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REVIEW ARTICLE

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Management of mild cognitive impairment (MCI): The need for national and international guidelines

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ABSTRACT

Objectives: To review available evidence of pharmacological and non-pharmacological treatment for MCI and analyse information and limitations in national and international guidelines.

Methods: Experts from several European countries conducted a qualitative review of the literature on MCI and treatments for MCI, as well as respective chapters in national and international guidelines on dementia/MCI. Psychotherapeutic/psychosocial treatments were excluded from the review.

Results: Consensus diagnostic criteria for MCI are available, making early recognition and accurate classification of MCI subtypes possible. MCI can be identified in a primary care setting. Further corroboration and differential diagnosis should be done at specialist level. Mixed pathologies are the rule in MCI, thus a multi-target treatment approach is a rational strategy. Promising evidence has been generated for multi-domain interventions. Limited evidence is available for different pharmacological classes that have been investigated in MCI clinical trials (e.g. acetylcholinesterase inhibitors). EGb 761® improved symptoms in some clinical trials; it is the only pharmacological treatment recommended in existing guidelines for the symptomatic treatment of MCI.

Conclusions: MCI is recognised as an important treatment target and some recent national guidelines have considered symptomatic treatment recommendations for MCI. However, more needs to be done, especially at an international level.

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Introduction

A better understanding of mild cognitive impairment (MCI), including its causes, underlying pathophysiological processes and earliest possible identification, has become a major public health priority (Winblad et al. 2016). The concept of MCI including definitions of subtypes and diagnostic criteria has been introduced and modified over time (Petersen et al. 1997). Recent national guidelines are only just beginning to consider pharmacological and non-pharmacological treatment options for patients with MCI (Lopez Trigo 2017; Petersen et al. 2018).

In this literature review, we aim to describe the concept of MCI concerning diagnosis, pathogenesis and treatment, to review the evidence of available pharmacological and non-pharmacological (both symptomatic and disease-modifying) treatments for MCI, and to analyse respective information and limitations in national and international guidelines.

The concept of MCI – diagnostic, pathogenetic and therapeutic aspects

Definition and diagnosis

In 1997, Petersen et al. defined mild cognitive impairment (MCI) as a clinical and neuropsychological syndrome which is characterised by emerging cognitive impairment, i.e. an intermediate state between

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physiological ageing and dementia (Petersen et al. 1997). Because of its potentially progressive character, MCI came to be recognised as a pathological condition. In the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), 'dementia' was reclassified as 'major neurocognitive disorder' by the American Psychiatric Association (APA) and 'mild neurocognitive disorder' was conceptualised as an early or less severe pathological state of cognitive decline which is closely related to MCI (American Psychiatric Association 2013). In their 11th Revision of the International Classification of Diseases (ICD-11), the World Health Organisation (WHO) has adopted the definition 'mild neurocognitive disorders' (World Health Organisation 2018). This aligns with the DSM-5 diagnostic guidelines by taking into account the pathological character of MCI (World Health Organisation 2018).

Different diagnostic criteria and subtypes of MCI have been proposed and modified over time (Table 1); (Elissa and Amos 2011; Jak et al. 2016) these shifts reflect the evolving recognition of MCI as an early disease state in the Alzheimer's disease (AD) continuum (Jack et al. 2018) as well as in the continuum of vascular cognitive impairment (Skrobot et al. 2018). In 2011, the National Institute on Ageing and the Alzheimer's Association (NIA-AA) published several sets of diagnostic criteria for AD at different stages, i.e. at the preclinical stage (Sperling et al. 2011), at the MCI stage (Albert et al. 2011) and at the dementia stage (McKhann et al. 2011) in recognition of the fact that the pathological process of AD affects the brain for many years before, finally, the dementia syndrome emerges. Patients with MCI have been phenotyped further as amnestic (aMCI) and non-amnestic MCI (naMCI), with impairments in multiple or single cognitive domains. In aMCI, memory loss is predominant and associated with a considerable risk of further development to AD (Albert et al. 2011) whereas non-amnestic presentations may frequently progress to non-Alzheimer's dementias. Comparable sets of diagnostic criteria for AD at different stages, including MCI, have been proposed by an International Working Group (IWG) (Dubois et al. 2007) and modified further (Dubois et al. 2016). In addition to a clinical diagnosis of MCI, the modified criteria proposed by the IWG and the NIA-AA include the presence of biomarkers indicative for AD pathophysiology; these criteria are commonly used in clinical practice in Europe for diagnosis and communication to MCI patients (Bocchetta et al. 2015; Bertens et al. 2019).

Biomarkers in MCI and predictors of progression

Operational use of biomarker evidence for amyloid pathology and neuronal injury allows to differentially assess the likelihood of progression to AD dementia at the MCI stage (Vos et al. 2015). These core AD biomarkers include: cerebrospinal fluid (CSF) concentrations of amyloid beta 42 (Aβ42), phospho-tau and total tau protein, medio-temporal lobe atrophy on MRI, a typical regional reduction of brain glucose metabolism on [18F]-fluorodeoxyglucose positron emission tomography (FDG-PET) and increased fibrillar Aβ burden assessed with amyloid PET) (Albert et al. 2011; Dubois et al. 2016; Jack et al. 2018). To base the diagnosis of AD at different stages of cognitive impairment, e.g. at MCI and dementia, on the same set of biomarker changes reflects a dramatic shift of the concept of AD (Dubois et al. 2016; Jack et al. 2018). Personalised risk predictions in patients with MCI based on differential biomarker constellations may be possible in the future (van Maurik et al. 2017).

Additionally, biological and epidemiological risk factors of disease progression from MCI to dementia have been identified, including apolipoprotein E4 (APOE-ε4), depression, loneliness, hearing impairment, diabetes, hypertension, older age, female gender and stronger cognitive impairment as reflected by lower mini-mental state examination (MMSE) score or higher AD assessment scale cognitive subscale (ADAS-cog) score (Li et al. 2016). In particular, behavioural markers such as sensitive neuropsychological tests hold potential for early identification of MCI in primary care (Davis et al. 2013).

Rationale for early intervention in MCI

Based on published criteria for MCI as defined by phenotyping, reported prevalence estimates range from 16% to 20% in studies predominantly recruiting patients aged ≥65 years (Roberts and Knopman 2013). Progression to clinically diagnosable dementia occurs at a higher rate from MCI than from normal cognition (Roberts and Knopman 2013; Langa and Levine 2014). While the average rate of progression from MCI has been reported to be 10–15% per year (Roberts and Knopman 2013; Langa and Levine 2014), there are patients diagnosed with MCI who tend to remain stable (i.e. do not develop dementia) (Ganguli et al. 2011), and a proportion of patients may even revert to normal (2% (Petersen et al. 2010) to 31% (Palmer et al. 2010) depending on the MCI criteria used and design of the study); reverse conversions occur mainly in population-based studies (Bruscoli and Lovestone 2004).

Table 1. MCI as a diagnostic entity: a time frame of milestones.

Year (Society/Author)	Definition	Diagnostic criteria	Additional criteria for AD aetiology included	Additional criteria for VD aetiology included	Reference
1997 (Petersen et al.)	MCI	• Complaint of defective memory • Normal activities of daily living • Normal general cognitive function • Abnormal memory function for age • Absence of dementia	No	No	(Petersen et al. 1997)
2004 (Winblad et al.)	MCI-revised (amnestic MCI, multidomain MCI amnestic, multidomain MCI non-amnestic, single non-memory MCI)	• Presence of a cognitive complaint from either the subject and/or family member • Absence of dementia • Change from normal functioning • Decline in any area of cognitive functioning • Preserved overall general functioning but possibly with increasing difficulty in the performance of activities of daily living	No	No	(Winblad et al. 2004)
2011 (NIA-AA; Albert et al.)[a]	MCI due to AD	• Concern regarding a change in cognition • Objective evidence of impairment in one or more cognitive domains, typically including memory • Preservation of independence in functional abilities • Not demented	Yes	No	(Albert et al. 2011)
2013 (American Psychiatric Association)	Mild neurocognitive disorder	• Modest cognitive decline in one or more cognitive domains based on ○ Concern and ○ Modest impairment in cognitive performance • Cognitive deficits do not interfere with capacity for independence in everyday activities • 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)	Yes	Yes	(American Psychiatric Association 2013)
2018 (NIA-AA update; Jack et al.)[b]	Alzheimer's pathologic change/AD with MCI	• Cognitive performance below expected range • Cognitive performance usually in the impaired/abnormal range based • on population norms • Evidence of decline in • cognitive performance from baseline • May be characterised by cognitive presentations not primarily amnestic • Neurobehavioural disturbance may also be a prominent feature of the clinical • presentation • Performs daily life activities independently, but cognitive difficulty may • result in detectable but mild functional impact on the more complex activities of daily life	No	No	(Jack et al. 2018)

(*continued*)

Table 1. Continued.

Year (Society/Author)	Definition	Diagnostic criteria	Additional criteria for AD aetiology included	Additional criteria for VD aetiology included	Reference
2018 (World Health Organisation)	Mild neurocognitive disorder	• Subjective experience of a decline from a previous level of cognitive functioning • Accompanying objective evidence of impairment in performance on one or more cognitive domains relative to that expected given the individual's age and general level of intellectual functioning that is not sufficiently severe to significantly interfere with independence in the person's performance of activities of daily living • The cognitive impairment is not entirely attributable to normal ageing • The cognitive impairment may be attributable to an underlying disease of the nervous system, a trauma, an infection or other disease process affecting specific areas of the brain, or to chronic use of specific substances or medications, or the aetiology may be undetermined	No	No	

MCI: mild cognitive impairment; AD: Alzheimer's disease; VD: vascular dementia.
[a]Based mainly on clinical criteria → intended for general clinical practice - three separate clinical entities: cognitively unimpaired; MCI: and dementia.
[b]Recommendations are "research framework", not to be considered as diagnostic criteria or guidelines → not intended for general clinical practice; continuous process in cognitive domains.

In MCI subjects positive for AD biomarkers, the three-year progression rate to AD-type dementia was 59% compared to only 4% in subjects with no abnormal AD biomarkers (Vos et al. 2015). Therefore, risk stratification and personalised prediction is a high priority (van Maurik et al. 2019).

MCI treatment interventions may serve two goals: 1) symptomatic improvement, i.e. improvement of cognitive functioning and non-cognitive symptoms; and 2) disease modification, i.e. prevention or delay of further cognitive decline to clinically manifest dementia. For dementia prevention, evidence from the literature does not support the use of any studied intervention to date (Brasure et al. 2018; Butler, McCreedy, et al. 2018; Butler, Nelson, et al. 2018; Fink et al. 2018). One randomised, placebo-controlled study reported a reduced likelihood of progression to AD with donepezil, as compared with placebo, for the first 12 months, but over three years of the study there was no significant difference in the probability of progression to AD (Petersen et al. 2005). Similarly, some benefit of donepezil was evident at the end of a three-year follow-up study among earlier-age AD onset carriers of APOE-ε4 and the Kalow variant of butyrylcholinesterase (BChE-K) genes (De Beaumont et al. 2016). Despite the lack of convincingly effective pharmacological or non-pharmacological therapies to reduce the risk of progression from MCI to dementia, some interventions have been shown to delay cognitive decline, and there remains a strong rationale for symptomatic treatment of MCI. Behavioural and psychological symptoms, also referred to as neuropsychiatric symptoms (NPS), are common in MCI patients and may be associated with greater functional impairment and progression to Alzheimer's dementia (Ismail et al. 2016). Depression, apathy and anxiety have been reported to occur in ∼40% of adults with MCI (Monastero et al. 2009; Gallagher et al. 2017).

Cognitive complaints are associated with lower quality of life (QoL), a higher depression and anxiety rate, higher perceived stress and lower general mental well-being (Pusswald et al. 2015; Stites et al. 2018). Notably, QoL is affected at early stages of cognitive decline (Bárrios et al. 2013). The treatment goal for MCI patients would be to effectively alleviate symptoms (cognitive, psychiatric and behavioural symptoms) and to improve QoL. Bárrios et al. showed that the QoL reported by patients with MCI is better than estimated by their caregivers (Bárrios et al. 2013). This trend for informants to rate QoL lower than patients is consistent with what is observed in more advanced stages of cognitive decline, i.e. dementia, and may be

due to the fact that MCI patients are less aware of their cognitive and functional decline compared with their caregivers (Bárrios et al. 2013). In a recent survey of patient and partner outcome and treatment preferences, QoL was given the highest priority for MCI, whereas distressing behaviours and caregiver outcomes (burden, mood and self-efficacy) had lower rankings (Smith et al. 2018). Nevertheless, several further studies have shown that the burden on the social environment due to patients' behavioural symptoms is a considerable problem in MCI, sharing some of the same characteristics (e.g. challenging behaviours) as caregiver burden in dementia (Paradise et al. 2015). Management of neurobehavioural symptoms may therefore be important to reduce the burden on caregivers of MCI patients (Hayashi et al. 2013).

In summary, both cognitive deficits and NPS in MCI develop to be a burden for patients, partners/family members and thus require treatment, i.e. 'watchful waiting' is a questionable option from the perspective of the affected subject. Any symptomatic treatment will be appreciated, even if secondary prevention or risk modification for dementia cannot be achieved as yet. Thus, it makes sense to offer MCI patients tailored symptomatic treatment for both cognitive impairment and NPS.

MCI And early dementia – mixed pathologies are the rule

Data from autopsy and imaging studies reveal that mixed pathologies in both probable AD and MCI are common, mainly in the elderly (Korczyn 2002; Schneider et al. 2009). Interactive associations between amyloid, neurofibrillary tangles, alpha synuclein, inflammation and mitochondrial dysfunction suggest a synergistic contribution to neurodegeneration (Schneider et al. 2009; Rabin et al. 2018). Furthermore, concomitant cerebrovascular disease pathologies (i.e. macroinfarcts, microinfarcts, atherosclerosis, arteriolosclerosis and cerebral amyloid angiopathy) as well as other concomitant neurodegenerative disease pathologies (i.e. Lewy bodies, TDP-43 and hippocampal sclerosis) are found in elderly individuals with AD pathology (Kapasi et al. 2017). Since many MCI patients, especially patients with aMCI, already have an underlying AD pathology, it is logical to investigate whether pharmacological treatment strategies for Alzheimer's dementia might be effective in the treatment of MCI (see below).

Cholinergic deficit has been identified as the major downstream pathophysiological cause of cognitive deficits in AD (Karakaya et al. 2013). Cholinesterase inhibitors are still the standard for symptomatic treatment of dementia due to AD (Mufson et al. 2008). However, in Alzheimer's disease at the MCI stage, choline acetyltransferase is upregulated in the human body anyway, resulting in normal ACh levels, and therefore, due to this compensatory and/or neuroplasticity response to the disease process, it is not rational to use AChE-I (Mufson et al. 2008). AChE-I have no general effect on other pathophysiological mechanisms of cognitive decline in neurodegenerative disorders, such as energy metabolism and mitochondrial function, or on neuronal plasticity (Ashford 2015; Müller et al. 2017). Current symptomatic agents with a single mode of action may only have limited impact on mixed pathologies, whereas therapy with a multifactorial mode of action (e.g. EGb 761®) promises to be a more rational choice in this context.

Overview of study data on existing interventions for MCI patients

Non-pharmacological interventions

Non-pharmacological lifestyle interventions such as cognitive training, moderately intensive physical exercise and diet, have shown promise in MCI, demonstrating symptomatic benefit, but not yet prevention of progression to dementia. Several randomised controlled trials (RCTs) have explored the relationship between physical activity and cognition in patients with varying degrees of cognitive impairment. A systematic review by van Uffelen et al. evaluating 23 RCTs, eight of which recruited MCI patients, reported modest benefits from exercise on several aspects of executive functions (van Uffelen et al. 2008). Most of these 23 RCTs, evaluated in a more recent systematic review, showed that non-pharmacological interventions, e.g. physical activity, cognitive training, and socialisation, among MCI subjects were beneficial (Horr et al. 2015). A meta-analysis by Strohle et al. reported small improvements in cognition of MCI patients with physical exercise (Strohle et al. 2015).

Several clinical trials explored the effect of multidomain lifestyle intervention strategies on the delay and/or prevention of cognitive decline in older individuals with differentially increased risk for further cognitive decline (Ngandu et al. 2015; Andrieu et al. 2017; Sherman et al. 2017; Anderson-Hanley et al. 2018).

The three-year Multidomain Alzheimer Preventive Trial (MAPT) study was the first trial to evaluate the effectiveness of a multidomain lifestyle intervention and omega-3 fatty acids compared to a placebo,

either alone or in combination, for the prevention of cognitive decline in non-demented elderly patients aged ≥70 years (Andrieu et al. 2017). The authors concluded that the multidomain intervention strategy had no significant effects on cognitive decline.

The two-year Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) trial showed that a multidomain intervention could improve or maintain cognitive functioning in at-risk elderly people (aged 60–77 years) from the general population. In the FINGER trial, the multidomain intervention including diet, exercise, cognitive training and vascular risk monitoring ($n = 631$) was compared against a control group who received general health advice ($n = 629$). The primary outcome measure was a change in cognition as measured through the comprehensive neuropsychological test battery (NTB) Z score. After the two-year intervention period, a significant beneficial effect of the intervention for the primary outcome was demonstrated; improvement in NTB total score was 25% higher in the intervention group than in the control group at two years. Significant improvements were also noted in executive functioning (83% higher in the intervention vs. the control group), and in processing speed (150% higher in the intervention group vs. the control group) (Ngandu et al. 2015).

Dietary supplements

Levels of certain nutrients were found to be lower in the brain and circulation in AD than in non-AD controls (Lopes da Silva et al. 2014). Thus, based on the notion that cognitive decline in MCI is a result of, for example, the loss of synapses (de Wilde et al. 2016), a specific nutrient combination, Souvenaid was developed. Souvenaid contains a mixture of omega-3-fatty acids, lipids, vitamins (B6, B12, C, E and folic acid) and selenium (Soininen et al. 2017). An EU-funded two-year RCT (LipiDiDiet) investigated the effects of Souvenaid on cognitive decline (and related measures) in prodromal AD (Soininen et al. 2017). The LipiDiDiet trial involved 311 MCI patients across 11 sites in four countries (Finland, Germany, the Netherlands and Sweden). Patients were randomised to receive either the nutritional intervention or an iso-caloric control drink for 24 months (Soininen et al. 2017). Although this trial showed that Souvenaid had no significant effect on the rate of decline in cognitive performance during prodromal AD, as measured using neuropsychological test battery composite scores over two years, favourable effects on memory and a clinically relevant combined measure of cognition and function were observed in sub-analyses (Soininen et al. 2017). Importantly, analysis of secondary endpoints showed reduced atrophy in brain regions controlling memory in the scans of patients treated with Souvenaid (Soininen et al. 2017).

In addition to the bioactive compounds in Souvenaid, a few other long-term studies with nutraceuticals, e.g. vitamin B and omega-3 fatty acids, report some positive effects of mitigating the cognitive decline in MCI patients (McAnany and Martirosyan 2016; D'Cunha et al. 2018). Sinn et al. (2012) conducted a six-month, double-blind, parallel RCT to investigate the benefits of supplementing the diet with docosahexaenoic acid (DHA)-rich and eicosapentaenoic acid (EPA)-rich fish oils for cognition, depressive symptoms and QoL in 50 elderly subjects (aged > 65 years) with MCI (Sinn et al. 2012). Although cognitive function did not improve in the intervention group compared to the control group, depressive symptom scores were significantly reduced after six months (Sinn et al. 2012).

The hypothesis that the pathological processes behind cognitive impairment may be partially attributable to free radicals has led to the evaluation of vitamin E supplements to treat Alzheimer's dementia and MCI. According to a recent Cochrane review, there was no overall benefit of vitamin E to prevent progression to dementia or improve cognitive function in patients with MCI or Alzheimer's dementia; however, only a few heterogeneous trials were identified in this systematic review (Farina et al. 2017). Notably, out of the four studies assessed, only one study by Petersen et al. (2005) assessed vitamin E in people with MCI (Petersen et al. 2005). They found no evidence that high-dose vitamin E combined with donepezil reduced the transition rate from MCI to dementia or improved cognitive function over three years (Petersen et al. 2005).

Pharmacological interventions

There is currently no effective pharmacological intervention for MCI. Nevertheless, treatments that alleviate symptoms of MCI can provide significant benefits to patients and a major research effort is directed towards interventions that slow the rate of cognitive decline. Potential agents for MCI treatment include AChE-I, glutamate receptor modulators, antioxidants, anti-inflammatory drugs, nootropics, immunomodulators, mainly amyloid antibodies, secretase inhibitors and Ginkgo biloba (Karakaya et al. 2013). Although numerous RCTs have evaluated anti-dementia drugs in the MCI stage, and some studies show symptomatic

relief (Grass-Kapanke 2011; Gavrilova et al. 2014), no study to date has shown efficacy at delaying progression from MCI to dementia. A systematic review by Cooper et al. found no evidence from 41 RCTs that any specific treatment was effective in reducing the transition rate from MCI to dementia (Cooper et al. 2013).

Three cholinesterase inhibitors, donepezil, rivastigmine and galantamine, approved for Alzheimer's dementia were evaluated for their ability to treat MCI or prevent the progression to AD. Doody et al. (2009) examined the effect of donepezil in 821 patients with aMCI. Patients were randomised to 48-week courses of donepezil or placebo (Doody et al. 2009). At 48 weeks, cognition (mean ADAS-cog scores) was significantly improved in the donepezil group compared with the placebo group, but the mean difference was only 1 point on the 89-point ADAS-cog scale. Most other measures of global impairment, cognition and function were not improved, which the authors concluded may possibly be because these measures are insensitive to the change in MCI (Doody et al. 2009). Moreover, adverse events possibly or probably related to treatment were significantly more common with donepezil than with placebo (47% vs. 25%) (Doody et al. 2009). The most frequent treatment-emergent adverse events assessed as probably related to donepezil treatment were diarrhoea (3.8%), nausea (2.6%) and abnormal dreams (2.6%) (Doody et al. 2009). In a second RCT study by Dubois et al. (2015), prodromal AD patients treated with donepezil did not differ from controls in their rate of decline, although they showed significantly less shrinkage of the hippocampus (45% reduced rate of hippocampal atrophy) (Dubois et al. 2015). A 24-week multicentre study of donepezil in MCI patients did not show any improvement in memory but did show some benefit in measures of attention, concentration and psychomotor speed. Of note, the rate of adverse effects was higher in donepezil-treated MCI patients in this study (88% donepezil treatment vs. 73% placebo treatment) than in former trials involving AD patients (Salloway et al. 2004). A Cochrane review which evaluated two studies including the aforementioned study by Salloway et al. (2004), concluded that donepezil lacks efficacy in MCI patients (Salloway et al. 2004; Birks and Flicker 2006). Non-significant delay of cognitive decline in MCI patients after two and four years, respectively, was revealed in clinical trials with galantamine (Winblad et al. 2008) and rivastigmine (Feldman et al. 2007). According to Winblad et al. (2008) the results of two large galantamine trials, GAL-INT-11 and GAL-INT-18, showed a slight but significantly increased mortality risk in the galantamine arm, suggesting caution using such pharmacological treatment in MCI patients (Winblad et al. 2008). There are several limitations in the studies with cholinesterase inhibitors which were performed before the introduction of metabolic biomarkers into clinical trials and therefore randomised subjects might comprise very heterogenic populations.

The N-methyl-d-aspartate (NMDA) receptor antagonist memantine is another approved anti-dementia drug (for moderate to severe AD). Memantine acts against the effects of the excitatory neurotransmitter glutamate, but it has not been well studied in MCI (Casey et al. 2010). A galantamine-memantine combination has not shown superiority to galantamine alone or placebo in relation to cognition in aMCI patients (Peters et al. 2012). Preliminary data from this one-year placebo controlled study showed a short-term cognitive benefit of the combination in a subgroup of prodromal AD patients; however, the study was interrupted early due to galantamine safety concerns (Peters et al. 2012).

Since β-amyloid (Aβ) has evolved as a potential major target for disease modification in AD, several compounds, e.g. beta- and gamma-secretase inhibitors and anti-amyloid antibodies have been investigated in 'early AD', i.e. in MCI up to mild dementia (Wang et al. 2017). None of the large clinical trials with amyloid as a target have been successful to date, thus questioning the pharmacological relevance of this hypothesis at this stage of disease (Morris et al. 2018). Interestingly, a recent open-label observational extended trial with disease-specific symptomatic combination therapy reported that CSF- and MRI-biomarkers can help to predict a marker-specific drug's efficacy relating to disease progression, i.e. progression from MCI to Alzheimer's dementia, and help to define neuropathological disease severity. The authors of this study concluded that testing symptomatic treatment effects of such pharmacological agents in future MCI clinical trials should include the assessment of biomarkers to enrol patients with abnormal target biomarker profiles (Joachim et al. 2018).

Anti-inflammatory agents were investigated for their effectiveness to prevent the onset of Alzheimer's dementia in patients with MCI. A double-blind, 13-month placebo-controlled trial in 257 MCI subjects was conducted with triflusal, a platelet aggregation inhibitor and non-selective, non-steroidal anti-inflammatory drug (NSAID). According to the authors, compared to placebo, patients in the triflusal group had a significantly lower risk of progression to Alzheimer's

dementia (hazard ratio, 2.10; 95% confidence interval: 1.10–4.01; $p = .024$). A trend, albeit non-significant, was observed in favour of triflusal regarding cognitive decline ($p = .096$; as measured by ADAS-cog). However, the trial was interrupted prematurely due to subject recruitment problems (Gomez-Isla et al. 2008).

Another agent that has been used for decades to treat age-associated cognitive impairment, AD and vascular dementia is Ginkgo biloba extract (GBE). Unlike synthetic single-compound active substances, GBEs are complex mixtures of active constituents. Their qualitative and quantitative composition depends on the manufacturing process and may therefore differ considerably between products. Unfortunately, in some countries, low-quality Ginkgo products are marketed as herbal dietary supplements; these products are essentially different from standardised, drug-quality extracts, such as EGb 761® (Diamond et al. 2000).

EGb 761® is a special standardised GBE manufactured by Dr. Willmar Schwabe GmbH & Co. KG. EGb 761® has demonstrated efficacy in the cognitive function and neuropsychiatric symptoms of patients with AD, vascular and mixed dementia comparable to that of AChE-I or memantine, but with fewer side-effects (Ihl et al. 2011).

EGb 761® offers broad multi-target effects, promising for many MCI patients. In relevant animal models and *in vitro* experiments, EGb 761® has demonstrated effects such as 1) improvement of mitochondrial function, 2) antioxidant effects, 3) enhancement of synaptic function and neuronal plasticity, 4) anti-inflammatory effects and 5) improvement of blood flow (Liu et al. 2015; Müller et al. 2017). Hence, the drug interferes with both vascular pathologies and neurodegeneration. Clinical benefits have been demonstrated in both vascular cognitive impairment and AD. Thus, and due to its excellent safety profile, EGb 761® can be applied without extensive diagnostic biomarker testing even in primary care settings.

Potential disease-modifying effects in MCI by EGb 761® have also been evaluated in two trials. The GEM (Ginkgo Evaluation of Memory) trial reported by DeKosky et al. did not support the use of EGb 761® to reduce the risk of developing AD or all-cause dementia in elderly individuals with normal cognition or MCI (DeKosky et al. 2008). However, low treatment compliance in this trial limited the validity of this finding and the study design limited applicability on MCI syndrome. In the GuidAge study, Vellas et al. reported that five years of treatment with EGb 761® in adults aged 70 years or older who spontaneously reported memory complaints did not reduce the risk of progression to AD compared with placebo (Vellas et al. 2012). Unfortunately, this trial was underpowered to reach a conclusion on efficacy since the overall progression rate to dementia was unexpectedly low. A protocol-specified subgroup analysis and a secondary analysis applying an appropriate statistical model for time-to-event data with non-proportionate hazards revealed a significant late-treatment effect (Scherrer et al. 2015). Notably, the 240 mg dose was well tolerated in long-term trials (Vellas et al. 2012).

EGb 761® showed effects on cognition and neuropsychiatric symptoms in patients with MCI. Evidence from a placebo-controlled double-blind study which included MCI patients older than 55 years with neuropsychiatric symptoms demonstrated that EGb 761® (240 mg daily) for 24 weeks improved NPS and cognitive performance (Gavrilova et al. 2014).

A placebo-controlled, double-blind study by Grass-Kapanke et al. (2011) analysed 300 subjects with very mild cognitive impairment (subjective complaints of impairment and at least one cognitive domain one standard deviation below appropriate normal) (Grass-Kapanke et al. 2011). Results showed that administration of EGb 761® for 12 weeks in aMCI subjects led to improvements in cognition and QoL (Grass-Kapanke et al. 2011). Lower cognition scores at baseline were associated with better treatment effects (Grass-Kapanke et al. 2011).

In addition to cognitive deficits, patients with MCI can experience motor dysfunction, including deficits in gait and balance (Verghese et al. 2002). Gschwind et al. investigated the efficacy of a GBE to improve gait stability (Gschwind et al. 2017). This GBE (120 mg) administered twice daily in MCI patients aged 50–85 years improved dual-task-related gait performance in MCI patients (Gschwind et al. 2017).

Furthermore, there is no safety risk to be derived from long-term trials. Since EGb 761® has a positive benefit/risk ratio, it can be recommended as a treatment for MCI. Based on literature evidence to date, standardised GBEs are recommended for use as herbal medicinal products for the improvement of (age-associated) cognitive impairment and quality of life in mild dementia (European medicines agency (EMA) 2014). Based on this recommendation, EGb 761® is already approved in several EU countries for this indication.

Existing guidelines for dementia and MCI

International (Ihl et al. 2011) and European (Hort et al. 2010; Sorbi et al. 2012) clinical practice guidelines on the diagnosis and management of AD/dementia are available in various countries. Tables 2 and 3

Table 2. Summary of guidelines, recommendations and considerations for interventions in patients with Alzheimer's disease and related dementias from different countries and consortia.

Country	Society	Type of guideline	Indication	Pharmacological symptomatic treatments (level of evidence)	Control of CV risk factors (level of evidence)	Physical and cognitive activation (level of evidence)	Behavioural/psychiatric symptoms (level of evidence)	Reference
World	WFSBP	Practice guidelines	Symptomatic AD and other dementia syndrome disorders	• AChE-I (B) • Memantine (B) • Ginkgo biloba (B) • Other	NR	NR	NR	(Ihl et al. 2011)
Europe	EFNS-ENS	AD practice guidelines	AD	• AChE-I (A) • Memantine (A)	Aspirin	Yes (B)	Yes (C); SSRI to treat AD depression (B)	(Hort et al. 2010; Sorbi et al. 2012)
Austria	ÖAG	consensus statement	AD	• AChE-I (A) • Memantine (A) • Ginkgo biloba (B)	Yes (B)	NR	NR	(Schmidt et al. 2010)
	ÖGPB		AD	• AChE-I • Memantine • Ginkgo biloba	Yes	NR	NR	(Kasper et al. 2015)
Czech Republic	CPS	consensus document	Incipient dementia	• AChE-I • Memantine • Ginkgo biloba • Other	Not recommended	Not recommended	NR	(Jirák 2014; Jirak 2017)
Germany	DGN, DGPPN	consensus document	Mild-moderate/ moderate-severe Alzheimer's dementia	• AChE-I (B) • Memantine (only for moderate-severe and not mild-moderate; B) • Ginkgo biloba (for Alzheimer's dementia and VaD with non-psychotic behavioural symptoms)	For VaD only	In mild-moderate dementia (B)	NR	(Deuschl et al. 2016)
Russia	RCMH	practice guidelines	AD	• AChE-I (A) • Memantine (A) • Ginkgo biloba (C)	Yes (C)	NR	NR	(Gavrilova et al 2013; Bogolepova et al. 2017)
	RMACPE		VaD	• Other				(Bogolepova et al. 2017)
	_		dementia					(Vasenina et al. 2017)
Switzerland	_	expert recommendation	Alzheimer's dementia	• AChE-I • Memantine (MMSE <20 criteria) • Ginkgo biloba	Yes	Yes	NR	(Kressig 2015)
UK	NICE	practice guidelines	AD and non-Alzheimer's dementias	• AChE-I (for AD) • Memantine	NR	Yes	Yes (for mild-moderate symptoms)	(O'Brien et al. 2017; National Institute for Health and Clinical Excellence (NICE) 2018)
China	ADC	practice guideline	Alzheimer's disease and other dementias	• AChE-I • memantine • Ginkgo biloba (EGb 761®) • nicergoline (for VaD)	NR	Yes	Yes	(Jia 2015; Alzheimer's Disease Chinese (ADC) 2017)

(*continued*)

Table 2. Continued.

Country	Society	Type of guideline	Indication	Pharmacological symptomatic treatments (level of evidence)	Control of CV risk factors (level of evidence)	Physical and cognitive activation (level of evidence)	Behavioural/psychiatric symptoms (level of evidence)	Reference
Asia	–	consensus document	Alzheimer's disease and vascular dementia	• AChE-I • memantine • Ginkgo biloba (EGb 761®) (A)	Yes	Yes	Yes; AChEI, Ginkgo biloba (EGb 761®), non-pharmacological treatment, antipsychotics (off-label), memantine, SSRIs, sedatives	(Kandiah et al. 2019)

AChE-I: acetylcholinesterase-inhibitors; AD: Alzheimer's disease; ADC: Alzheimer's Disease Chinese; BPSD: Behavioural and Psychological Symptoms of Dementia; CPS: Czech Psychiatric Association; DGN: German Society for Neurology; DGPPN: German Society for Psychiatry, Psychotherapy, and Nervous Diseases; EFNS-ENS: European Federation of Neurological Societies - European Neurological Society; MCI: mild cognitive impairment; MMSE: mini-mental-state examination; NICE: National Institute of Health and Clinical Excellence; NR: not reported; ÖAG: Österreichische Alzheimer Gesellschaft; ÖGPB: Österreichische Gesellschaft für Neuropsychopharmakologie und Biologische Psychiatrie; RMACPE: Russian Medical Academy for Continued Professional Education; SSRI: selective serotonin reuptake inhibitors; VaD: vascular dementia; WFSBP: World Federation of Societies of Biological Psychiatry.

summarise existing guidelines, recommendations and considerations for both pharmacological and non-pharmacological interventions in patients with AD or dementia (Table 2) and MCI (Table 3) from different countries and consortia. Typically, for Alzheimer's dementia, based on evidence to date, AChE-I and Ginkgo biloba are recommended for symptomatic treatment of mild to moderate dementia in most countries, as well as memantine for moderate-to-severe dementia. There is a section dedicated to MCI in the current international dementia guidelines published by the World Federation of Societies of Biological Psychiatry (WFSBP) (Ihl et al. 2011), but it only addresses potential non-pharmacological interventions to reduce the progression to dementia, and not options for symptomatic treatment (i.e. cognition and NPS). There was a paucity of data and thus of recommendations for MCI treatment in both earlier international guidelines (Hort et al. 2010; Ihl et al. 2011; Sorbi et al. 2012) and in some of the earlier country-specific guidelines listed in Table 3. The published European national dementia guidelines or consensus reports only occasionally mention interventions for MCI (e.g. Austria, Germany, Russia, Czech Republic and Switzerland), but never in much detail.

Most recently, a practice guideline update summary on MCI was published by the American Academy of Neurology (AAN) (Petersen et al. 2018), and a Spanish MCI consensus document published by the Spanish Society of Geriatrics and Gerontology (SEGG) (Lopez Trigo 2017). The AAN guideline does not recommend any pharmacological treatment for MCI but mentions that cholinesterase inhibitors may be considered; (Petersen et al. 2018) however, this has been disputed due to lack of efficacy data (Valenzuela et al. 2018). No studies on either EGb 761® or other Ginkgo extracts were considered in this update (Petersen et al. 2018). Notably, in the MCI-specific Spanish consensus document, EGb 761® at a dose of 240 mg is recommended as the only proven and approved intervention for treating age-related MCI (Lopez Trigo 2017).

In summary, recommendations reported in international and national dementia guidelines are inconsistent and do not consider the recent diagnostic concepts nor the most recent pharmacological and non-pharmacological treatment evidence. The role of biomarkers as a tool for diagnosing the MCI stage of AD is not considered; and treatment outcomes in MCI only focus on the lack of risk reduction for progression to dementia. Neither new clinical trial data demonstrating symptomatic effects on NPS nor the emerging

Table 3. Summary of guidelines, recommendations and considerations for interventions in patients with mild cognitive impairment from different countries and consortia.

Country	Society	Type of guideline	Indication (criteria)	Pharmacological symptomatic treatments (level of evidence)	Control of CV risk factors (level of evidence)	Physical and cognitive activation (level of evidence)	Behavioural/ psychiatric symptoms (level of evidence)	Reference
Austria	ÖAG	consensus statement	MCI (various)	• NE • In early premedication phases dietary supplements (also containing Ginkgo biloba) may be useful in certain cases	Yes	Yes	NR	(Schmidt et al. 2010)
	ÖGPB		MCI (ICD-10, DSM-4 TR)	• NE	Yes	NR	NR	(Kasper et al. 2015)
Czech Republic	CPS	consensus document	MCI (Preserved activities of daily living)	• Ginkgo biloba	No	No	NR	(Jirák 2014; Jirak 2017)
Germany	DGN, DGPPN	consensus document	MCI (as defined by (Albert et al. 2011)	• NE for risk reduction	NE for risk reduction	NE for risk reduction	NR	(Deuschl et al. 2016)
Russia	RCMH/ RMACPE	practice guidelines	MCI (MoCA, DSM-5)	• Ginkgo biloba (approved for MCI) • Citicolic, Actovegine, Piribedil, Piracetam for VCI • Other	Yes	Yes	NR	(Gavrilova et al 2013; Bogolepova et al. 2017; Vasenina et al. 2017)
Spain	SEGG	Consensus document	MCI (MoCA, CamCog)	• Ginkgo biloba (240 mg dose approved for ACI) • Citicolin for VCI • Other	Yes	Yes	NR	(Lopez Trigo 2017)
Switzerland	_	expert recommendation	MCI	• Ginkgo biloba	Yes	Yes	NR	(Kressig 2015)
USA	AAN	practice guidelines	MCI	• AChE-I (off-label use only)	Yes	Yes	Yes	(O'Brien et al. 2017; National Institute for Health and Clinical Excellence (NICE) 2018; Petersen et al. 2018)
China	ADC	practice guideline	MCI	• Ginkgo biloba (EGb 761®) • TCM	Yes	Yes	NR	(Jia 2015; Alzheimer's Disease Chinese (ADC) 2017)
Asia	–	consensus document	MCI	• EGb 761®	Yes	NR	NR	(Kandiah et al. 2019)

AAN: American Academy of Neurology; AChE-I: acetylcholinesterase-inhibitors; ACI: age-related cognitive impairment; AD: Alzheimer's disease; ADC: Alzheimer's Disease Chinese; CamCog: Cambridge Cognitive Examination; CPS: Czech Psychiatric Association; DGN: German Society for Neurology; DGPPN: German Society for Psychiatry, Psychotherapy, and Nervous Diseases; DSM-4: The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; ICD-10: International Statistical Classification of Diseases (10th edition); MCI: mild cognitive impairment; MMSE: mini-mental-state examination; MoCA: montreal cognitive assessment; NE: no evidence; NR: not reported; ÖAG: Österreichische Alzheimer Gesellschaft; ÖGPB: Österreichische Gesellschaft für Neuropsychopharmakologie und Biologische Psychiatrie; RMACPE: Russian Medical Academy for Continued Professional Education; SEGG: Sociedad Española de Geriatria y Gerontologia; TCM: traditional Chinese medicine.

evidence for multi-domain interventions were considered. The lack of any recommendation for the treatment for MCI appears outdated and MCI as a condition to be treated is insufficiently addressed. There is a strong need to integrate advances of evidence into national and international guidelines to generally recognise the importance of MCI in the Alzheimer continuum and to improve the management of MCI.

Conclusion

No clinical trial with any pharmaceutical ingredient has provided evidence of disease modification in MCI or AD to date. Thus, the general strategy to focus on a single molecular event as the most promising target for disease-modification (e.g. anti-amyloid) should be re-considered. A multi-target intervention may be a more rational choice for a multi-factorial disease, such as AD, particularly at the stage of MCI. Because of the longer time frame of all interventions in MCI compared to interventions in dementia, they should include symptomatic pharmacological treatment, changes in nutrition and lifestyle modification, including mental, physical and social activity. Furthermore, it is important to consider symptomatic treatment effects associated with an improvement of QoL.

Psychotherapeutic interventions were not discussed in this paper, but their value for helping patients with cognitive impairments cope with the burden these ailments bring about in daily life has been examined elsewhere (Ueda et al. 2013; Simon et al. 2015). Some evidence that older adults with depression and cognitive deficits can benefit from cognitive behavioural therapy has been demonstrated (Simon et al. 2015).

With the underlying causes of MCI becoming better understood, further effective interventions to treat MCI both symptomatically as well as aetiologically may be developed. A current treatment option in MCI is EGb 761® (240 mg/day) for the symptomatic treatment of cognitive impairment and associated NPS.

In order to improve management of MCI and to recognise the importance of this disease stage within the Alzheimer disease continuum, it appears mandatory to update existing guidelines with respect to available evidence. Some national guidelines/consensus documents have taken up EGb 761® as a symptomatic treatment option for MCI due to its favourable benefit/risk ratio. However, as the underlying causes of MCI are better understood, more effective interventions to treat MCI both symptomatically as well as aetiologically will be developed.

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