood	Positive	Positive
MCI: unlikely due to AD	Negative	Negative

DSM-V Diagnostic criteria for mild NCD (2013) [9]

Clinical criteria:

- Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (self/informant/clinician report or on objective measures of cognitive performance)
- Preserved independence in functional abilities
- The cognitive deficits do not occur exclusively in the context of a delirium
- The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia)
- No dementia

Further characterization:

Specify potential underlying etiology*:

- Alzheimer's disease
- Frontotemporal dementia
- Lewy body disease
- Vascular disease
- Traumatic brain injury
- Substance/medication use
- HIV infection
- Prion disease
- Parkinson's disease

NIA-AA, National Institutes on Aging-Alzheimer's Association workgroup; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, fifth edition; AD, Alzheimer's disease; Aβ, amyloid beta peptide; PET, positron emission tomography; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; MRI, structural magnetic resonance imaging

*For coding purposes, the DSM-5 states that mild NCD should be coded using the current The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code of 331.83 ('mild cognitive impairment, so stated'). Although the DSM-5 states that the underlying etiology for mild NCD be determined as part of the diagnostic process, additional codes for the presumed/potential etiology (e.g., AD, FTD, DLB, etc.) for mild NCD are not to be used

In 2011 the National Institute on Aging-Alzheimer's Association (NIA-AA) workgroup proposed criteria specifically for *MCI due to AD* for use in clinical and research settings (see Table 1) [8]. The purpose of these criteria is to identify symptomatic but non-demented patients whose underlying etiology is AD [8]. While the NIA-AA core clinical criteria are nearly identical to the revised Mayo Clinic criteria for MCI [2, 3], they incorporate and provide a guideline for the use of AD biomarkers in predicting the progression of MCI to AD [8]. Although the NIA-AA recommends that a diagnosis of MCI due to AD be made based on the core clinical criteria [2, 3, 8, 9], they suggest that biomarkers could be used in research settings to aid in the identification of MCI subtypes (i.e., MCI due to AD and MCI that is unlikely due to AD). Currently, two main sets of biomarkers are used in research and clinical trials to aide in the identification MCI due to AD: 1) biomarkers of amyloid beta (Aβ) deposition and 2) biomarkers of neuronal injury. According to the NIA-AA workgroup [8], valid indicators of Aβ deposition are: 1a) Cerebrospinal fluid (CSF) concentrations of Aβ42 (decreased CSF Aβ42 levels [10]) and 1b) positron emission tomography (PET) amyloid imaging [11]. Valid indicators of neuronal injury are: 2a) CSF concentrations of tau/phosphorylated tau (increased CSF tau/ptau levels) [10], 2b) hippocampal volume or medial temporal atrophy or rate of brain atrophy on measured using structural MRI [12], and 2c) decreased glucose metabolism in temporoparietal regions on fluorodeoxyglucose (FDG) PET imaging [13]. Although the NIA-AA guidelines are primarily intended for use in research settings, rather than informing clinical assessment, the expectation is that these AD biomarkers may eventually guide clinical care for MCI patients with underlying AD pathology [14].

The American Psychiatric Association has recently published new criteria for dementia in the fifth edition of the *Diagnostic and Statistical Manual for Mental Disorders* (DSM-5) [9]. The new diagnostic category of 'neurocognitive disorders' (NCD; see Table 1) encompasses the group of disorders in which the primary clinical deficit is in cognitive function that is *acquired*, rather than developmental, that represent a decline from a previous level of cognitive functioning [9]. The DSM-5 takes a two step approach that first involves 1) differentiating between normal neurocognitive function, mild NCD, and major NCD (or dementia), and then 2) determining the underlying etiology (e.g., AD, vascular dementia, FTD, DLB, etc.) [9]. The category of mild NCD is considered the pre-dementia phase of cognitive impairment and the DSM-5 criteria for mild NCD (see Table 1) overlap with the revised Mayo Clinic core criteria [2, 3] for MCI. As with the term MCI, changes associated with mild NCD are distinct from those associated with normal aging but are not severe enough to qualify for dementia. The criteria for mild NCD include: a) Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (self/informant/clinician report or evident on neuropsychological tests), b) the cognitive deficits do not interfere with capacity for independence in everyday activities, c) the cognitive deficits do not occur exclusively in the context of a delirium, and d) the cognitive deficits are not better explained by another mental disorder [9]. Although outside the scope of this manuscript, it is worth mentioning that the change to the new diagnostic category of 'neurocognitive disorders' is not without controversy [15]. However, as mentioned previously, the core criteria for mild NCD (as well as the with the NIA-AA criteria) overlap with the Mayo Clinic's revised criteria (see Fig. 1), thus although the terminology used in the DSM-5 is different, the criteria (with respect to MCI) remain largely the same.

Longitudinal Course of Disease

Although a great deal of work has been done to characterize the clinical profile of MCI, much less is known about the neuropathological profile of MCI. Studies have shown that the neuropathological profile of MCI is heterogeneous and changes observed in patients with MCI are similar to those observed in patients with dementia and in the cognitively normal elderly [16, 17]. However, given that MCI can represent many different underlying conditions, each with their own putative underlying etiology, it is not surprising that a single neuropathological profile for MCI has not been found as different causes of dementia (such as AD, vascular dementia, DLB, etc.) have different underlying pathological profiles (Aβ plaques and neurofibrillary tangle pathology, vascular pathology, and Lewy body pathology, respectively) [17]. MCI patients with cognitive deficits limited to non-memory domains, the non-amnestic type, (e.g., executive control, language or visuospatial abilities) are considered to be less common than the amnestic type [18, 19] and may represent preclinical dementias that are not related to AD, such as FTD or DLB [20]. The longitudinal course of MCI is most clear for patients with a-MCI (or MCI due to AD), as these patients constitute a high risk group for AD, with nearly 10 % to 15 % of a-MCI patients progressing to a diagnosis of probable AD each year, relative to only 1 % to 2 % of the general elderly population [1, 21]. While some studies have found that patients with MCI are often indistinguishable from elderly individuals who are cognitively intact, in terms of AD pathology, patients with a-MCI generally exhibit an intermediate degree of the histopathological hallmarks of AD [16].

Briefly, AD is characterized histopathologically by the presence of amyloid plaques, composed of an Aβ protein core, and neurofibrillary tangles, composed of hyperphosphorylated aggregates of the microtubule-associated protein tau [22]. Current theories suggest that Aβ plaque deposition precedes neurofibrillary tangle deposition [23]. However, the formation and extent of neurofibrillary tangles is more highly correlated with the level of cognitive

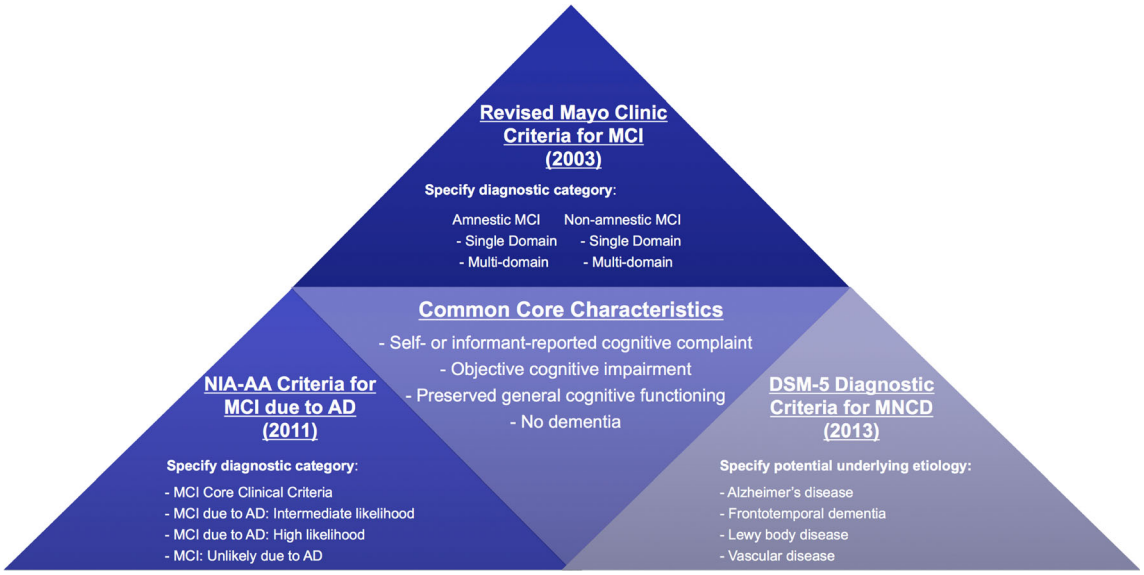

Fig. 1 Comparison of current diagnostic criteria for mild cognitive impairment (MCI). Common core characteristics shared by each diagnostic system are indicated in the center triangle. Criteria included are as follows: Revised Mayo Clinic Criteria [2, 3], the National Institute on Aging-Alzheimer's Association workgroup (NIA-AA) criteria for MCI due to Alzheimer's disease (AD) [8], and the Diagnostic and Statistical Manual of Mental Disorders, fifth edn. (DSM-5) [9]

decline and neurodegeneration seen in AD than Aβ plaque load [24]. Autopsy studies have revealed that the neurodegeneration in AD follows a specific sequence beginning in entorhinal cortex and hippocampus and then progressing to limbic regions [25]. Additionally, extensive degeneration of the cholinergic innervations to the neocortex from the nucleus basalis of Meynert and the medial septal nucleus occurs early in the AD disease process [25]. As the disease becomes more advanced, neurodegeneration is widespread and can be found throughout neocortical and subcortical regions, with significant atrophy of the temporal, parietal, and frontal cortices [25]. While not fully understood, it is believed that the complex pathologic cascade that ultimately leads to AD begins years to decades before clinical symptoms manifest [26, 27], further illustrating the importance of identifying patients in the earliest stages of the disease when, it has been hypothesized, therapeutic interventions may have greater efficacy. Currently, studies with potentially disease-modifying drugs are being performed in prodromal AD (i.e., individuals with dominantly inherited mutations that lead to early-onset AD) and MCI due to AD (www.clinicaltrials.gov).

As mentioned previously, patients with MCI are at an increased risk for developing AD relative to the general population [1, 21]. Despite this increased risk, some MCI patients seem to remain stable or return to normal over time [4]. Although some data suggest that the rate of reversion to normal cognition may be as high as 25 to 30 % [4], it is important to note that reversion to normal cognition at the time of short-term follow-up does not eliminate the possibility of later progression to dementia. In fact, a recent study showed that MCI cases, including those who reverted to normal cognition, still had a high risk of progressing to dementia, suggesting that a diagnosis of MCI at any time has prognostic value [28•].

Issues to Consider When Making a Clinical Diagnosis of MCI

While each of the diagnostic systems has distinct differences (see Table 1), they share the following common core characteristics (Fig. 1): 1) self- or informant-reported cognitive complaint, 2) objective cognitive impairment, 3) 4) preserved general functional abilities, and 5) no dementia. Regardless of the classification system used, there are a number of important issues to take into account when considering a diagnosis of MCI.

Underlying Etiology

Once it has been determined that the patient meets the core clinical criteria for MCI (Fig. 1), it is important to consider the likely *primary* etiology driving the MCI. In theory, this has the benefit of allowing the clinician to inform the patient and the patient's caregivers of their likely prognosis and disease course, allowing patients and their families to better prepare and plan for future care, and financial and legal matters, if necessary. However, we recognize that determining the likely primary underlying etiology in a patient group with, by definition, *mild* cognitive impairments can be challenging. Typically, information that can be used to determine underlying etiology can be inferred from the patient's history and

through additional testing (e.g., neuroimaging, genetic testing, and neuropsychological assessment). This may include seeking evidence for:

1) AD pathology: including impairment in episodic memory, progressive decline in cognition, evidence of Aβ deposition (decreased CSF Aβ42 levels [10] or positive Aβ PET scan [11] and evidence of neuronal injury (as defined by the NIA-AA workgroup) [8] (increased CSF *tau/ptau levels* [10], medial temporal lobe and posterior cingulate atrophy and ventricular enlargement evident by structural MRI [12, 13], if such information is available, and presence of AD genetic risk factors (discussed further in 'Genetic Testing' section), which suggests pathological processes associated with AD [8];
2) Lewy body pathology: including prominent visual hallucinations, motor features of Parkinsonism (e.g., bradykinesia, rigidity, etc.), and rapid eye movement sleep abnormalities, which suggests pathological processes associated with DLB [29, 30];
3) Vascular disease: multiple vascular risk factors, the presence of extensive cerebrovascular disease evident by structural MRI, and/or "step-wise" decline, which suggests pathological processes associated with vascular dementia [30];
4) Frontotemporal degeneration: including prominent behavioral (e.g., disinhibition) or language disturbances early in the course of disease (memory disturbance is often observed later in disease), atrophy of frontal lobe structures evident by structural MRI, decreased glucose metabolism in the frontal and temporal lobes evident by FDG PET, and/or genetic mutations in the *MAPT* gene on chromosome 17 [31], which suggests pathological processes associated with FTD [32].

It is important to note that the pathological features of some of these disorders can exist in combination (e.g., Aβ plaques, Lewy bodies, and vascular disease), particularly among individuals in advanced age [8]. Therefore, in the clinic, it may be difficult to determine which pathological feature is the primary cause of the cognitive impairment. However, determining the likely primary underlying etiology is not only important for informing the patient and their families of prognosis and likely disease course, it may also help inform which treatments (if any) may be most appropriate. The issue of therapeutics will be discussed further in the section 'Current and Emerging Treatments' (below).

Genetic Testing

The most extensively studied genetic association with MCI and AD is with the *Apolipoprotein E* (*APOE*) gene located on chromosome 19 [33, 34]. Variation in *APOE* is represented by three alleles: *ε2*, *ε3*, and *ε4* [35]. Individuals with one *APOE*ε4 allele have a five to six fold greater risk of developing AD, and individuals with two *APOE*ε4 alleles are at ~20 times greater risk for developing AD [33, 36]. The *APOE*ε3 allele is the most commonly occurring allele and is considered to be neutral; the *APOE*ε2 allele is thought to be protective [37]. Research suggests that individuals who meet the clinical criteria for MCI who are also *APOEε4* positive are more likely to progress to AD within a few years than individuals who are *APOEε4* negative [38]. While it is likely that additional genes confer some risk for developing AD, and would therefore also confer risk for MCI due to AD, *APOE* remains by far the most significant genetic risk factor for AD identified thus far [39]. However, it is important to note that although presence of an *APOEe4* allele confers an increased risk of developing AD, it *does not* in and of itself guarantee development of AD. Therefore, *APOE* genotyping should not be used as a diagnostic test and should be used primarily to identify MCI patients with a higher risk for progression from MCI to AD.

Assessing Patients with Late-Life Depression for MCI

Depressive symptoms have been found to occur in up to 63 % of individuals with MCI [40]. Although depression is frequently associated with MCI and dementia [41–47], the role of depression as a risk factor for MCI and dementia is not fully understood. Differentiation between cause and effect is particularly challenging when assessing patients with late-life depression for MCI since depression by itself is associated with a number of cognitive deficits, including difficulty concentrating, distractibility, forgetfulness, reduced reaction time, memory loss, and indecisiveness [48]. The mechanisms behind the association between depression and cognitive decline are not fully understood and different mechanisms have been proposed [42, 49, 50]. Depression could be a risk factor for dementia, an early dementia symptom, a reaction to cognitive and functional disability, or a symptom of a related risk factor, such as cerebrovascular disease [51].

Since patients with late-life depression are at an increased risk for developing cognitive decline and dementia [16, 52], we recommend including a cognitive assessment at the time the patient begins treatment for their depression. Once the depression is in remission, the cognitive assessment should be repeated. If cognitive impairment is present, even with successful treatment of depression, this should be viewed as suspicious and monitored closely. We also recommend including a depression screening for patients with MCI, since having both cognitive deficits and late-life depression have been shown to be negative prognostic factors for efficacy of antidepressants [53]; for such patients, more aggressive treatment for depression may be needed.

Importance of Subjective Cognitive Decline

Greater emphasis on early detection and diagnosis of cognitive impairment has lead to the conceptualization of 'pre-MCI,' in which individuals perceive subjective changes in their cognitive abilities but perform within normal limits on cognitive tests [54•]. There is increasing evidence to support that subjective cognitive decline (SCD), even with normal performance on cognitive tests, is associated with increased likelihood of AD biomarker abnormalities and with an increased risk for future cognitive decline and AD [54•, 55–61]. In fact, one of the core criteria for MCI is subjectively reported change in cognitive abilities (Fig. 1) [2, 8, 9]. Although SCD is non-specific and could potentially reflect numerous conditions such as normal aging, psychiatric conditions, neurologic and medical disorders, substance use, and medication effects, current evidence suggests that the following factors increase the likelihood of future cognitive decline in individuals with SCD: 1) subjective decline in memory, rather than other domains of cognition, 2) onset of SCD within the last 5 years, rather than presence of SCD for several years and 3) age at onset of SCD ≥60 years [54•]. The primary goal of identifying individuals at the 'pre-MCI' stage is to define target populations for interventions at a stage before progressive neuronal loss and irreversible cognitive impairment have occurred [62]. For the clinician, making the distinction between SCD that may indicate future cognitive decline and changes in cognition related to either psychiatric illness (e.g., depression) or normal aging can be challenging. However, if patients with SCD fit any of the aforementioned factors relating to increased likelihood of future cognitive decline, we recommend that those patients be followed and periodically reassessed.

Current and Emerging Treatments

Pharmacological Treatments

Currently, there is no pharmacological treatment that is approved for MCI. Given that MCI represents a high-risk group for developing AD, many of the drugs that are approved for treating AD have been evaluated in several clinical trials as potential therapeutics for MCI. The neuropathology of AD is characterized by early loss of basal forebrain cholinergic neurons, leading to decreased cholinergic transmission, which is associated with deficits in memory and cognition [63]. Cholinesterase inhibitors (such as donepezil, rivastigmine, and galantamine) work by preventing the breakdown of acetylcholine and are FDA approved to treat mild to severe AD [64, 65]. These drugs mainly provide symptomatic, short-term benefits, without affecting the underlying pathogenic mechanisms of AD [64]. Studies evaluating the efficacy of cholinesterase inhibitors for the treatment of MCI have yielded mixed results (see Table 2 for details) [66–70]. Systematic reviews and meta-analyses evaluating the efficacy of cholinesterase inhibitors for the treatment of MCI have concluded that there is no convincing evidence that cholinesterase inhibitors have an effect on cognitive test scores or on progression to AD in patients with MCI [76, 77, 78•]. One potential explanation for the inconclusive results in studies evaluating the efficacy of cholinesterase inhibitors for the treatment of MCI, other than a true absence of drug efficacy, is the heterogeneity of the patient populations used for the studies [14]. It is possible that these studies included MCI patients with non-AD related etiologies in which there is no cholinergic component [14]. The use of cholinesterase inhibitors may therefore only be appropriate for MCI patients with underlying AD pathology.

As mentioned previously, loss of basal forebrain cholinergic neurons is known to occur early in the AD process [63]. Specifically, nicotinic cholinergic receptor loss has been demonstrated in patients with AD [79] and is linked to the histopathological hallmarks of AD [80] and cognitive impairment [81]. Studies have shown that nicotinic agonists improve cognitive performance patients with AD [82–86]; therefore, nicotinic agonists could be useful in treating MCI. Recently, Newhouse et al. [71•] examined the efficacy of transdermal nicotine therapy on cognitive performance in nonsmoking patients with a-MCI and demonstrated improvement in primary and secondary cognitive measures of attention, memory, and mental processing over 6-months of treatment (see Table 2 for details). While this initial study provides evidence for nicotine-induced cognitive improvement in patients with a-MCI, larger studies will be needed to determine if the effects observed are clinically important over the long term.

Other pharmacological treatment studies have evaluated B vitamins [72, 73], vitamin E [67], and omega-3 fatty acids [74•, 75] (see Table 2 for details) and in general have not proven effective in treating MCI (for more extensive review see [78•]). Higher homocysteine levels are recognized as a risk factor for cognitive impairment and AD and can be reduced through the use of B vitamins (folic acid, B_{12} and B_6) [72]. Two studies (see Table 2) have evaluated the efficacy of B vitamins for treatment of MCI [72, 73]. One study demonstrated that B vitamins appeared to slow cognitive and clinical decline in MCI patients with elevated homocysteine [72], however B vitamins were found to have no effect in another study [73]. Therefore it remains unclear whether B vitamins are useful in treating MCI and may only be appropriate for use in MCI patients with elevated homocystine.

It has been suggested that omega-3 fatty acids, such as docosahexaenoic acid (DHA) and eicosapentaenoic acid

Table 2 Pharmacological treatment studies in patients with mild cognitive impairment (MCI)

Treatment Type	Study Drug	Study	Study Design	Participants	Conclusion(s)
Cholinesterase Inhibitors	Donepezil	Doody et al. [66]	51-week, multicenter, double-blind, RPCS	N=778 a-MCI patients • n=391 Donepezil • n=387 Placebo	• Donepezil demonstrated small improvement on the primary measure of cognition but there was no change on the primary measure of global function. Responses on subjective measures suggest subjects perceived benefits with donepezil treatment.
	Donepezil or Vitamin E	Petersen et al. [67]	3 year, multicenter, double-blind, RPCS	N=769 MCI patients • n=253 Donepezil • n=257 Vitamin E • n=259 Placebo	• Donepezil therapy was associated with a lower rate of progression to AD during the first 12 months of treatment, however the rate of progression to AD after three years was not lower among patients treated with donepezil than those given placebo.
	Donepezil	Salloway et al. [68]	24-week, multicenter, double-blind, RPCS	N=270 MCI patients • n=133 Donepezil • n=137 Placebo	• No significant difference found between treatment and placebo groups on primary efficacy measures. Donepezil group showed improvement on secondary measures of global cognition.
	Galantamine	Winblad et al. [69]	Two 24 month, multicenter, double-blind, RPCS	Study 1 N=990 MCI patients • n=494 Galantamine • n=496 Placebo Study 2 N =1,058 MCI patients • n=532 Galantamine • n=526 Placebo	• Galantamine was not effective in preventing progression to dementia. Treatment groups showed improvement on secondary measures of global function, executive function, and attention, however they study drug was associated with higher incidence of bradycardia.
	Rivastigmine	Feldman et al. [70]	Up to 48 month, multicenter, double-blind, RPCS	N=1018 MCI patients • n=508 Rivistigmine - n=510 Placebo	• Rivastigmine was not effective in preventing progression to AD or on cognitive function.
Nicotine	Transdermal nicotine Nicotrol® patch	Newhouse et al. [71•]	6 month double-blind, RPCS	N=67 a-MCI patients • n=34 Nicotine • n=33 Placebo	• Patients with a-MCI treated with 6 months of transdermal nicotine showed improvement in primary and secondary cognitive measures of attention, memory, and mental processing, but not in ratings of clinician-rated global impression.
B Vitamins	Folic acid, B12 & B6	de Jager et al. [72]	2 year, double-blind, RPCS	N=266 a-MCI patients • n=133 B vitamins • n=133 Placebo	• B vitamins appeared to improve executive functioning and slow cognitive and clinical decline in people with MCI with elevated homocysteine relative to placebo.
	Folic acid, B12 & B6	van Uffelen et al. [73]	1 year, double-blind, RPCS	N=152 MCI patients • n=78 B vitamins • n=74 Placebo	• Vitamin B supplementation did not improve memory in older adults with MCI.
Vitamin E	Vitamin E or Donepezil	Petersen et al. [67]	3 year, multicenter, double-blind, RPCS	N=769 MCI patients • n=257 Vitamin E • n=253 Donepezil • n=259 Placebo	• Vitamin E did not reduce incident dementia and had no benefit in patients with a-MCI.
Omega-3 Fatty Acids	EPA-rich or DHA-rich fish oil	Sinn et al. [74•]	6 month, double-blind, RPCS	N=50 MCI patients • n=17 EPA- rich fish oil • n=18 DHA-rich fish oil • n=15 Placebo	• DHA-rich fish oil improved verbal fluency and both DHA- and EPA-rich oil reduced depressive symptoms after 6 months.
	DHA & EPA	Chiu et al. [75]	24 month, double-blind, RPCS	N=23 MCI patients • n=12 DHA & EPA • n=6 Placebo	• DHA and EPA improved may improve general clinical function in patients MCI.

RPCS, randomized placebo-controlled study; NSAIDS, non-steroidal anti-inflammatory drugs; COX-1, Cyclooxygenase-1; COX-2, Cyclooxygenase-2; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; a-MCI, amnestic MCI; AD, Alzheimer's disease

(EPA), may play an important role in cognitive function in patients with AD [87], and may therefore be useful in treating MCI. One study evaluating the efficacy of DHA- and EPA-rich fish oil to treat depressive symptoms in patients with MCI found that both DHA- and EPA-rich fish oil reduced depressive symptoms after 6 months of treatment [74•]; another study found that DHA and EPA improved general clinical function in patients MCI (see Table 2) [75]. These studies suggest that omega-3 fatty acids may be useful for improving mood symptoms in patients with MCI, although further studies with larger sample sizes are needed to determine if the effects observed are clinically important.

Non-Pharmacological Treatments

There is some evidence that suggests non-pharmacological interventions, such as cognitive training and physical exercise, may be beneficial for patients with MCI [17]. It is hypothesized that such activities may be neuroprotective or compensatory [17]. Two systematic reviews highlighted several studies that demonstrated that cognitive training improved performance on tests of global cognitive functioning, memory, and metamemory in patients with MCI [88•, 89]. Although promising, a limitation of these findings is the small sample sizes of the individual studies; therefore, larger studies are needed to confirm that cognitive training is beneficial for improving cognitive performance in patients with MCI.

In addition to cognitive training, there is increasing evidence that suggests that aerobic exercise may be protective against cognitive decline [90]. A systematic review evaluating the effect of aerobic exercise on cognitive performance in patients with dementia, traumatic brain injury, multiple sclerosis, and chronic stroke found modest improvements in several areas of cognition [91]. Specifically, aerobic exercise improved cognition in people with dementia, improved attention and cognitive flexibility in patients with traumatic brain injury, improved attention in people with multiple sclerosis, and enhanced motor learning in people with chronic stroke [91]. Given that aerobic exercise has been shown to be beneficial in other neurological disorders, it could prove beneficial as a non-pharmacological treatment in patients with MCI. As with cognitive training, large randomized controlled trials will be needed to determine if aerobic exercise is beneficial for improving cognitive performance specifically in patients with MCI.

Recommendations for Clinicians

We recommend that elderly patients be routinely asked about their cognitive functioning. If available, informants should be asked to confirm any reports of cognitive decline experienced by the patient. Clinicians should consider using a structured instrument that examines diverse aspects of functional abilities, psychiatric, and cognitive functioning, such as the Older Adult Self-Report (OSAR) and the informant-based Older Adults Behavior Checklist (OABCL) that has been validated to correlate with evaluations of cognitive impairment [92]. Reports from patients and their informants about subjective changes in cognitive functioning should prompt more focused office evaluation and patients with SCD should be followed and periodically reassessed. Patients that meet criteria for MCI should be evaluated as to the potential cause. Consider comprehensive neuropsychological testing, screening for depression, brain imaging (quantitative MRI or PET), genetic testing (*APOE* status), and neurological exam. Patients with predominantly a-MCI and evidence for AD pathology should be considered for cholinergic therapies as well as non-pharmacological interventions, such as cognitive training or aerobic exercises. Regardless of treatment, longitudinal follow-up is important.

Conclusions

MCI is a complex and evolving diagnosis. While there is general agreement that there is an interval between optimal cognitive functioning and clinical dementia when individuals experience cognitive decline, current knowledge is limited by the lack of consistent findings in the identification of risk and progression factors, specific pathological and clinical markers, as well as difficulties in finding effective treatments [17]. One possible explanation for the apparent gaps in knowledge about MCI concerns the fact that many different etiologies can give rise to the clinical syndrome of MCI. Though not all patients with MCI will progress to a diagnosis of dementia, current evidence indicates that these patients are at a significantly increased risk for developing future cognitive decline relative to the general population and should therefore be monitored longitudinally and considered for treatment as effective treatments become available.

Compliance with Ethics Guidelines

Conflict of Interest Jennifer N. Vega declares that she has no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any new studies with human or animal subjects performed by any of the authors.

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