CLINICAL NUTRITION HIGHLIGHTS

Science supporting better nutrition

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Mild Cognitive Impairment.

From assessment to innovative interventions.

Nestlé Nutrition Institute

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INTRODUCTION by the Editor-in-Chief

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It is common knowledge that as people age, they experience changes in their memory and other cognitive functions. There is a wide variety of situations, ranging from subtle changes with little or no impact on daily life to those that herald the onset of dementia. Over the past few decades, this issue has been clinically developed around historical terms such as benign senescent forgetfulness, age-associated memory impairment, late-life forgetfulness or age-related cognitive decline, all of them pertaining to processes linked to aging. This proved to be too imprecise, and the age criterion has been gradually abandoned in favour of a concept based on operational criteria regardless of subject age or the underlying process.

Thus, the concept of Mild Cognitive Impairment (MCI) was introduced. Its main characteristics include a mild impairment of memory and/or other cognitive functions measured by neuropsychological tests, which may have an impact but does not significantly affect the activities of daily living and the patient retains his/her independence.

MCI is a very common clinical condition, with an overall prevalence of between 3% and 20% in people over 65 years of age, according to different studies. This prevalence is age-dependent, reaching a frequency of 45% in people 95 years old and older.

The evolution of MCI over time can also be very variable, ranging from cases that revert to normal or do not worsen to those that convert into dementia. In the latter, the MCI is simply an early stage of dementia.

With approximately 50 million people worldwide living with dementia, this disorder is one of the 10 most burdensome health conditions among the elderly and its prevalence will continue to grow in the coming decades due to the expected population aging.

It is therefore of the utmost importance to detect the presence of MCI, whether or not it is the prodromal stage of dementia, and to treat it with the available therapeutic tools.

This monograph, written by leading authors in the field, begins with a description of the concept of MCI, from its historical evolution through to the current diagnostic criteria and the relevance of MCI in the prevention of dementia. One chapter is devoted to the new concept of Mild Behavioral Impairment, a situation similar to MCI but in which subtle psychological or behavioral changes may alert to a possible incipient dementia. In addition, methods for the detection and assessment of MCI, from the practical standpoint, are presented.

The final chapters in the monograph are devoted to treatment. There is currently no formal pharmacological treatment for MCI. However, many interventions are possible. Space is devoted to describing the non-pharmacological treatments and prevention. In addition, the attempts at finding a pharmacological treatment and molecules that may have this potential are described. Finally, emphasis is placed on nutritional interventions for MCI. To date, this has been the most fruitful therapeutic approach, yielding interesting recent developments such as ketogenic-oral nutritional supplements that improve brain energy status and cerebral blood flow, thus improving patients' cognitive functioning. This undoubtedly heralds a significant advance in the management of this clinical condition, which affects an increasing number of people around the world.

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THE HISTORICAL EVOLUTION OF MILD COGNITIVE IMPAIRMENT

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1. The origins of mild cognitive impairment: benign senescent forgetfulness and incipient amnestic syndrome

While descriptions of dementia date back to antiquity, the concept of mild cognitive impairment (MCI) is relatively new[1]. It was Voijtech Adalbert Kral, a consultant neuropsychiatrist to the Montreal Hebrew Old People's and Sheltering Home, and his collaborating psychologist, Blossom Temkin Wigdor, who in the late 1950s and early 1960s reported the first systematic observations of elderly people that presented memory complaints while maintaining their overall intelligence and functional capacities[2]. Two surveys conducted with all of the Home's 162 residents, including a psychiatric evaluation, physical examination, cognitive testing and other ancillary medical tests, indicated memory loss in all the residents studied compared to normative data from young adults. Subsequently, two types of so-called "senescent memory impairment" were described, together with other types of cognitive deterioration, based on groups of patients sharing clinical characteristics and prognosis[3,4].

A type of "benign" memory dysfunction, namely "benign senescent forgetfulness" (BSF), was characterized by the subject's inability to recall relatively unimportant data or parts of an experience (e.g., a name, a place or a date), although they were able to recall the experience of which the forgotten data were part. Quoting Kral's original description, *the same data which are not available for recollection on one occasion may be recalled at another time.* An example was provided of a *woman of about 80 who remembered that she had attended, some years ago, the wedding of her son in a New England city, but was unable to remember the name of that city.* When asked again on another occasion, she remembered the name of the city. Therefore, the forgotten data seemed to belong to the remote rather than to the recent past. Moreover, the subjects were aware of their shortcoming, attempted to compensate for it by circumlocution and were even able to apologize for it[4]. With the exception of very few individuals, memory impairment remained constant in character and severity over an observation period of more than two years in the people in that group[3].

In contrast to BSF, another group of residents was characterized by the inability to recall not only relatively unimportant data and parts of an experience but also the actual experience. Continuing with the above example**,** *"had the lady [...] suffered from this type of memory impairment, she might have forgotten the wedding of her son which she attended and not only the name of the city where it took place"*[4]. In this "malignant memory dysfunction" group, the loss of recent memories led to disorientation, initially in time and space, and subsequently also with regard to personal details. In addition, the patients remained unaware of their deficits and frequently produced confabulations usually related to their habitual premorbid activities. The patients of this group presented a higher mortality rate after a four-year follow-up period.

While Kral's malignant memory dysfunction strongly evokes dementia (of mild to moderate severity, most probably due to Alzheimer's disease or another neurodegenerative condition), the benign type of memory dysfunction (i.e., BSF) does not fit into the current concept of MCI easily. In fact, it is closer to the concept of subjective cognitive decline[5] or even healthy aging.

However, there was another group described by Kral and Wigdor, characterized by prominent memory dysfunction, which they called "incipient amnestic syndrome" (IAS). The patients of that group displayed a significant deficit in memory performance compared to patients with BSF or depression, although their global intelligence and person-

al functioning were preserved. Clearly, these patients fit into the current view of MCI (amnestic) as a transitional clinical zone between healthy cognition and dementia[2,6]. Regrettably, IAS was not mentioned in Kral's most famous publications[3,4] and nor were diagnostic criteria provided to differentiate it from the benign and malignant types of memory dysfunction[2].

Despite the questionable pathological substrate and lack of operative definition, BSF inspired fresh research in the field of age-related cognitive deterioration and pushed it towards early detection. Moreover, Kral's comprehensive approach integrating medical, psychiatric and neurological aspects, conducting cognitive testing, considering psychological and social factors, and eventually treatment-oriented, contributed a new vision of cognitive impairment and dementia which, departing from the established psychogeriatric taxonomy (Table 1)[7,8], has reaped countless fruits to this day.

Table 1. General taxonomy of psychogeriatric disorders at the time of Kral's descriptions of memory dysfunction.

MAIN CATEGORIES	INDIVIDUAL CONDITIONS	DEFINITION	CURRENT EQUIVALENT TERMS
Neuropsychiatric disorders due to organic brain disease	Acute confusion	A rapidly evolving clouding of consciousness produced by some extraneous cause or appearing for no discoverable reason	Confusional state, confusional syndrome, delirium
	Senile psychosis (or senile dementia)	A gradual and continually progressive failure in the common activities of everyday life along with a clinical picture dominated by failure of memory and intellect and disorganization of personality	Late-onset Alzheimer's disease
	Arteriosclerotic psychosis	Dementia associated with (1) focal signs and symptoms indicative of cerebrovascular disease or (2) presenting a remittent or markedly fluctuating course at some stage of the dementing process and combined with emotional incontinence, preservation of insight, or seizures	Vascular dementia
	Parkinson's disease	A gradual and progressive disorder characterized by shaking, stiffness and difficulty with walking, balance and coordination	Parkinson's disease
	Parkinson's disease with psychiatric disturbances	Same as above, also displaying delusions or hallucinations	Parkinson's dementia, Lewy body dementia
	General paresis of the insane	A variety of possible symptoms (fatigue, headache, insomnia, dizziness, unstable gait, etc.), followed by mental deterioration and personality changes as disease progresses, initiating 10-30 years after syphilis infection	Neurosyphilis
Functional psychoses	Depression	A condition characterized by persistent feeling of sadness, loss of interest and lack of hope, usually accompanied by changes in appetite or sleep	Depression
	Manic-depressive psychosis (or manic-depressive illness)	A condition characterized by extreme mood swings that include emotional highs (mania or hypomania) and lows (depression)	Bipolar disorder
	Late paraphrenia	Well-organized system of paranoid delusions with or without auditory hallucinations in the setting of a well-preserved personality and affective response	Late or very late-onset schizophrenia
	Neuroses of later maturity	Flat depression associated with a feeling of weakness, sleeplessness, irritability, physical complaints and hypochondriacal fears	Dysthymia, adaptive disorder

Based on refs. 7 and 8.

The Figure 1 provides a historical perspective of the different visions and constructs used to define the transition zone between healthy cognition and dementia.

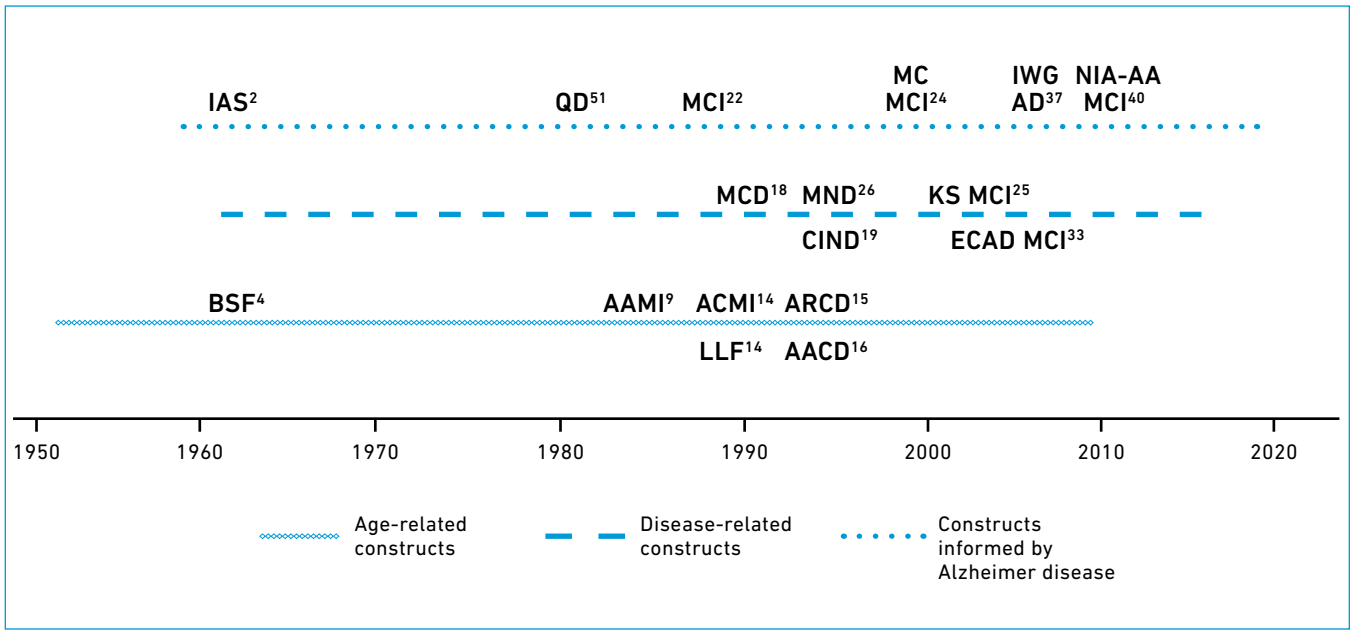

Figure 1. Landmarks in the development of mild cognitive impairment. AD: Alzheimer disease; AACD: age-associated cognitive decline; AAMI: age-associated memory impairment; ACMI: age-consistent memory impairment; ARCD: age-related cognitive decline; BSF: benign senescent forgetfulness; CIND: cognitive impairment no dementia; ECAD: European Consortium on Alzheimer's Disease; IAS: incipient amnestic syndrome; IWG: International Working Group; KS: Key Symposium; LLF: late-life forgetfulness; MC: Mayo Clinic; MCD: mild cognitive disorder MND: mild neurocognitive disorder; QD: questionable dementia.

2. Age-associated memory impairment

After two decades of popularity, BSF was questioned, mainly due to a lack of precise diagnostic criteria and insufficient validation[2,9,10]. Focusing on the experience of memory loss as reported by healthy elderly people, a workgroup convened by the National Institute of Mental Health (NIMH) elaborated the "age-associated memory impairment" (AAMI) construct to facilitate communication among investigators, stimulate research and ultimately improve the treatment of later-life memory loss. According to the proposed diagnostic criteria, memory loss should be one standard deviation (SD) below the mean performance for young adults on standardized recent memory tests. Several examples of the memory tests to be utilized were provided. In addition, specific criteria regarding age limits, the preservation of intellectual function and absence of dementia were included (Table 2)[9].

Although the approach's adequacy may be questioned, the AAMI construct possessed unquestionable merit, since operative diagnostic criteria were provided for the first time ever. However, the AAMI concept also harbored certain contradictions and other issues. On the one hand, the construct was created to identify people experiencing normal age-related memory impairment, while on the other it was assumed that some elderly people would not experience such memory loss. In addition, since one of the objectives of AAMI was to test pharmacological and non-pharmacological treatments to improve memory, certain pathological substrates or mechanisms were implicitly assumed. However, so-called normal age-related memory changes may represent physiological brain changes to compensate or adapt to aging, which would sacrifice certain aspects of cognition (e.g., episodic memory) in favor of other mental capabilities (e.g., semantic memory or judgment)[11].

Table 2. Clinical constructs in the history of mild cognitive impairment

	AGE LIMITS	COGNITIVE SYMPTOMS	PSYCHOMETRIC CRITERIA	MECHANISM/ SUBSTRATE	REf.
BSF	Not specified (advanced age is assumed)	Inconsistent difficulty in recalling non-essential parts of past experiences, expressed by the patient.	Not specified (memory mildly impaired, global intelligence preserved).	Aging	4
IAS	Not specified (advanced age is assumed)	Prominent memory deficit.	Not specified (memory clearly impaired, global intelligence preserved).	Aging/ pathology	Kral and Wigdor 1963 (taken from ref. 2)
AAMI	≥50 years	Memory complaints reflected in everyday problems (e.g., names of persons, misplacing objects, items to be purchased) of gradual onset, expressed by the patient.	Performance (1) ≤1 SD below the mean established for young adults in tests of secondary memory with adequate normative data, (2) ≥9 on the Vocabulary subtest of the WAIS, and (3) ≥24 on the MMSE.	Aging	9
ACMI	50-79 years	Perceived decrease in day-to-day memory that is verified by standardized self-report memory questionnaires.	Performance (1) ±1 SD of the mean established for age in ≥75% of memory tests[1] and (2) 90-130 on verbal and performance scores of the WAIS.	Aging	14
LLF	50-79 years	Perceived decrease in day-to-day memory that is verified by standardized self-report memory questionnaires.	Performance 1-2 SD below the mean established for age in ≥50% of memory tests[1] and (2) 90-130 in verbal and performance scores of the WAIS.	Aging/ pathology	14
MCD	Not specified	Symptoms related to memory, attention, thought, language or visuospatial functioning, most of the time during at least two weeks, reported by individual or informant.	Cognitive tests detect abnormalities.	Medical or neurological condition	18
ARCD	Not specified (advanced age is assumed)	Problems remembering names or appointments, or difficulty in solving complex problems, reported by the individual.	Objectively identified decline in cognitive functioning within normal limits given the person's age.	Aging	15

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AACD	Not specified (advanced age is assumed)	Report by the individual or informant of cognitive decline of gradual onset, present for at least six months.	Performance ≤1 SD of the mean of adequate tests according to age, education, sex, race and culture; the following areas should be evaluated: memory, attention, thinking, language, and visuospatial functioning.	Aging	16
MND	Not specified	Deficit in at least two of the following cognitive domains: memory, executive function, attention/ processing speed, perceptual-motor, or language deficit, most of the time during at least two weeks, reported by individual or informant, causing marked distress or impairment in social, occupational or another important area of functioning.	There is evidence from neuropsychological testing or quantified cognitive assessment of an abnormality or decline in performance.	Neurological or medical condition.	15
CIND	≥65 years	Any type.	Cognitive deficits in standardized cognitive test and clinical examination (psychometric criteria not specified).	Neurological, psychiatric or medical condition.	19
MCI (Mayo Clinic)	Not specified	Memory complaint.	Memory performance usually <1.5 SD of the mean according to age.	Aging/ pathology (Alzheimer disease).	24
MCI (Key Symposium)	Not specified	Any cognitive symptom or evidence of decline on cognitive tests.	Not normal cognitive performance.	Neurological, psychiatric or medical condition.	25
MCI (MCI-ECAD	Not specified	Cognitive complaints from the patients or their families, including reporting of a decline in cognitive functioning during the past year.	Impairment in memory or in another cognitive domain.		33

[1]At least four tests of secondary memory must be administered. AACD: aging-associated cognitive decline; AAMI: age-associated memory impairment; ACMI: age-consistent memory impairment; ARCD: age-related cognitive decline; BSF: benign senescent forgetfulness; CIND: cognitive impairment no dementia; IAS: Incipient amnestic syndrome; LLF: late life forgetfulness; MCD: mild cognitive disorder MMSE: Mini-Mental State Examination; MND: mild neurocognitive disorder; SD: standard deviation; WAIS: Wechsler Adult Intelligence Scale; ECAD: Working Group of the European Consortium on Alzheimer's Disease.

Another issue with the AAMI construct is related to the use of young adult performance for comparison purposes. If the elderly symptomatic and young comparison groups are close in terms of the historical time at which the tests were performed, a lower performance in these tests could be attributed to differences in childhood environment, quality of education and familiarity with the testing conditions, which would presumably benefit younger people, yielding an excess of false positives. If more adequate, non-contemporaneous comparison groups were utilized, false positives could still emerge due to a lack of motivation, sensory deficits or other reasons. Ultimately, AAMI might provide little more than a diagnostic label, and eventually the overtreatment, of anyone over 50 complaining of poor memory[12]. As an additional limitation, AAMI bears the risk of missing cognitive decline in those subjects suffering deterioration in other cognitive domains, different from memory[13].

3. Age-consistent memory impairment and late-life forgetfulness

Three years after the publication of the AAMI diagnostic criteria, a refinement of the definition, together with three subtypes, was proposed to increase its reliability and distinguish between the hypothetical risk groups better. Consequently, age limits were established (50-75 years of age), and at least four secondary memory tests had to be administered. In addition, the inclusion criteria of the sufficient Vocabulary and Mini-Mental State Examination (MMSE) test scores were eliminated and replaced with the performance of the complete Wechsler Adult Intelligence Scale (WAIS) (Table 2)[14].

As in the original NIMH criteria, to be diagnosed with AAMI (revised), the patient had to score at least 1 SD below the mean established for young adults in one or more memory tests. To be diagnosed with age-consistent memory impairment (ACMI), the patient had to score within ±1 SD of the mean established for age in 75% or more of the tests administered. To be diagnosed with late-life forgetfulness, performance had to fall 1-2 SD below the mean established for age in at least 50% of the tests.

4. Age-related cognitive decline

The 1990s witnessed the advent of several constructs examining incipient cognitive impairment beyond memory. The most conspicuous constructs were "age-related cognitive decline" (ARCD), proposed by the American Psychiatric Association and included in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)[15], and "aging-associated cognitive decline" (AACD) which, acknowledging the influence of the APA construct, was proposed by a working party set up by the International Psychogeriatric Association (Table 2)[16]. In a prospective study of 485 young-elderly subjects, AACD demonstrated high stability during a 4-year follow-up, although conversion to dementia was not observed[17].

5. Focusing on pathology rather than aging: mild cognitive disorder

One commonality of all the aforementioned constructs was the exclusion of dementia. In addition, patients who suffered from a medical or psychiatric condition that could explain their cognitive symptoms were usually not considered. Such an approach might not be suitable for studying elderly people, as the same individual often presents a variety of medical processes in combination. Departing from that line of research, two new constructs were included in the most widespread classifications of mental disease: "mild cognitive disorder" (MCD)[18] and "mild neurocognitive disorder" (MND)[15]. Like previous constructs, the presence of mild cognitive deficit (not dementia) had to be reported and documented; however, as significant step forward, a physical or neurological disease or condition known to cause cerebral dysfunction should be present (Table 2). This opened up the way for future MCI constructs due to specific neurological diseases.

In a similar line, investigators from the longitudinal Canadian Study of Health and Aging introduced another entity, namely "cognitive impairment, no dementia" (CIND)[19]. This term was intended to classify individuals aged 65 and over in a population-based study according to a standardized cognitive test and clinical examination. Persons with

non-dementia-related etiologies, such as delirium, chronic alcohol and drug use, psychiatric illness, intellectual disability, memory loss, previously diagnosed as AAMI, and other cerebral disorders (e.g., cerebrovascular disease) causing cognitive deficits, were labeled as CIND. These broad inclusion criteria determined a high prevalence of CIND (~30%)[20] and were associated with an increased risk of future dementia[21].

6. Mild cognitive impairment in the context of Alzheimer disease

As illustrated above, the initial constructs created to identify elderly people that experienced minor cognitive difficulty focused on memory and assumed that the symptoms were due to so-called "normal" aging. With these premises, the scientific findings were somewhat poor, in view of the scant progress made in understanding the mechanisms involved and the possible treatments. Therefore, subsequent definitions broadened the focus to include problems in cognitive domains beyond memory, as well as cases that exceeded the psychometric limits of normality. At the same time, other constructs emerged to accomodate patients that evinced mild cognitive problems due to neurological, psychiatric or systemic pathologies. However, it was not until the 1990s that research became aligned and showed exponential growth, primarily driven by Alzheimer disease.

In fact, the term "mild cognitive impairment" was first utilized by Barry Reisberg's group of investigators at New York University (NYU) to define a specific clinical stage in Alzheimer's disease between subjective cognitive complaints and dementia[22]. The Reisberg group demonstrated that most patients with MCI developed dementia after a two-year follow-up period[23].

Some years later, researchers from the Mayo Clinic, led by Ronal Petersen, proposed a similar construct, also in the context of early Alzheimer's disease. According to the Mayo Clinic criteria, MCI should be characterized by the presence of a) subjective memory complaint, b) normal activities of daily living, c) normal general cognitive function, d) abnormal memory for age (usually performance <1.5 standard deviations below the mean established for people of the same age group), and e) the person was not demented. Longitudinal performance demonstrated that subjects with MCI thus defined declined at a faster rate than control subjects, albeit less rapidly than patients with mild Alzheimer's disease[24].

Amid social concern over the spread of Alzheimer's disease, the Mayo Clinic criteria, somewhat more operational than the NYU criteria, sparked enormous interest among researchers, albeit not without some controversy. In fact, an adaptation of the Mayo criteria that lowers the requirement for conducting psychometric tests and affords greater importance to cognitive evolution and clinical judgment is probably now the most utilized definition of MCI, in usual practice and in research[25].

7. Mild cognitive impairment in modern times

Over the last two decades, in a climate of consensus and clinical-biological convergence, the concept of MCI has been elaborated further according to clinical phenotype, and specific criteria are being proposed for the early diagnosis (i.e. at the MCI stage) of entities most frequently associated with cognitive impairment.

7.1. Mild cognitive impairment as a syndrome

The current view of MCI as a pathological, beyond-aging and etiologically heterogeneous syndrome (Table 3) is best represented by two constructs: MCI, as defined by experts from the Key Symposium held in Stockholm, Sweden, in 2003[25], and "mild neurocognitive disorder" (MND), as defined by the American Psychiatric Association in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V)[26].

The Key Symposium criteria for MCI accomplished two goals: (1) to broaden beyond memory classification scheme, and (2) to recognize that MCI could result from a variety of etiologies and not just Alzheimer's disease[25]. The phenotypic diversification of MCI permits an etiological approach in clinical practice, which is useful for diagnosis, prognosis and treatment (Figure 2)[6]. In fact, the Key Symposium criteria enjoy observational support[27] and

Table 3. Mild cognitive impairment: what it is and what it should not be

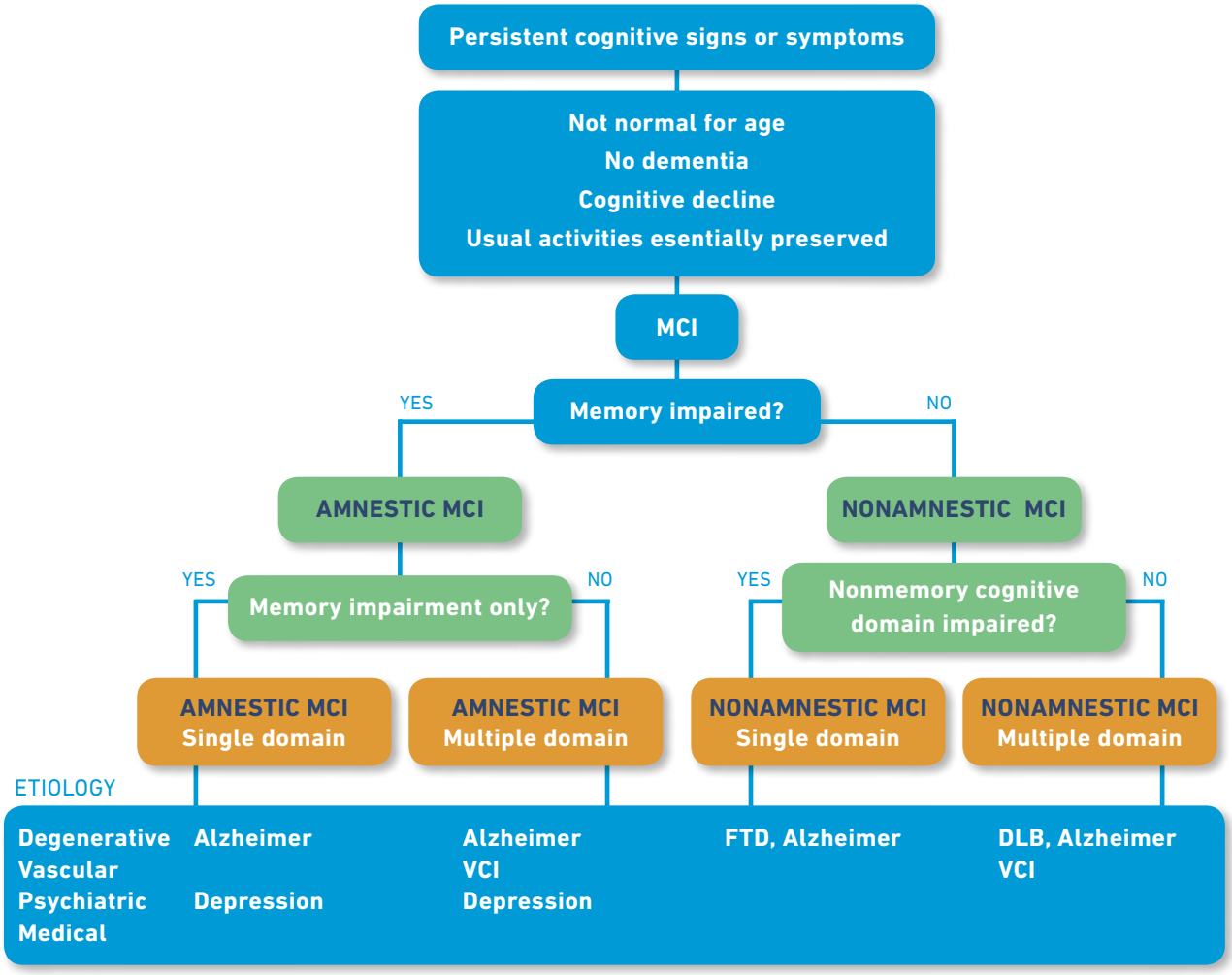
	WHAT IT IS	WHAT IT SHOULD NOT BE
Symptoms	New, chronic and persistent symptoms, cognitive in nature, raising concern in the patient or the informant	Life-time personal traits, adaptive reactions, obvious consequences of known conditions
Setting	Medical office, memory clinic	Advertisements, devices, population surveys (they could be useful for detection)
Diagnosis	Based on the traditional clinical method, which includes anamnesis -integrating medical, neurological, and psychiatric symptoms-, physical examination, cognitive testing, other ancillary tests, psychosocial factors and finally the clinician's judgment	Based on cognitive performance cutoffs
Substrate	Brain pathology or dysfunction	Aging
Etiology	Varied etiology, according to the individual patient (as befits its syndromic nature)	Single and same etiology for all patients (e.g., Alzheimer's disease)
Treatment	Global approach: promote healthy lifestyle, control medical conditions, optimize medications, search for etiology-specific treatments	Only focused on etiology-specific therapies to prevent dementia (keep that for research context)

pathological validation[28], showing that multidomain MCI predicts the conversion to dementia better than isolated amnestic forms[29]. In addition, these criteria present a flexible framework for the evolution of the concept, acknowledging that biomarkers could help to define the clinical diagnosis and natural course better in the future, and the practical guidelines have been periodically reviewed[30-32]. Further definitions of MCI have essentially been aligned with the Key Symposium vision and criteria[33].

The DSM-IV "Dementia, delirium, amnestic, and other cognitive disorders" category was extensively revised in the DSM-5 and was renamed "Neurocognitive disorders", straddling three entities: delirium, major neurocognitive disorder (previously called dementia) and mild neurocognitive disorder (MND). The concept of MND was introduced in the DSM-IV and developed in its revised version (DSM-IV-TR) to replace the concept of "Cognitive disorder not otherwise specified". It was defined as cognitive dysfunction presumably due to the direct effect of a general medical condition that does not meet the dementia or delirium criteria, affects at least two cognitive domains and has a mild impact on functioning (e.g., it can be compensated for with additional effort)[34].

The DSM-5 version of MND resembles the DSM-IV version in name only. While the DSM-IV defined MND based on a single criterion, the DSM-5 defines MND using several cognitive and related criteria. The DSM-5 definition of MND is anchored in four criteria and two specifiers. The four criteria refer to cognitive changes, functional activities and the exclusion of delirium and competing mental disorders, while the two specifiers are the presumed etiologies of MND and the presence or absence of behavioral problems. The main difference between MND and the MCI Key Symposium criteria is that the research work that led to the construct of MCI involved primarily elderly study participants (although age was not part of the definition of MCI), whereas MND includes acquired cognitive disorders of all age groups. In fact, DSM-5 essentially discusses the epidemiology and diagnostic markers of MND by establishing congruence between MCI and MND. While the later category may improve diagnostic reliability, it has yet to stand up to scientific scrutiny to be considered a valid construct[35,36].

Figure 2. Algorithm for the diagnosis and interpretation of MCI in regular practice (modified from reference 6). DLB: dementia with Lewy bodies; FTD: frontotemporal dementia; MCI mild cognitive impairment; VCI: vascular cognitive impairment.



7.2. Mild cognitive impairment as a disease

From the Alzheimer's perspective of MCI, a very influential landmark was established by the International Working Group (IWG), which defined the diagnostic criteria for Alzheimer's disease which for the first time ever did not include the dementia requirement[37]. Clinically focused on a core of early and significant episodic memory impairment, the IWG Alzheimer criteria also stipulated that there should be at least one or more abnormal biomarkers from

1.- Structural magnetic resonance imaging (MRI) structural neuroimaging,
2.- Positron emission tomography (PET) molecular neuroimaging,
3.- Cerebrospinal fluid (CSF) analysis of amyloid beta or tau proteins.

Some years later, the term "prodromal Alzheimer's disease" was coined to name patients who, fulfilling the aforementioned criteria, had MCI due to Alzheimer's disease[38]. A few years later, influenced by new criteria established for preclinical Alzheimer's disease[39], MCI due to Alzheimer's disease[40], and dementia due to Alzheimer's disease[41] by a consortium of the National Institute of Aging and the Alzheimer Association (NIA-AA), the IWG criteria were extended to include patients in the preclinical stages of Alzheimer's disease, as well as patients with atypical phenotypes (IWG-2 criteria)[42]. The IWG criteria were a milestone in that for the first time ever they made it possible for Alzheimer's disease to be diagnosed before the

onset of dementia. These criteria facilitated the design of clinical trials to delay the onset of dementia[43,44] and are being included in regular practice in many memory clinics.

As was mentioned above, the NIA-AA consortium issued MCI criteria due to Alzheimer's disease, expanding the initial IWG criteria to include the atypical clinical variants. In addition, two categories of biomarkers were distinguished for diagnostic approach purposes: "Aβ", comprising CSF $A\beta_{42}$ and PET amyloid imaging and "biomarkers of neuronal injury", which referred to CSF tau/p-tau, hippocampal or medial temporal lobe atrophy on MRI, and temporoparietal/precuneus hypometabolism or hypoperfusion on PET or single-photon emission tomography (SPECT). According to those biomarkers, different hypothetical levels of diagnostic certainty are proposed. The evidence of both Aβ and neuronal injury together confers the highest probability that the Alzheimer pathophysiological process is present. Conversely, if these biomarkers are negative, they may provide information about the likelihood of an alternate diagnosis. Biomarker findings are known to be possibly contradictory, and a great deal remains to be learned about the outcome in these situations. Neither is it known whether the best predictions of the rate of progression depend on the degree to which the individual patient expresses neuronal injury biomarkers[40].

Following the path taken in Alzheimer's disease, diagnostic criteria for MCI or the prodromal state of other neurological entities have been produced. Recently, the Prodromal Dementia with Lewy Bodies (DLB) Diagnostic Study Group proposed operationalized diagnostic criteria for probable and possible "MCI with Lewy bodies" which are intended for use in research settings, pending their validation for use in clinical practice[45]. Previously, diagnostic criteria for MCI due to Parkinson's disease were published by the Movement Disorder Society[46] and criteria for MCI due to cerebrovascular disease were proposed by a consortium of experts led by the American Heart Association and the American Stroke Association[47]. (Table 4)

The DSM-5 also opened the door to the possibility of diagnosing cognitive impairment in the absence of dementia (namely MND) secondarily to Alzheimer's disease, Parkinson's disease, vascular disease and other conditions (i.e., frontotemporal lobar degeneration, Huntington's disease, prion disease, traumatic brain injury, human immunodeficiency virus infection, substance abuse, medications, other medical condition and multiple etiologies)[26]. However, these etiological subtypes, for which diagnostic criteria are included, are the same for both mild and major neurocognitive disorders. This is questionable, since establishing aetiology in MND is more difficult and may therefore have to remain unspecified in many patients[48].

One way or another, the preservation of independence in usual activities and lack of dementia are required in all the MCI-related constructs described in this chapter. It is also implicitly assumed that functional compromise due to physical or other circumstances is permitted. However, the dividing line between functional compromise due to cognitive, physical or other causes may not be clear, particularly in the elderly, people with physical comorbidity or lacking motivation due to psychiatric conditions or other circumstances. In some MCI-related definitions, nuances which permitted a certain degree of supervision or even help to conduct the more complex usual activities were introduced. In this regard, the most permissive classification is that of the NIA-AA, which states that patients with MCI may receive *minimal aids or assistance to perform complex functional tasks which they used to perform previously, such as paying bills, preparing a meal, or shopping*[40].

Since cognitive and functional capacities are inextricably interlinked, an assessment of patient performance integrating both aspects may be particularly sensitive for detecting and keeping track of the clinical manifestations of Alzheimer's disease[49]. The Clinical Dementia Rating (CDR) scale was developed specifically for this purpose by Charles Paul Hughes, Leonard Berg and other investigators from Washington University in St. Louis[50,51]. Subjects are assigned a rating of healthy (CDR 0), questionable (CDR 0.5), mild (CDR 1), moderate (CDR 2), or severe dementia (CDR 3) according to their performance in the three cognitive (i.e., memory, orientation and judgment and problem-solving) and the three functional (i.e., community affairs, home & hobbies and personal care) domains. The rate of CDR 0.5 ("questionable dementia") was included for subjects who were *neither clearly demented nor healthy*[50]. The cognitive symptoms raised by the patients or his/her family focused on memory, although forgetfulness did not interfere significantly with the subject's life. According to the investigators, many of the subjects in the group had syndromes consistent with Kral's benign senescent forgetfulness, whereas others probably had normal cognitive function but might

Table 4. MCI as disease: diagnostic criteria for the most frequent entities

	Prodromal Alzheimer disease (IWG-2)	MCI due to Alzheimer disease (NIA-AA)	MCI due to Parkinson's disease	Prodromal Lewy body disease	Vascular MCI
Symptoms	Episodic memory impairment over more than six months	Episodic memory, executive, spatial or language symptoms documented from the patient, preferably corroborated by an informant, or on the basis of observation by the clinician	Insidious decline in cognitive abilities reported by either the patient or informant, or observed by the clinician	Concern in the patient, informant, or clinician regarding cognitive decline	Persistent (weeks or months) cognitive impairment, different from aphasia, without previous history of gradually progressive cognitive deficit
Cognitive testing	Objective evidence of an amnestic syndrome of the hippocampal type	It is important to examine episodic memory, executive functions, language, visuospatial skills and attentional control; performance is typically 1-1.5 SD below the mean for age and education-matched peers (these ranges are guidelines and not cutoff scores); longitudinal assessment is recommended	Level I diagnosis is given based on abbreviated cognitive assessment, while level II diagnosis is made based on a comprehensive neuropsychological assessment (level I criteria provide less diagnostic certainty than level II) The relevant cognitive domains are attention/working memory, executive, language, memory and visuospatial functions	Objective evidence of impairment in at least one cognitive domain; the cognitive impairment may include any domain, but is more likely to be associated with attention-executive and/or visual processing deficits	A minimum of four cognitive domains should be assessed: executive/ attention, memory, language and visuospatial functions; the classification should be based on an assumption of decline in cognitive function from a prior baseline and impairment in at least one cognitive domain
Biomarkers	At least one of (1) decreased $A\beta_{42}$ together with increased tau or p-tau in CSF (2) increased tracer retention on amyloid PET, or (3) autosomal dominant mutation in PSEN1, PSEN2, or APP	Two categories of biomarkers are proposed (1) Aβ (i.e., CSF $A\beta_{42}$ and PET amyloid) and (2) biomarkers of neuronal injury (CSF tau/p-tau, hippocampal/ medial temporal atrophy on MRI, and temporoparietal/ precuneus hypometabolism or hypoperfusion on PET or SPECT); the use of biomarkers is only recommended for research	Not needed, but diagnosis of Parkinson disease must be clinically established	Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET; polysomnographic confirmation of REM sleep without atonia; reduced MIBG uptake on myocardial scintigraphy	Diffuse, subcortical cerebrovascular pathology and silent infarcts (based on neuroimaging studies, mainly MRI)
Disease variants/ phenotypes	Posterior, logopenic, frontal, and Down syndrome variants	Visual, language, and executive variants	Single domain and multiple domain phenotypes (on the basis of comprehensive neuropsychological assessment)	MCI, delirium-onset, and psychiatric-onset presentations	Amnestic, amnestic plus other domain, nonamnestic single domain, and nonamnestic multiple domain phenotypes

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Certainty levels	Not defined	High likelihood (Aβ+, neuronal injury+); intermediate likelihood (Aβ+, neuronal injury unknown or Aβ unknown, neuronal injury+); unlikelihood (Aβ-, neuronal injury-)	Not defined	Not defined	Probable, possible and unstable vascular MCI is defined according to temporal relationship between vascular event and onset of cognitive deficits, global clinical course, imaging evidence and concomitant conditions (e.g., neurodegenerative disease)
Reference	42	40	46	45	47

$A\beta_{42}$: 42-aminoacid amyloid peptide; APP: amyloid-precursor protein; CSF: cerebrospinal fluid; IWG-2: International Working Group, revised criteria; MCI: mild cognitive impairment; MIBG: meta-iodobenzylguanidine; MRI: magnetic resonance imaging; NIA-AA: National Institute of Aging - Alzheimer's Association; PET: positron emission tomography; PSEN1: presenilin 1 gene; PSEN2: presenilin 2 gene; REM: rapid eye movement; SPECT: single-photon emission tomography.

be mildly depressed or excessively concerned about minor forgetfulness, while others were probably in a very early stage of Alzheimer-type senile dementia[50].

The diagnosis of questionable dementia demonstrated high sensitivity and pathological validity[52], and three stages of early Alzheimer's disease are currently distinguished (i.e., MCI, MCI due to Alzheimer's disease, and very mild Alzheimer's disease) according to the sum of scores in the six categories ("sum of boxes"). The CDR has become the most widely used tool for staging early cognitive deterioration in both usual practice and research settings. In fact, with the support of biomarkers, this tool consistently proved to be more sensitive than conventional cognitive tests in detecting the effect of pharmacological treatment in the initial stages of Alzheimer's disease[44,53].

8. Conclusions

Sixty years after the seminal work by Kral and Wigdor, the concept of MCI has been consolidated, its area of influence has expanded and it has yielded a vast body of fruitful research. Now that sterile debates about the frequency and validity of the different constructs have been overcome, the aim of the scientific community - and society at large - has converged in the early detection of and research into this condition that may eventually lead to treatments that can stop, or at least slow down, brain damage and the speed of cognitive decline. For this purpose, MCI functions as an adequate syndrome to guide clinical detection, optimize the use of biomarkers and efficiently reach an accurate etiological diagnosis (Figure 2)[6].

Research into MCI should continue to expand, focusing particularly on non-amnestic, atypical cases of Alzheimer's disease, as well as on non-Alzheimer dementias, in the earliest clinical stages. Further cognitive typification of MCI subtypes should be helpful in this process, as should the incorporation of behavioral, psychological and motor symptoms, together with new specific biomarkers. As research into biomarkers evolves, they will likely be matched to different MCI phenotypes, eventually increasing diagnostic accuracy and the capacity to predict the clinical course[6,54]. Clearly, the study of the relationships between biomarkers and clinical features should be a melting pot for furthering our knowledge of vascular and neurodegenerative processes associated with cognitive impairment and for finding and predicting the response to treatments[54].

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The historical and current development of MCI presents certain limitations. Affective, behavioral, perception and thought disturbances are not even mentioned in the diagnostic criteria, despite being characteristics associated with etiology and prognosis[55,56]. The role of behavior as a herald of dementia, which could be particularly useful for identifying cases due to frontotemporal dementia, will be specifically addressed in this monograph (chapter 4). The definition and typification of MCI due to chronic medical processes, depression[57] and other psychiatric conditions would help to characterize these patients, improve differential diagnosis and monitor treatment response. The interest in MCI will also be extended to include neurological conditions beyond cerebrovascular disease and primary dementias[58], further reflecting the increasing societal value of mental capacities as key determinants of quality of life.

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MILD COGNITIVE IMPAIRMENT: RELEVANCE AND ROLE IN THE PREVENTION OF DEMENTIA

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1. The global burden of dementia

Dementia is already in the top 10 of the most burdensome health conditions among the elderly[1], and its prevalence will continue to grow in the coming decades due to the population aging. Some 50 million people in the world live with dementia, a number that is expected to increase to 152 million by 2050. Dementia affects individuals, their families and the economy, with global costs estimated at about US$1 trillion per year[2].

Alzheimer's disease and vascular pathology are the most frequent types of brain lesions observed in people with dementia[3]. However, the correlates between brain lesions and cognitive deterioration are not tight, particularly in the very elderly (i.e., aged 90 and above)[4], suggesting the possibility of achieving protection from lifetime brain threats through life-style modifications and other interventions[5].

Compared with the general population, dementia shortens the life span. In population studies, patients with vascular dementia, dementia with Lewy bodies and Parkinson's dementia usually present the shortest survival, followed by mixed dementia and Alzheimer's disease[6]. In fact, the pathological and clinical evolution of Alzheimer's disease is usually very slow. A mean duration of 19 years has been reported from the inception of amyloid peptide aggregation until the onset of symptoms[7]; an interval of seven years was reported between prodromal symptoms and dementia, and a nine-year period was estimated from dementia to death[8]. Hence, mean time from the onset of symptoms to death in Alzheimer's disease, which is the most frequent cause of dementia, is 16 years.

Reports from cross-sectional studies have consistently demonstrated an increase in the overall cost of dementia across the different stages of severity, due to the loss of functional autonomy and the need for continuous assistance and care. Monthly bills of €1,514, €2,082 and €2,818 per individual with dementia were attributed to people in mild, moderate and severe stages, respectively, of Alzheimer's disease[9]. In addition, dementia increases the risk of institutionalization in comparison to the non-demented elderly, further increasing the societal bill. In a data set extracted from family physicians' electronic health recordings, median times of 3.9 years and 5.0 years were reported from the diagnosis of dementia until institutionalization and death, respectively, which was considerably shorter than institutionalization and death times for non-demented people of the same age[10]. Clearly, any intervention that delayed the most advanced stages of dementia would not only reduce personal suffering but would also deliver enormous benefits to society.

2. Is there a potential for the prevention of dementia?

As a decreasing trend in the incidence of dementia is consistently reported[11,12], the growing body of epidemiological evidence supports the role of potentially modifiable risk factors. Based on a review of the existing epidemiological studies, twelve factors were identified by the Lancet Commission that could account for around 40% of worldwide dementias. Quoting those experts, *it is never too early and never too late in the life course for dementia prevention*[13]. Early-life (i.e., younger than 45 years) risk factors, such as a lower level of education, would affect cognitive reserve, while midlife (i.e., 45-65 years) and later-life (i.e. older than

65 years) factors would trigger neuropathological processes. Age-associated risk factors, such as hearing impairment, depression, physical inactivity, diabetes and low social contact could be relevant targets for late-life modification and hypothetically the prevention of the transition from MCI to dementia (Table 1).

Table 1. Modifiable risk factors of dementia

EARLY-LIFE FACTORS	Lower level of education, obesity, air pollution
MIDLIFE FACTORS	Hypertension, smoking**, obesity, depression, excessive alcohol consumption, traumatic brain injury, air pollution.
LATE-LIFE FACTORS*	Smoking**, hearing impairment, depression, physical inactivity, diabetes, low social contact, air pollution.

**Target factors to hypothetically prevent transition from mild cognitive impairment to dementia; **active or passive. Based on ref. 13.*

3. The epidemiology of mild cognitive impairment

The incidence of MCI was analyzed in a population-based prospective study conducted in the Mayo Clinic (Olmstead County, MN) in people aged 70 to 89 years. An overall age- and sex-standardized incidence rate of 6.4 per 100 person-years was found. A higher incidence for both amnestic and nonamnestic MCI subtypes was demonstrated in older males and in people with fewer years of education[14]. Other studies confirmed the age-related gradient of MCI incidence and the association with low education, presenting a range of overall incidence of 2.0-7.5 per 100 person-years[15,16].

The prevalence of MCI and its subtypes varies according to the study setting, the type of participants, the criteria utilized and other methodological questions. Population and community studies, mostly conducted in people over the age of 60 utilizing the Mayo Clinic criteria, presented a range of prevalence of 3%-20%[17-19]. The prevalence of MCI is consistently age-dependent, reaching a frequency of 45% in people aged 95 years and older[20].

While the incidence of MCI is higher than that of dementia[12], the prevalence of MCI and dementia in the population are quite similar[21]. Moreover, unlike dementia, an exponential increase in the prevalence of MCI has not been consistently reported[20]. This is mainly because while dementia is a chronic relatively stable condition, a considerable proportion of MCI cases (17%-59%) revert to normal cognition[22-25].

4. MCI and the risk of dementia

Even not being a stable condition, MCI has consistently been associated with a higher risk of future dementia. Community and population-based studies found annual conversion rates of 5%-6%, while studies conducted in memory clinics presented indices of around 10%[26]. These figures are relevant for the prevention of dementia, given that the annual conversion rate of dementia for cognitively normal elderly people was reportedly 1%-2%. Moreover, epidemiological studies directly comparing people with MCI and normal cognition confirmed that MCI increases the risk of dementia, with risk ratios ranging from 2.5 to almost 9[19].

The early and accurate identification of people with MCI who will develop dementia is of the utmost importance for adequate counselling to be provided to patients and their families and to test potential treatments. The severity of cognitive impairment is by far the strongest dementia predictor[18,27] although obviously other markers should be preferred to propitiate early intervention. Medial temporal lobe atrophy on MRI[28], predominantly posterior hypometabolic pattern on 18F-fluorodeoxyglucose-positron emission tomography (18FGD-PET) and, more recently PET amyloid imaging, have demonstrated

their efficacy in predicting dementia conversion due to Alzheimer's disease[29], although these techniques are expensive and not always comfortable.

Considerably less expensive, albeit not always feasible or tolerable for the patient, the measurement of 42-amynoacid-amyloid peptide ($A\beta_{42}$), 40-amynoacid-amyloid peptide ($A\beta_{40}$), total tau protein and phosphorylated tau protein (p-tau) have also been introduced into memory clinics as predictors of progression from MCI to dementia due to Alzheimer's disease[30]. It is to be hoped that more suitable predictors will soon be available, with the greatest expectations pinned on plasma measurement of two microtubule-related, neuronal specific proteins, namely p-tau for Alzheimer's disease[31], and neurofilament light chain (NfL) for other neurological conditions[32,33].

5. The role of MCI in dementia prevention

Since dementia is an age-associated chronic condition, a reduction in the rate of progression from MCI to dementia would certainly lead to a reduction in the overall prevalence of dementia. In addition, disease-modifying interventions, acting in the MCI stage of dementia, would propitiate a delay of the more severe clinical stages of disease, thus maintaining the quality of life of patients and families. MCI clearly offers a critical window of opportunity for testing the possible disease-modifying therapies and reducing the economic and social cost of dementia considerably.

As was already mentioned, several risk factors for dementia have been identified, some of which present a higher prevalence with advancing age (Table 1). Using population attributable risk models, which operate on the strength of the association between the risk factor and the outcome and the frequency of the risk factor, considerable reductions in dementia prevalence were hypothesized provided that these factors were at least partially controlled. However, a causal relationship between risk factor and medical condition is assumed in those models, although this would not necessarily be the case. For instance, a low level of education, theoretically contributing to the largest proportion of Alzheimer cases worldwide, could be a surrogate marker of other conditions, such as poor diet during childhood or a less stimulus-rich family environment. Moreover, cause and effect relationships regarding risk factors in aging-associated medical conditions are usually complex and several multidirectional pathways probably concur. Hence, predictions of dementia reduction, based on risk factor control, should be cautiously viewed[5,11].

Nevertheless, a great deal of data have been accrued in the last two decades regarding the potentially modifiable risk factors of dementia in people with MCI. Epidemiological and clinical studies are particularly valuable for identifying risk factors that may point towards the pathophysiological mechanisms involved. A systematic review searched and pooled longitudinal studies reporting modifiable risk factors for incident dementia after MCI. Modifiable risk factors were defined as potentially changeable conditions, e.g., through lifestyle modifications or medication. When possible, data from three or more studies were combined and pooled odds ratios were calculated. Separate analyses were conducted for amnesic and nonamnestic MCI, as well as for Alzheimer's and all-type dementia.

As the most consistent result, diabetes was associated with any-type dementia and with dementia due to Alzheimer's disease, suggesting an additive effect of diabetes-associated vascular damage. In addition, one high-quality epidemiological study reported that individuals with treated diabetes were less likely to convert to Alzheimer's dementia than the untreated subjects, suggesting a modifiable risk. A trend of hypertension and risk of dementia was observed, although the results were variable and statistical significance was not reached. Regarding alcohol consumption, heavy drinking predicted conversion from any-type MCI to dementia, while the evidence as to whether moderate alcohol use predicts dementia was inconsistent.

The same study found that the presence of neuropsychiatric symptoms in people with any-type MCI, but not their overall levels of symptoms, predicts conversion to all-cause dementia. Regarding individual symptoms, depression was consistently associated with the development of dementia and a trend was observed for apathy (Table 2)[34].

Table 2. Potentially modifiable risk factors for incident dementia in people with MCI

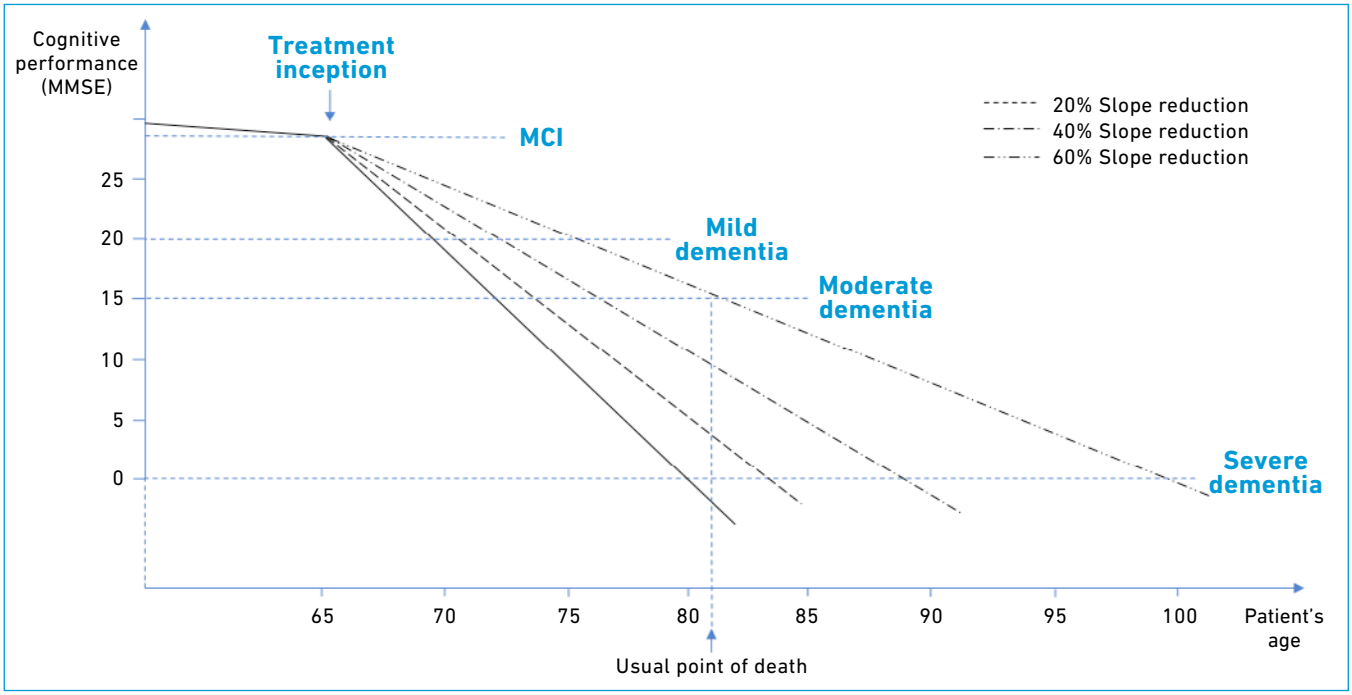
	POOLED ODDS RATIO (95% CI)	NUMBER OF STUDIES (EP/CL)	COMMENTS
Diabetes	1.65 (1.12 to 2.43)	4/3	Studies in amnestic MCI (reporting conversion to Alzheimer's dementia) or any type of MCI (reporting conversion to all-cause dementia) reported similar findings.
Hypertension	1.19 (0.81 to 1.73)	4/3	Consistent neutral results for any-type MCI to all-cause dementia, but inconsistent regarding conversion from amnestic MCI to Alzheimer's dementia.
Hypercholesterolemia	0.92 (0.50 to 1.68)	2/1	Consistent neutral results for any-type MCI to all-cause dementia, but inconsistent regarding conversion from amnestic MCI to Alzheimer's dementia.
History of smoking	0.45 (0.24 to 0.84	1/2	The protective effect was not significant after control for age, indicating competing risk of mortality.
Depressive symptoms	1.35 (0.89 to 2.06)	4/9	There was heterogeneity, with the epidemiological studies that reported conversion from any-type MCI consistently finding that depressive symptoms predicted all cause dementia, while findings from studies in amnestic MCI and clinical studies were less consistent.
Apathy	1.62 (0.63 to 4.17)	0/5	In the largest study, apathy without depressive symptoms predicted conversion from amnestic MCI to Alzheimer's dementia, although apathy in the context of depressive symptoms was not a significant predictor.

CI: confidence interval; CL: clinical studies; EP: epidemiological studies; MCI: mild cognitive impairment. Based on ref. 34.

Studies were also found indicating a protective effect of adherence to the Mediterranean diet, self-reported use of folate and vitamin B12 supplements, physical activity, as well as high serum folate level, while increased risk of dementia was reported in people with low body mass index, atrial fibrillation, high homocysteine or high serum copper levels[34]. Overall, the findings reported suggest that managing the components of the metabolic syndrome, dietary interventions and social interventions are effective in preventing dementia in people with MCI. However, once again, it should be noted that associations in naturalistic longitudinal studies do not imply causation, which should be confirmed by randomized controlled trials.

While the treatment and control of potentially modifiable risk factors is clearly relevant to the prevention of dementia in low- and middle-income countries[13], targeting the specific pathological pathways might be preferable in developed countries, where there is little room for the control of vascular risk factors and lifestyle modifications. In that line, promising results have been reported with monoclonal antibodies, targeting amyloid oligomers, as well as other treatments, showing a reduction in the slope of cognitive and functional decline in the 22%-60% range[35,36]. According to a constant cognitive model based on typical Alzheimer's disease[8], a treatment (or combination of treatments) with a 60% effect on the slope of deterioration, beginning five years before the theoretical onset of dementia, would delay the onset of dementia by 7.5 years and propitiate a virtual disappearance of the severe dementia stage (Figure1).

Figure 1. Dementia prevention model in different possible scenarios of disease-modifying treatments. MCI: mild cognitive impairment; MMSE: mini-mental state examination. Based on ref. 8.



6. Conclusions

Now that the coronavirus-2 severe acute respiratory syndrome (SARS-CoV-2) pandemic has hopefully been overcome, the population's survival expectations will rise again, and the prevalence of dementia will return to steady growth, as will the associated socioeconomic burden. In the developed countries, an adequate childhood environment, improved lifestyle and the treatment of vascular risk factors are already contributing to mildly reduce dementia incidence, but that will not be enough to significantly alleviate its tremendous burden, in a horizon of increasing population aging.

In recent decades, the expansion of our knowledge of the vascular and neurodegenerative mechanisms associated with cognitive deterioration has been remarkable, particularly regarding Alzheimer's disease. In most cases of neurodegenerative conditions - which constitute the vast majority of dementias - patient dependence is preceded by a long period of small but persistent failures in episodic memory, executive function or other cognitive areas, namely MCI. This period provides a unique therapeutic window to modify the underlying pathophysiological processes and avoid the development of dementia, or at least delay the state of total dependence to which those affected would otherwise be irremediably destined.

Using mathematical simulation models, it has been estimated that 14% of people aged above 60 years are in the early stages of Alzheimer's disease, 38% of whom will develop dementia, with an expected time to conversion to dementia of nine years[37]. These people may be quite accurately identified by means of clinical measurements in combination with biomarkers, which will be soon feasible and widely available for Alzheimer's disease and, in the future, for other dementias. MCI therefore provides a vast enriched human substrate and a critical time window to test the efficacy of pharmacological interventions, non-pharmacological trials and risk factor modification. At the same time, the putative biological and psychological mechanisms of disease should be tested and confirmed[38].

Even in combination with cognitive and functional measurements, biomarkers do not provide an absolute certainty of clinical evolution in patients with MCI[29,39]. For this reason, controlled trials will continue to be necessary to evaluate treatment effects. In the case of Alzheimer disease, the availability of medications that may modify the biological and clinical course of the disease seems close[35,36] and, hopefully, that will also be the case for Lewy body disease and other neurodegenerative conditions in the future. Proactive and collaborative attitude is necessary on the part of health professionals and society at large to identify the people affected, investigate the pathophysiological processes involved and work optimistically to find and provide remedies.

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CLINICAL ASSESSMENT OF MILD COGNITIVE IMPAIRMENT

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Introduction

Although recently published meta-analyses have estimated prevalence rates of Mild Cognitive Impairment (MCI) in individuals aged 60 and above in clinical or community settings, the precise prevalence of MCI is not known due to underdiagnosis or misdiagnosis, as reported in several publications[1,2,3].

The diagnosis of cognitive deficits in elderly patients in an efficient way is quite a challenging task. This is especially true, if cognitive changes are subtle and clinicians are confronted with restraints regarding the time they can invest in such processes.

The 5th edition of the Diagnostic and Statistical Manual of Mental Disorders [DSM-5; American Psychiatric Association (APA), 2013] introduced the new diagnostic term of "Mild NeuroCognitive Disorder" (NCD) to describe the syndromes of cognitive impairment irrespective of specific etiology[4]. Mild NCD is defined as:

A. Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual motor, or social cognition) based on:

A.1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and

A.2. A modest impairment in cognitive performance, preferably documented by standard neuropsychological testing or, it its absence, another quantified clinical assessment.

B. The cognitive deficits do not interfere with capacity for independence in everyday activities (i.e., complex instrumental activities of daily living such as paying bills or managing medication are preserved, but greater effort, compensatory strategies, or accommodation may be required)[5].

Furthermore, DSM-5 states: "Neuropsychological testing, with performance compared with norms appropriate to patient's age, educational attainment, and cultural background, is part of the standard evaluation of NCD and is particularly critical in the evaluation of mild NCD. (...) For mild NCD, performance typically lies in -1– -2 standard deviation range (between the 3rd and 16th percentiles)"[6].

This definition of mild NCD requires the consideration of two important aspects for the clinical assessment (Table 1). First, there needs to be a cognitive evaluation assessing the six cognitive domains outlined in DSM-5, and second, there must be some kind of evaluation regarding the impact of a cognitive impairment on the patient's everyday activities.

Clearly, DSM-5 prefers an in-depth neuropsychological assessment for the evaluation of cognition. Almost every specialized institution uses a set of neuropsychological tests – a battery – to assess at least five of the six domains, outlined in DSM-5. These kind of test batteries are probably not suited to be used by all clinicians. They require training in test administration, scoring and interpretation that can only be properly provided by specialists, e.g., neuropsychologists.

Table 1. The distinction between DSM-5 mild and major neurocognitive disorder.

	MILD NEUROCOGNITIVE DISORDER	MAJOR NEUROCOGNITIVE DISORDER
Cognition	-1 — -2 SD below appropriate norms in one or more of six cognitive domains	< -2 SD below norms below appropriate norms in one or more of six cognitive domains
Everyday activities	**Independent in everyday activities** (i.e., complex instrumental activities of daily living such as paying bills or managing medication are preserved, but greater effort, compensatory strategies, or accommodation may be required).	**Impairment in everyday activities** of sufficient severity, such that others will have to take over tasks that the individual was previously able to complete on his/her own.

Figure 1. A general procedure for the evaluation of MCI can follow the steps.

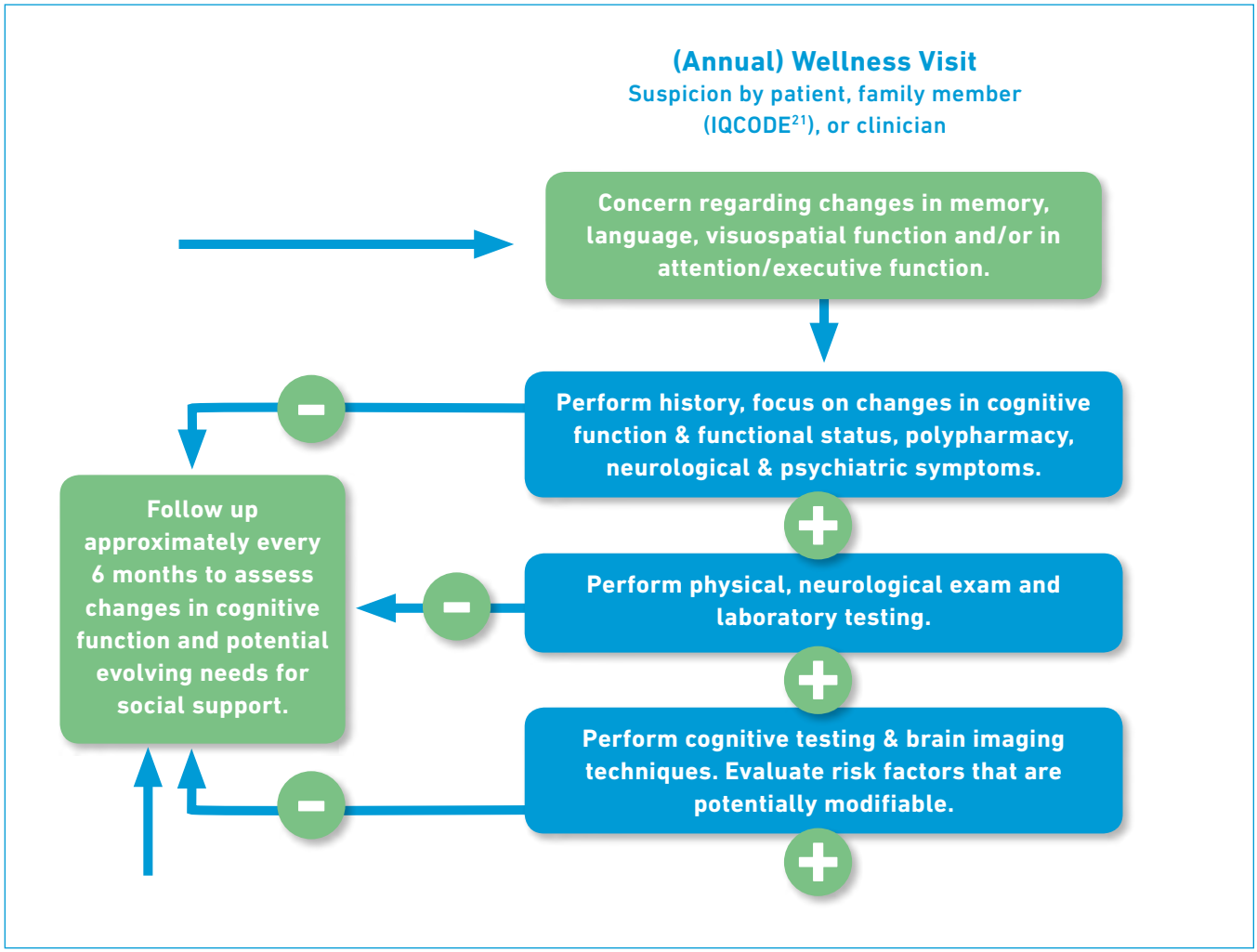


Figure 2 illustrates an efficient diagnostic process after the suspicion of cognitive impairment that has been extensively used in our Clinic and can be proposed elsewhere.

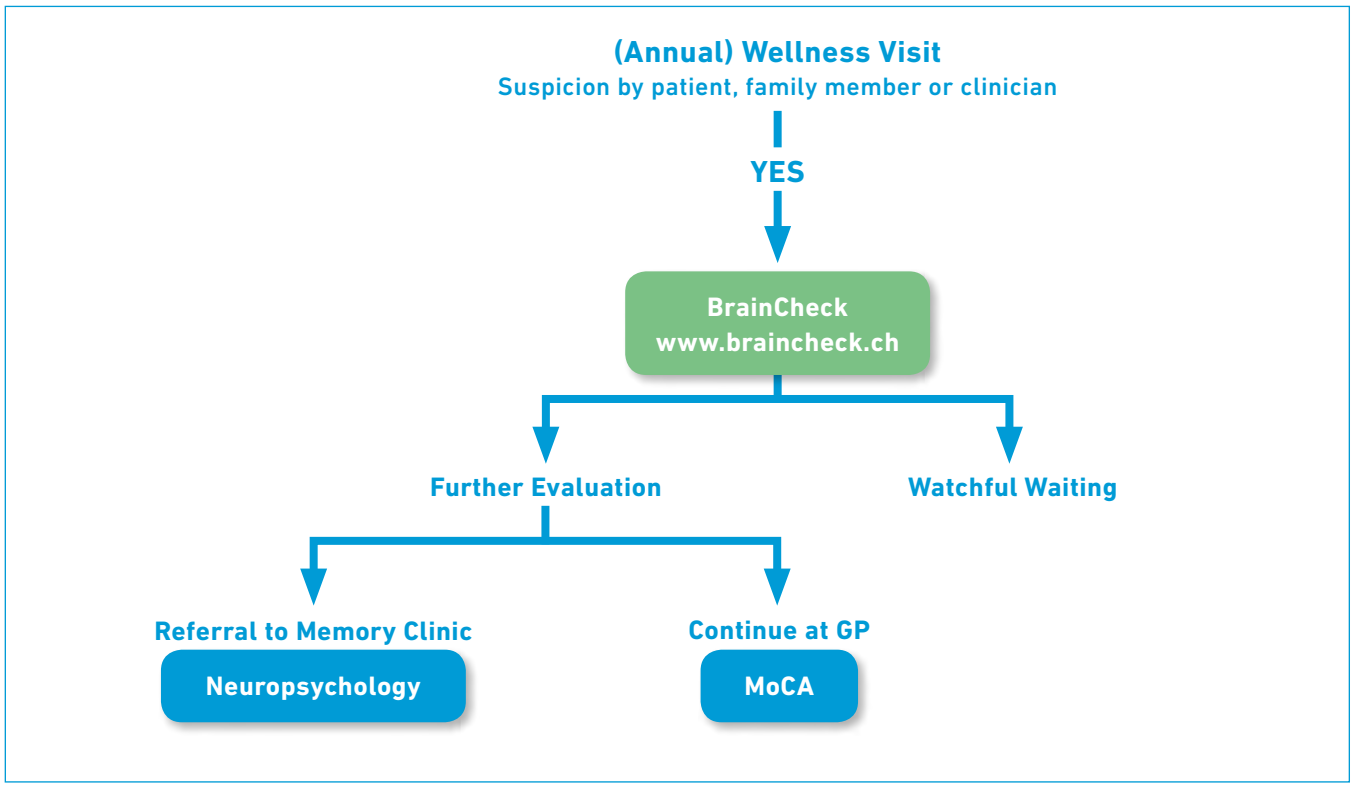
In general, patients should undergo:

A) Cognitive assessment,

B) Functional assessment or capacity for independence in everyday activities,

After that, it makes sense to identify which patient to consider for a more detailed diagnostic work-up in order to identify the possible cause of a neurodegenerative disorder. Laboratory testing can be performed, but biomarkers and neuroimaging is not usually recommended at this stage.

Figure 2. Illustration of the cognitive diagnostic algorithm.



A.- The cognitive assessment

As already stated above, non-specialists are confronted with time restraints. Tools for screening and assessment for MCI have not been specified and standardized in the diagnostic criteria for MCI, resulting in a diversity of instruments used in clinical and research settings[7] . Thus, the question arises which tool should be used if only about 15 minutes can be invested.

Scott and Mayo recommended the selection of screening tools to be based upon the clinical preference, the availability of an informant (yes/no), and the patient characteristics (e.g. the ability to write or draw); as no single screening tool is appropriate for all patients or clinicians[8]. The selection of screening tools can also depend on the healthcare setting.

Here we provide some screening and assessment tools validated and currently use in the clinical practice.

a) The Mini-Mental State Examination (MMSE)

In general clinical practice, the Mini-Mental State Examination (MMSE)[9] is widely used all over the world for assessing cognitive impairment as it requires only 10 to 15 minutes to administer and offers acceptable sensitivity and specificity to detect dementia[10]. However, its sensitivity to detect MCI is unacceptably low. Petersen[11] and Lin[12] suggested a cut-off score of 27 for MCI as it displayed the highest sensitivity (45%–60%) and specificity (65%–90%) on the scale. Galvin et al[13] suggested that the accuracy of MMSE could be age- and education-level dependent. Using a standard cut-

off for MCI (e.g. MMSE<23) could result in false positives in people with lower education level and/ or older age[14].

b) The Clock Drawing Test

Other screening tool such as the Clock drawing test[15] has also proven its utility. A combination of both the Mini-Mental State Examination and the Clock drawing tests proved to be an time-efficient screening procedure[16].

c) The Montreal Cognitive Assessment (MoCA)

In order to overcome the shortcomings of the MMSE and other tools, the Montreal Cognitive Assessment (MoCA) test was introduced[17] (www.mocatest.org) and may serve the purpose to identify cognitive impairment in a quite satisfactory way. It takes about 10 to 15 minutes and briefly assesses the following cognitive abilities: 'Visuo-spatial' / 'Executive' / 'Naming' / 'Memory' / 'Attention' / 'Language' / 'Delayed Recall' / and 'Orientation'. A critical point to consider when using the MoCA as a tool to identify cognitive impairment is the elimination of the influence of demographic factor, such as age, gender, and education. In a norming study[18] from Basel, Switzerland, 283 cognitively healthy individuals were administered the MoCA. 'Age', 'education', and 'gender' were taken into account, and demographically-adjusted MoCA standard scores created. On web pages like www.mocatest.ch clinicians can enter patients MoCA raw scores, their age, education, and gender and receive a demographically-adjusted MoCA standard score. Interestingly, the influence of these demographic factor is quite impressive. For example, let us assume, that two patients scored 26/30 points on the MoCA. Patient A is a man, 90 years old, with only 7 years of education. His MoCA standard score would be +1.4, whereas the MOCA standard score of patient B, a woman, 65 years of age, with 20 years of education would be -1.33. The MocA score of patient A is well within normal limits, whereas the MoCA standard score of patient B is clearly pathological. A MoCA standard score between -1 and -2 standard deviations would fulfill the DSM-5 criterion for mild NCD.

d) BrainCheck

A few years ago, our group developed a tool – the "BrainCheck"[19] – that allows clinicians to decide whether (a) a further evaluation is necessary or (b) watchful waiting is indicated. When the tool was created, general practitioners, who partook in the task force, insisted that the instrument should, due to time constraints, only require two (!) minutes to administer. Instead of trying to convince these practitioners, we were confronted with the tasks to recommend what they should or can do within two minutes.

First, we adopted the idea of a case-finding tool[20] which states, that not everybody – for example above a certain age – should be screened for a possible cognitive impairment. Rather, this should be done only if one or more of the following situations occur:

- The patient reports cognitive problems, and/or
- A family member or close friend raises concerns about cognitive worsening, and/or
- The clinician's "gut feeling" tells him or her that there might be something wrong

Second, it seemed important to include information from the patient and do some kind of formal cognitive assessment.

Third, it became clear, that information from a spouse or family member should complement the new instrument.

After a rigorous selection process of possible steps[19], the following solution emerged:

1. Three questions to the patients:
Q1: Have you experienced a recent decline in your ability to memorize new things?
Q2: Have any of your friends or relatives made remarks about your worsened memory?
Q3: Do your memory or concentration problems affect your everyday life?

2. The Clock Drawing Test (CDT), i.e., draw the face of a clock with all the numbers and hands. When done, please write down the time your clock face shows in numbers!
It turned out, that the scoring of the CDT should only focus on two criteria, i.e., "Are there two distinguishable hands?" and "Has the test, including writing down the time in numbers, been solved successfully?"

3. The very short version[21] of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)[22].

Especially the inclusion of information from a family member or friend made this tool unique and very valuable. In a study in Switzerland with 113 patients diagnosed with mild cognitive impairment (MCI) or with mild Alzheimer dementia and 70 cognitively healthy participants, the "BrainCheck" showed a correct classification rate of 89.9%[19]. The tool can be found, downloaded and used for free in English, French, German, Italian and Chinese on www.braincheck.ch. Readers are encouraged to visit and play on this website. Due to the hierarchical handling of the results, it is very possible, that the time required for the "BrainCheck" may be even less than two minutes depending on the patient's answers to the first three questions. Thus, in our opinion, it cannot get more efficient than this. By adopting the case-finding idea and using such an efficient new tool, we now have identified those patients that should undergo a diagnostic evaluation.

e) The Short- Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)

The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) in its short 16-item version, as a standalone test, is one of the most widely used methods and has been adopted by clinical researchers across different cultures and languages (https://rsph.anu.edu.au/research/tools-resources/informant-questionnaire-cognitive-decline-elderly).Find your IQCODE in your language).

It consists of a structured interview based on informant responses that is used to assess for possible cognitive decline in the elderly[23].

It is based on a structured interview, in which responses of informants (family or relatives of patients) who know the patients well are collected[1]. It is a reliable and validated informant-based instrument for assessing changes in everyday cognitive dysfunction, over a 10-year period.

f) Consortium to Establish a Registry for Alzheimer's Disease – Neuropsychological Assessment Battery (CERAD-NAB),

In the US and in German-speaking Europe, the Consortium to Establish a Registry for Alzheimer's Disease – Neuropsychological Assessment Battery (CERAD-NAB)[24], has established itself as the current standard for neuropsychological assessment in neurodegenerative disorders. The CERAD NAB consists of the following tests: 'Animal Fluency', 'Picture Naming', 'Mini-Mental Status', 'Word list – Learning', 'Figures – Copy', 'Word list – Recall', 'Word list – Recognition', 'Figures – Recall', 'S-words', and 'Trail Making Test (A and B)'. Figure 3 illustrates again the importance to use demographically-adjusted (gender, age, and education) standard scores. While the CERAD-NAB

Figure 3. Demographically-adjusted (gender, age, and education) standard scores.

Variable	Points	Maximun
Semantic Fluency (Animals)	17	n/a
Boston Naming Test	13	15
MMSE	27	30
Word list - Total	14	30
Word list - Trial 1	3	10
Word list - Trial 2	5	10
Word list - Trial 3	6	10
Word list - Delayed Recall	4	10
Word list - Intrusions	1	0
Word list - Savings, %	67	100
Recognition Discriminability, %	95	100
Figures - Copy	10	11
Figures - Delayed Recall	7	11
Figures - Savings, %	70	100
Phonemic Fluency (S - Words)	7	n/a
Trail Making Test, Part A (sec)	55	n/a
Trail Making Test, Part B (sec)	190	n/a
Trail Making Test, B/A	3.5	n/a

serves the purpose to assess – with the exception of social cognition – all DSM-5 cognitive domains, it is sometimes considered to be almost too easy for very highly educated individuals and patients in very early stages of a neurodegenerative process.

Let us assume that two patients have obtained exactly the same results on the CERAD-NAB. Patient 1 is a 88 years old man with 9 years of education. His demographically-corrected standard score all lie within normal limits, i.e., > 1 standard deviation below normal. Patient 2 is a 65 years old woman with 20 years of education. All of her demographically-adjusted standard scores are pathological.

A very interesting version of such a more demanding set of tests is the TOMMORROW Neuropsychological Assessment Battery (TOMM-NAB)[25]. The TOMM-NAB assesses five of the six domains in DSM-5 with at least two measures each. Moreover, it will most likely not suffer from ceiling effects (Table 2).

Table 2. Measurements of the TOMMORROW Neuropsychological Assessment Battery (TOMM-NAB)

COGNITIVE DOMAIN (DSM-5)	COGNITIVE TEST/SUBTEST
Memory	CVLT-II long-delay free recall[26] CVLT-II short-delay free recall[26] BVMT-R delayed recall[27]
Executive function	Trail Making Test B[28] Digit span backward[29]
Language	Semantic fluency (animals) [30] Lexical fluency (total words)[30] MiNT visual naming test[31]
Attention	Trail Making Test A[28] Digit span forward[29]
Visuospatial function	Clock-drawing test[32] BVMT-R copy accuracy[27]

A very recent and interesting project aimed at harmonizing neuropsychological tests for neurocognitive disorders[33]. Future directions of this bold initiative will consist of exploring hurdles and needs to implement this test battery in academic and non- academic memory clinics, creating and validating local versions for different languages, and creating tools to support adoption.

One of the DSM-5 domains, social cognition, is a quite new criterion and no consensus exists on how to assess it. Social cognition encompasses our ability to recognize emotions in faces and to be able to consider another person's mental state (thoughts, desires, intentions) or experience. In addition, socially acceptable behaviors as assessed with questionnaire may provide insights into possible problems with social cognition. The problem with this new cognitive domain is that it is culturally quite different. Thus, most likely, every culture will have to develop its own assessment tool.

B.-The assessment of capacity for independence in everyday activities

It is more complex to assess whether the cognitive deficits, i.e., standard scores between -1 and -2 in one or more of the 6 cognitive domains, also have a negative impact on the patient's daily life. Which parameters should be used to assess "independent living"? Naturally, it is more difficult to show the absence of an impact, than the presence of one.

In DSM-5, there is an implicit distinction between complex instrumental activities of daily living (complex IADL), which may be affected to some extent, and more basic activities of daily living (ADL), which should not be affected at all. IADL are activities that usually require to handle an instrument such as: 'using telephone', 'shopping', 'food preparation', 'housekeeping', 'doing laundry', 'using means of transportation', 'taking care of own's medication', 'handling finances'[34]. Basic ADL usually refer to activities that include 'bathing', dressing', going to toilet', 'moving around the house', continence', and 'feeding'[35].

Currently there is no tool available that would be able to help the clinician to accurately identify the specific aspects of independence in everyday activities in MCI individuals. The question to be asked to the patient and family member is:

Are there any activities in your daily life that you did earlier and would still like to do, but are no longer able to carry-out on your own?

A very good list of such possible activities – much more extensive than the list provided in DSM-5 – can be found in the Amsterdam-IADL-Questionnaire-Short Version (A-IADL-Q-SV)[36].

The A-IADL-Q (-SV) assesses impairments in a broad range of daily activities. Activities were chosen to be suitable for both men and women and for different age groups. More up-to-date activities related to everyday technology use were also included. The A-IADL-Q-SV can be obtained from the developers after registration and is free for use in all public health and non-profit agencies (https://www.alzheimercentrum.nl/professionals/amsterdam-iadl/). Using the A-IADL-Q-SC as a check list (see below) will enable clinicians to address a great variety of everyday activities, that might have become problematic (Table 3).

Table 3. The Amsterdam-IADL-Questionnaire-Short Version (A-IADL-Q-SV)

Carrying out household duties	**Obtaining money from a cash machine**
Doing the shopping	**Paying using cash**
Buying the correct articles	**Making appointments**
Cooking	**Filling in forms**
Preparing sandwich meals	**Working**
Making minor repairs to the house	**Using a computer**
Operating domestic appliances	**Emailing**
Operating the microwave oven	**Printing documents**
Operating the coffee maker	**Operating devices**
Operating the washing machine	**Operating the remote control**
Paying bills	**Playing card and board games**
Using a mobile phone	**Driving a car**
Managing the household budget	**Using a sat-nav system**
Using electronic banking	**Using public transport**
Using a pin code	**Being responsible for his/her own medication**

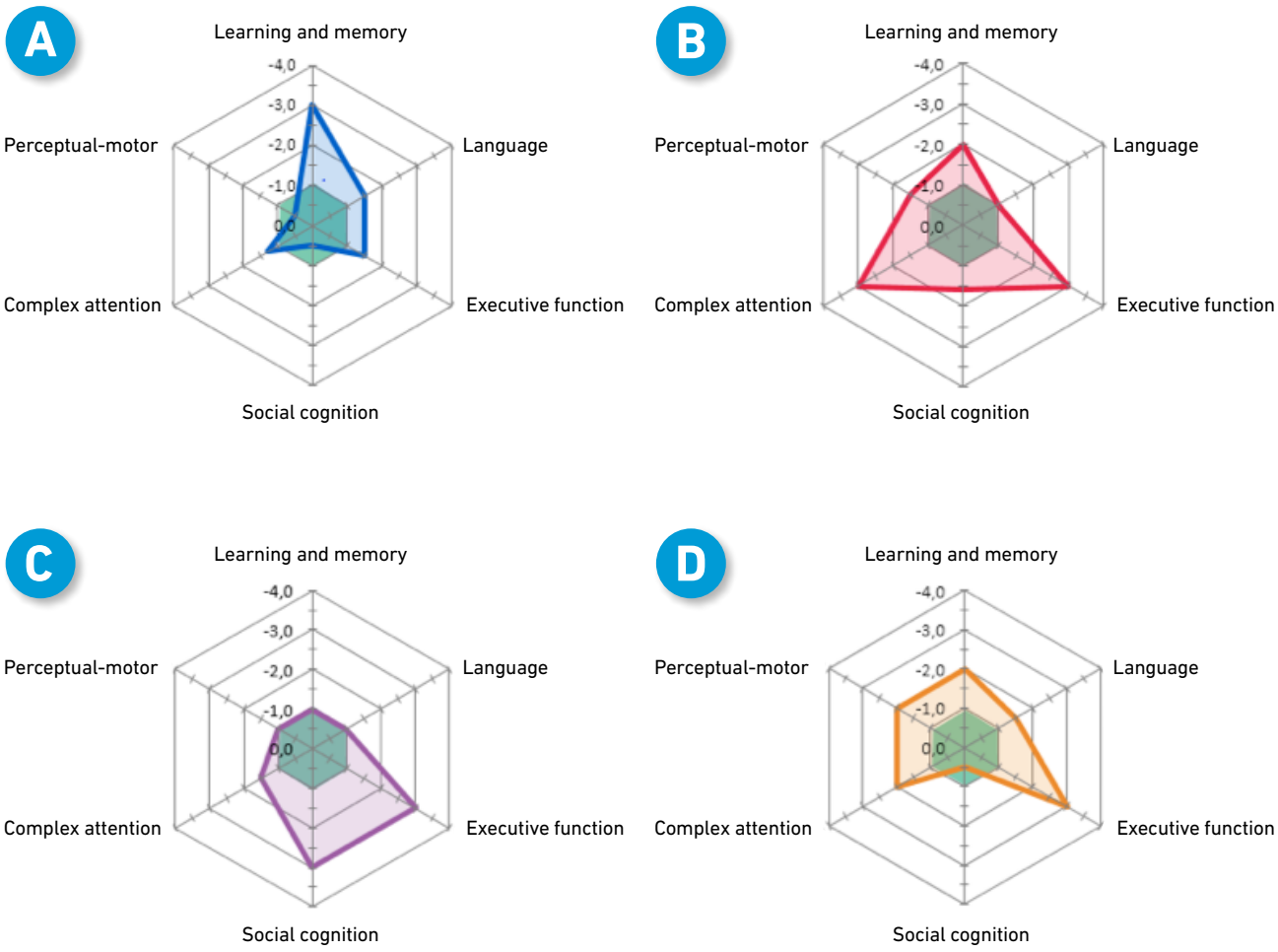
Identifying the possible causes of mild neurocognitive disorder

Once the presence of a neurocognitive disorder has been established the next step must be to find its most probable cause. Of course, this requires a comprehensive medical-neurological examination[37] and ancillary tests.

Also, the neuropsychological profile may contribute to find the most likely cause of a neurodegenerative disorder. Figure 4 illustrates four prototypical cognitive profiles, that may help clinicians in this endeavor.

Blood tests can help identify possible causes of MCI, some of them potentially reversible. It is well known that a deficiency of Vitamin B12, B6 and folic acid leads to increases in overall homocysteine concentration and is an independent predictor of the risk for cognitive decline and dementia[42]. Hyperhomocysteinaemia, deficiency of vitamin

Figure 4. Panel A shows the prototypical cognitive profile of mild Alzheimer's dementia[38], panel B shows the prototypical cognitive profile of mild dementia due to Huntington's disease[39]; panel C shows the prototypical cognitive profile of behavioral variant of mild frontotemporal dementia[40], and panel D shows the prototypical cognitive profile of mild Parkinson's disease dementia[41].



B12, B6 and B9 (folic acid) coud be assessed to identify potentially reversible forms of MCI, as well as a complete blood count, electrolytes, glucose, calcium, and thyroid function.

The recommendations from the National Institute on Aging-Alzheimer's Association (NIA-AA) on diagnostic guidelines do not recommend routine neuroimaging in the clinical assessment of mild cognitive impairment but propose to use them in research to determine the etiology and prognosis of MCI[43].

Conclusion

The assessment of MCI is based first of all on the suspicion of cognitive difficulties, expressed by the patient or his environment. The clinician must assess the person's cognitive functioning and also his or her functional status, with respect to activities of daily living. This can be done by using simple tests such as the MoCA test or the BrainCheck to assess cognition and the Lawton, Katz or Amsterdam-IADL-Questionnaire-Short Version tests to assess functionality. Once the existence of MCI has been established, an attempt should be made to determine its origin and begin intervention with the therapeutic means available.

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MILD BEHAVIORAL IMPAIRMENT. A NEW CONCEPT FOR PRE-DEMENTIA STATES

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Introduction

The neuropsychiatric symptoms (NPS) of dementia were described by Alois Alzheimer already in the initial report of the disease that now bears his name[1]. They affect practically all patients with dementia at one point or another in their evolution. Thus, 75% of the patients with dementia in the Cardiovascular Health Study had NPS during the month prior to the evaluation[2] and in the Cache County Study 97% of the patients presented NPS during a 5-year follow-up[3]. These symptoms are associated with a worse disease prognosis[4] and earlier death[5]. In addition, more NPS are found in cognitive impairment prior to dementia than in the cognitively healthy population, but less than in established dementia[6], reaching even 60% of patients with mild cognitive impairment (MCI)[7].

The "cognitive paradigm" prevailing for decades has given a testimonial value to NPS, as phenomena without influence on the development or progression of dementias. In fact, they were traditionally excluded as a relevant part of the diagnosis of dementia until the NIA-AA criteria included them within the core criteria for the diagnosis of dementia from any cause[8]. Subsequently, the 2014 IGW-2 criteria also echoed this change in the conception of the disease[9].

NPS are very different from each other and can be caused by different brain disturbances. Among others, they have been associated with psychological reactions to the neurodegenerative process[10], trauma[11], vascular lesions[12], pharmacological effects[13], genetic origin[14], presence of neurofibrillary tangles[15], pyramidal cell decrease[16], dysfunction in striatal dopamine metabolism[17], neuroinflammatory mechanisms[18] or hypometabolism in specific cortical regions[19].

The need for an early diagnosis has recently generated considerable interest in the pre-dementia or prodromal stages of the different diseases that cause dementia. Thus, the concept of MCI, a transitional state between normality and dementia[20] was developed and its clinical characterization progressively improved[8].

Until recently, it had not been possible to agree on criteria regarding NPS as symptoms prior to dementia. Furthermore, it is common for patients with NPS during non-demential stages to receive psychiatric diagnoses and not one of a neurodegenerative process. This confusion is especially common in the behavioral variant of Frontotemporal Dementia (with figures close to 50% according to Woley et al.[10]).

This chapter aims to show the significance of neuropsychiatric symptoms in phases of neurodegenerative processes previous to dementia as a new avenue for early detection and treatment.

Neuropsychiatric symptoms (NPS) as early manifestations of dementia

There is evidence and increasing consensus that NPS can be early manifestations of dementia in subjects with mild cognitive impairment or even in cognitively asymptomatic subjects, as evidenced by the original article by Taragano[21]. Studies in the general population[22,23] and in clinical cohorts support the idea that NPS in MCI increase the risk of incident dementia with an annual progression rate of 25% in MCI with NPS[24] versus an annual conversion rate of 10-15%[25]. Likewise, the presence of NPS in cognitively normal aged people also increases the progression to dementia as indicated by different studies such as the Alzheimer's

Disease Cooperative Study[26], Alzheimer's Disease Research Center[27], the Danish Psychiatric and Medical Registry[28], the Mayo Clinic Study of Aging[29], the Medical Research Council Cognitive Function and Aging Study[30], and the National Alzheimer's Coordinating Center[31,32]. All this should mean that, despite the absence of cognitive symptoms, the appearance of NPS in the elderly population makes it necessary to periodically assess the subsequent appearance of a neurodegenerative disease.

Table 1.- Prevalence rate of each neuropsychiatric symptom in MCI and its association with disease progression

Symptom	Prevalence of NPS in MCI			Association with MCI progression
	study setting	prevalence rate,%	NPS measure	
Depression	clinic-based populaton-based	83 20.1	NPI NPI	Evidence is conflicting
Apathy	clinic-based populaton-based	39.5 14.7	NPI NPI	Associated with a 7-fold risk of MCI progression
Anxiety	clinic-based populaton-based	26.3 11.6	NPI DSM	Associated with greater and faster cognitive deterioration in MCI
Irritability	clinic-based populaton-based	44.7 12.9	NPI NPI	Increases the risk of MCI progression
Sleep problems	clinic-based populaton-based	48 13.8	CERAD-BRSD, HDRS NPI	Association between sleep disturbances and MCI progression is conflicting
Agitation	clinic-based populaton-based	38 11.3	CERAD-BRSD, HDRS NPI	Increases the risk of progression
Aberrant motor behaviour	clinic-based populaton-based	5.3 3.7	NPI NPI	Results are conflicting
Appetite/Eating disorders	clinic-based populaton-based	5.3 7.4	NPI NPI	n.s.
Disinhibition	clinic-based populaton-based	2.6 1.9	NPI NPI	n.s.
Euphoria	clinic-based populaton-based	0 1.3	NPI NPI	n.s.
Hallucinations	clinic-based populaton-based	2.6 1.3	NPI NPI	Significantly increases the risk of MCI progression
Delusions	clinic-based populaton-based	10.5 3.1	NPI NPI	Significantly increases the risk of MCI progression

NPI, Neuropsychiatric Inventory; MCI, mild cognitive impairment; CERAD-BRSD, Consortium to Establish a Registry for Alzheimer's Disease Behaviour Rating Scale for Dementia; DSM, Diagnostic and Statistical Manual of Mental Disorders; HDRS, Hamilton Depression Rating Scale; n.s., not significant.

Source: E. Martin et al. 2020[53]

Origin and development of the concept of Mild Behavioral Impairment (MBI)

The growing evidence of the presence of NPS in patients with mild cognitive impairment and even in cognitively healthy people, as well as the verification of an increased risk of dementia in this population with NPS, have demonstrated the need for a better categorization of these symptoms.

The idea that there are NPS that can precede dementia was pointed out by Taragano in 2003. This author defined the concept of Mild Behavioral Impairment (MBI) as cases with recent-onset behavioral disturbances associated with mild cognitive impairment. The first criteria posed MBI as a transitional state between normality and frontotemporal dementia characterized by persistent behavioral changes and mild psychiatric symptoms, especially disinhibition, without significant memory complaints, in the absence of problems in activities of daily living and without dementia[21]. Using these criteria, conversion to dementia was twice as high in patients with MBI as with MCI[33].

Since then, several authors have tried to link the appearance of neuropsychiatric symptoms with an increased risk of developing dementia: In the 2003 study by Copeland, changes in personality (passivity and agitation) were longitudinally associated with accelerated functional deterioration in patients with cognitive changes but without a diagnosis of dementia[34]. Gallagher et al[35] found a high prevalence of neuropsychiatric symptoms in patients with mild cognitive impairment. The presence of anticipatory anxiety and purposeless activity were associated with poorer baseline cognitive status and increased risk of conversion to Alzheimer's. Sacuiu et al. found a higher risk of progression to Alzheimer's in those patients with MCI and chronic depressive symptoms associated with the degree of frontal atrophy[36]. Fujishiro et al published in 2015 a rare case of Alzheimer's disease that debuted 8 years before the diagnosis of degenerative disease as a delusional disorder. The patient responded clinically to treatment with acetylcholinesterase inhibitors and the diagnosis and relative preservation of the hippocampus was confirmed by autopsy[37].

A Spanish study[38] proposed other criteria for mild behavioral disorder consisting of:

1) Any persistent and recent-onset behavior disorder (or manifest exacerbation of a previous socially acceptable behavior): alterations in motivation (apathy), impulsivity, maniform behavior, agitation-aggressiveness, irritability or thought disorders in the form of delusions
2) Exclusion of affective disorders such as depression or anxiety
3) Cognitive impairment in one or more cognitive areas assessed by an objective test
4) Independence for the instrumental activities of daily life (although there may be certain difficulties in social relationships)
5) Must not meet DSM or ICD criteria for dementia. The exclusion of depression and anxiety is due to the fact that their high prevalence reduces specificity. The application of these criteria in 201 patients with MCI showed a high risk of conversion to dementia of any origin (OR = 5.5).

As can be seen, the concept of MBI has matured from a first conceptualization referring to the early manifestations of frontotemporal dementia towards the idea that these symptoms can present as early manifestations of any type of dementia.

The International Society to Advance Alzheimer`s Research and Treatment (ISTAART), has recognized the presence of NPS with onset in adults and elderly people as a state "at risk of cognitive impairment and dementia". An international working group was created that has agreed on diagnostic criteria for mild behavioral impairment (MBI)[39], as a step forward to previously defined criteria Taragano[21] and de Mendonça[40]. Based in different findings, five MBI domains are proposed:

- Decreased interest, drive and motivation (apathy),
- Affective-emotional dysregulation (mood and anxiety symptoms),
- Impulse dyscontrol (agitation, aggression, and abnormal reward salience),
- Social inappropriateness (impaired social cognition)
- Abnormal thoughts and perception (psychotic symptoms i.e. delusions and hallucinations).

These criteria are based on the assumption that neurodegeneration can manifest itself in the form of personality changes, behavioral problems, or psychiatric symptoms. The criteria require the presence of a functional alteration, even if it is minimal, attributable to the NPS and not to cog-

nitive decline. The presence of MCI is not required to establish the diagnosis of MBI and thus MBI can be diagnosed in people with MCI or with normal cognition. Table 2 shows the MBI ISTAART criteria

Table 2.- ISTAART Diagnostic criteria for Mild Behavioral Impairment (MBI)

1.- Changes in behavior or personality observed by patient, informant, or clinician, starting later in life (age ≥50 years) and persisting at least intermittently for ≥6 months. These represent clear change from the person's usual behavior or personality as evidenced by at least one of the following:
A. Decreased motivation (e.g., apathy, aspontaneity, indifference) **B.** Affective dysregulation (e.g., anxiety, dysphoria, changeability, euphoria, irritability) **C.** Impulse dyscontrol (e.g., agitation, disinhibition, gambling, obsessiveness, behavioral perseveration, stimulus bind) **D.** Social inappropriateness (e.g., lack of empathy, loss of insight, loss of social graces or tact, rigidity, exaggeration of previous personality traits) **E.** Abnormal perception or thought content (e.g., delusions, hallucinations)
2.- Behaviors are of sufficient severity to produce at least minimal impairment in at least one of the following areas:
A. Interpersonal relationships **B.** Other aspects of social functioning **C.** Ability to perform in the workplace The patient should generally maintain his/her independence of function in daily life, with minimal aids or assistance.
3.- Although comorbid conditions may be present, the behavioral or personality changes are not attributable to another current psychiatric disorder (e.g., generalized anxiety disorder, major depression, manic or psychotic disorders), traumatic or general medical causes, or the physiological effects of a substance or medication.
4.- The patient does not meet criteria for a dementia syndrome (e.g., Alzheimer's disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia, other dementia). MCI can be concurrently diagnosed with MBI.

Using these criteria, the prevalence of MBI was 43.1% in subjective cognitive decline (SCD) and 48.9% in MCI in a community population-based study[41]. In a memory clinic population, the prevalence was 76.5% in people with SCD and 85.3% in MCI[42]. In a primary care population, the prevalence of MBI was determined to be 5.8% in SCD[43] and 14.2% in MCI[44].

The neuropsychiatric symptoms measurement scales

The evaluation of NPS in dementias has usually been carried out using instruments specifically designed for this disease, which assess the symptoms individually or as a whole, as is the case of the Neuropsychiatric Inventory (NPI)[45], which is the most frequently used. In the absence of specific scales for people without dementia, the use of instruments validated in dementia to explore NPS in healthy people or with MCI is very common[46]. This implies, in our opinion, an important methodological error, since these scales do not adequately capture the NPS suffered by cognitively normal subjects or with MCI, which are of a different nature or more subtle and, on the contrary, the symptoms that they do explore (e.g. agitation, delusions, hallucinations, etc.) rarely appear or do so with much less intensity in the non-demented population.

The Mild Behavioral Impairment Checklist (MBI-C)

Following the publication of the MBI ISTAART criteria, a panel of experts from different countries developed the Mild Behavioral Impairment Checklist (MBI-C)[47]. Its objective was to operationalize the concept of MBI, allowing the measurement of symptoms that help to identify prodromal or preclinical forms of dementia and the prediction of the risk of dementia when NPS appear.

The MBI-C is designed to be used in adult or elderly population with or without cognitive disturbances with possible mental symptoms that could precede the onset of dementia. Its main objective is to detect patients who would fall into the category of "risk of dementia" or "predementia". It is designed to be used in both clinical and research contexts. It is based mainly on the information provided by an

informant or family member close to the patient. Its administration does not need a specific training.

The scale comprises 34 items. To facilitate completion, the items are firstly dichotomous, that is, the symptom is present or not. If the symptom is present, it is scored according to severity (mild, moderate, severe). Care has been taken about the wording of the items in order to simplify their content and favor their intelligibility, providing examples that facilitate the understanding of the statements also by caregivers and informants of the person under study.

The MBI-C makes it possible to note whether the answers given have been assessed by the patient, an informant or the clinician (the three spheres from which behavioral disorders can be defined), although it should be noted that due to the nature of the items, the instrument is mainly aimed at collecting information from an external informant or caregiver. In fact, the results that it offers are different when used as self-reported or informant-reported with only weak correlations between both forms of administration as reported by Crease et al.[48]. This study included a total of dyads of 5,742 of patients and informants and reported a lower prevalence of MBI if the MBI-C was self-administered. The most common MBI-C items were those related to the affective domains (mood/anxiety symptoms), being present in 34% and 38% of the sample, respectively and the least common were those related to abnormal thoughts and perception (psychotic symptoms) that were present in 3% and 6% of the sample.

The MBI-C has demonstrated internal consistency, test-retest reliability and discriminative validity from the NPI[44,49]. Cutpoints have been stablished at 8,5 for SCD and 6,5 for MCI demonstrating acceptable sensitivity and specificity for clinically diagnosed MBI with the ISTAART criteria[43]. The 8.5 cut point is also associated with subtle cognitive decline in healthy older adults[50].

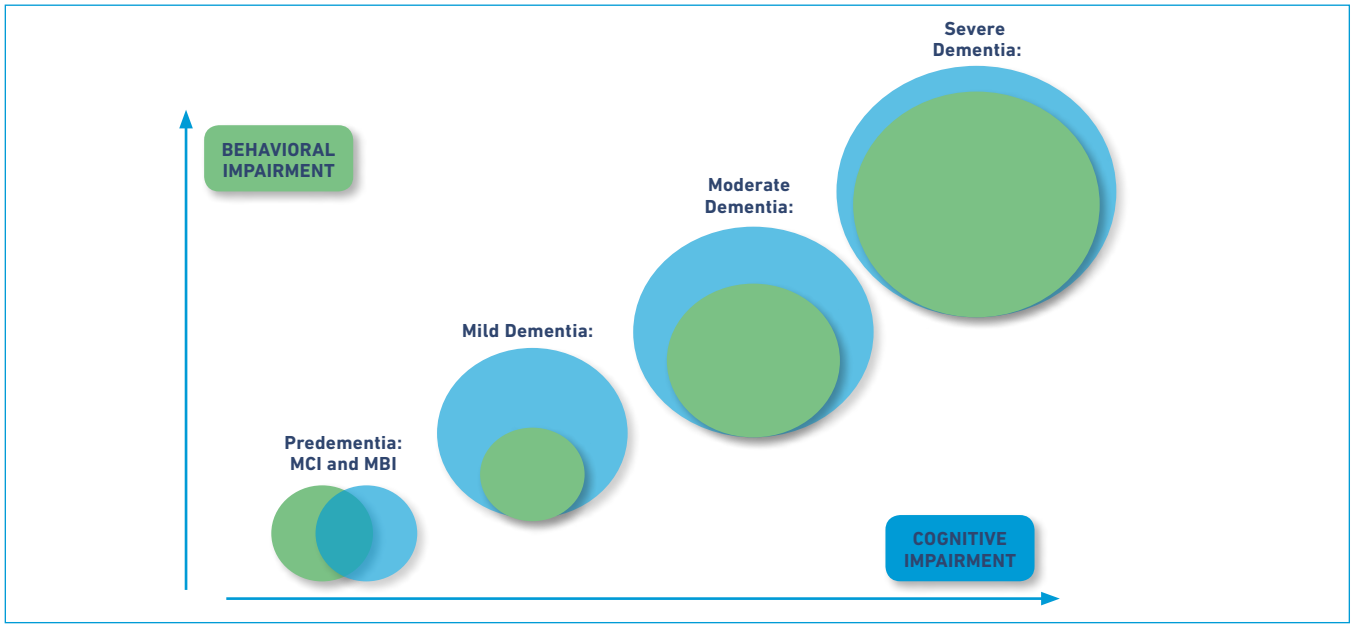
Some neuroimaging and biomarker studies have confirmed the validity of the MBI-C. The scale ratings were associated with worsening cognition and temporal lobe atrophy in Parkinson's disease patients[51]. Furthermore, a study with ß-amyloid PET in people with normal cognition supported the utility of the MBI-C in case finding for early stage neurodegenerative disease before the appearance of manifest cognitive impairment[52].

The scale has already been translated into several languages. Extensive information about it and its different versions can be obtained on the Web site: www.mbitest.org

Relevance of the Mild Behavioral Impairment concept

The ISTAART criteria attempt to encompass in a single concept, mild behavioral impairment, the NPS that may

Figure 1.- Cognitive and Behavioral symptoms in pre-dementia and dementia stages



be markers of a neurodegenerative process. The presence of isolated NPS and previous attempts at conceptualization have shown their relationship with the subsequent development of dementia, with even higher links than those found for other risk factors for dementia such as MCI.

Despite the attempt to differentiate late-onset psychiatric disorders by establishing specific criteria that exclude primary psychiatric disorders, possibly some subsyndromic psychiatric disorders may continue to meet MBI criteria, as the specificity of the ISTAART criteria to be able to differentiate them is not yet known.

The MBI-C scale has been developed with the aim of improving the description and measurement of the mental symptoms included in the MBI paradigm. The goal of the MBI-C scale is the detection of cases, considering its use in both clinical and research settings, in order to detect NPS and monitor their changes over time.

As a consequence, with the spread of the concept of MBI and the tool developed for its assessment, it will be possible to detect a higher number of incipient cases or patients at risk of developing dementia than with the previous methods, based only on cognitive deficits. These cases could be treated earlier and also participate in future research studies.

The MBI-C scale can serve a variety of functions. The standardization of some operational criteria and a tool based on them favors the estimation of prevalence, avoiding the disparity of MBI figures based on the various criteria used. The prevalences obtained in the studies carried out to date cannot be extrapolated to the ISTAART criteria, since the duration of symptoms according to these criteria is at least 6 months, compared to instruments such as the NPI that only provide information on symptoms in the last month.

In addition, the MBI ISTAART criteria and the MBI-C scale can be used to predict cognitive decline and dementia, as well as to identify symptoms and domains that may be the focus of pharmacological and non-pharmacological interventions. They may also be useful in neuroimaging and biomarker studies, to assess whether there are differentiated or overlapping neurobiological mechanisms between the different domains explored in mild behavioral impairment and between these and cognitive and functional impairment.

Future perspectives

The concept of MBI, its operationalization using the ISTAART criteria and the MBI-C scale represent a new approach to clinical and research in the pre-dementia phases.

There is a whole set of questions regarding NPS that precede dementia that could be answered by applying the MBI ISTAART criteria and using the MBI-C scale. In the first place, the real prevalence of MBI can be better specified. Advances can be made in order to elucidate whether NPS are risk factors or just markers of cognitive decline. Given their different nature, it could happen that some NPS were risk factors and others were not. Furthermore, it would be of great interest to examine whether behavioral disturbances in different areas predict different neurodegenerative conditions such as Alzheimer's disease, frontotemporal dementia or Lewy body dementia.

Another question that could be answered is, if it is demonstrated that a certain symptom is a risk factor for dementia or for its rapid progression, whether its pharmacological or non-pharmacological treatment can reduce or slow down the conversion to dementia. It is also interesting to assess the predictive capacity of the MBI and its different dimensions, as well as the comparison in terms of sensitivity and specificity with other more restrictive criteria. Yet another question is whether there may be patients with MBI who do not progress to dementia or are even cured with treatment, as is the case with patients with MCI, where some individuals remain stable without evolving to dementia and others improve. Furthermore, which dimensions of the MBI construct are most related to neurodegenerative processes and which may be ill-defined forms of primary psychiatric disorders of advanced age.

Conclusions

Neuropsychiatric symptoms are common in patients with mild cognitive impairment and in healthy people at risk for dementia. These symptoms can be confused with the primary psychiatric disorders of advanced age, their distinction being important since NPS would be related to an increased risk of dementia. The proper categorization of these NPS can allow detecting people at risk of dementia in

early stages, facilitating early treatments. Until now, there were no well-defined criteria about NPS in the early stages of neurodegenerative processes that lead to dementia. The existence of the ISTAART criteria will allow clinicians and researchers to improve the detection of cases and to categorize them appropriately.

The MBI-C is a scale developed by a panel of dementia experts based on the new MBI ISTAART criteria. Its potential utility is the description and measurement of changes, in the global score and in the different subscales, of the main NPS that can precede dementia.

This is a call to action to incorporate the detection of MBI into daily clinical practice by using the MBI-C scale and the MBI diagnostic criteria. The early detection of a greater number of cases of people at risk of developing dementia will allow the implementation of preventive and therapeutic activities with the currently available agents and others that will come in the near future.

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NON-PHARMACOLOGICAL INTERVENTIONS FOR MILD COGNITIVE IMPAIRMENT

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Non-pharmacological interventions have been a subject of great interest for many decades among the healthcare professionals involved in the treatment of Alzheimer's disease and related disorders. Clinical research intended to demonstrate the effectiveness of this type of interventions has gradually been conducted, the objective obviously being to provide scientific evidence to validate their use in daily practice. Before this review is initiated, an attempt should be made to define the so-called non-pharmacological interventions.

Definition of Non-pharmacological Interventions

A non-pharmacological intervention could be defined as a **science-based, non-invasive, non-pharmacological human health intervention intended to prevent, treat or cure a health problem**. It takes the form of a product, method, programme or service whose content must be known by the user[1]. The implementation of non-pharmacological interventions requires relational, communicational and ethical skills.

Ideally, the effects of non-pharmacological interventions must be explained by biological, cognitive, behavioural and social processes and are addressed by efficacy studies.

This last point is important, because it means that the effectiveness of non-pharmacological interventions is not taken for granted, even if they have been known and used for many years. The conduct of a clinical study for a non-pharmacological intervention will therefore call for the same scientifically sound methods as for pharmacological interventions. The greatest possible rigour must be exercised, although this generates constraints and difficulties, because non-pharmacological interventions are very heterogeneous and do not yet meet the characteristics expected of drugs trials. In the field of health in general, the description of non-pharmacological intervention is insufficient[2]. For dementias, Alzheimer's disease and related disorders, the proliferation of studies has prompted reviews that evaluate the efficacy and safety of non-pharmacological interventions[3]. (cf. in particular Cochrane: https://dementia.cochrane.org/non-pharmacological-interventions)

Only in a second phase did article reviews focus on the use of these interventions in mild cognitive impairment (MCI). Most of these systematic reviews have identified possible benefits of non-pharmacological interventions, although the conclusions are often quite similar:

«More controlled studies are needed to establish a protocol of recommendations regarding the systemization of exercise, necessary to produce benefits in the cognitive functioning in older people with MCI »[4].

«Both cognition-based intervention and physical exercise had the potential to improve global cognitive function. Nevertheless, future standard randomized clinical trials are still needed to identify the clinical value»[5].

«Cognitive training focused on compensation interventions and selected psychotherapeutic interventions may influence how cognitive changes impact daily living. However, confidence in these findings is limited due to methodological limitations.»[6].

«Non-pharmacological therapy could have an indicative role in reducing the case of MCI or dementia. However, given the heterogeneity of the included randomized clinical trials, more preregistered trials are needed that explicitly examine the association between non-pharmacological therapy and cognitive decline prevention, and consider relevant moderators.»[7].

One of the most recent reviews[8] emphasised that meta-analyses are difficult to conduct due to the variation in outcome measures used by the studies. In this context, the article set out to map trends in which outcome measures are used in non-pharmacological treatment trials in MCI and mild dementia. Ninety-one (91) studies were included in the review.

In 2008, a European-wide consortium of dementia researchers[9] recommended 22 measures straddling 8 domains including:

- Quality of life
- Mood
- Global functioning
- Behaviour
- Daily living skills
- Caregiver mood
- Caregiver burden
- Staff morale

The scoping review by Couch et al. found that 11 of these 22 measures were used by the studies included in the review. The interventions were grouped thematically by type. The most frequently tested type of intervention was cognitive training (n=37) followed by physical activity (n=25), combined physical activity and cognitive training (n=4), multicomponent psychosocial interventions (n=4) and support groups (n=3).

The following were tested in two studies:

- Animal-assisted therapies,
- Art-based therapies,
- Case management,
- Chinese calligraphy,
- Music based interventions
- Reminiscence therapy

Cognition/memory was measured in all the types of intervention, and unsurprisingly, cognitive measures were the most frequently used, the most popular being the Mini-Mental State Examination.

The next most frequently measured domain were neuropsychiatric symptoms, with depression being the most commonly measured. The Geriatric Depression Scale was the most used instrument in this domain, followed by the Neuropsychiatric Inventory, which examines a greater number of symptoms. Other neuropsychiatric symptoms measured were apathy and agitation resulting from memory problems. Quality of life and well-being were measured 15 times in all the studies included.

The third most common domain for MCI studies was physical performance, whereas caregiver measures were the third most common type of measures used in early dementia studies.

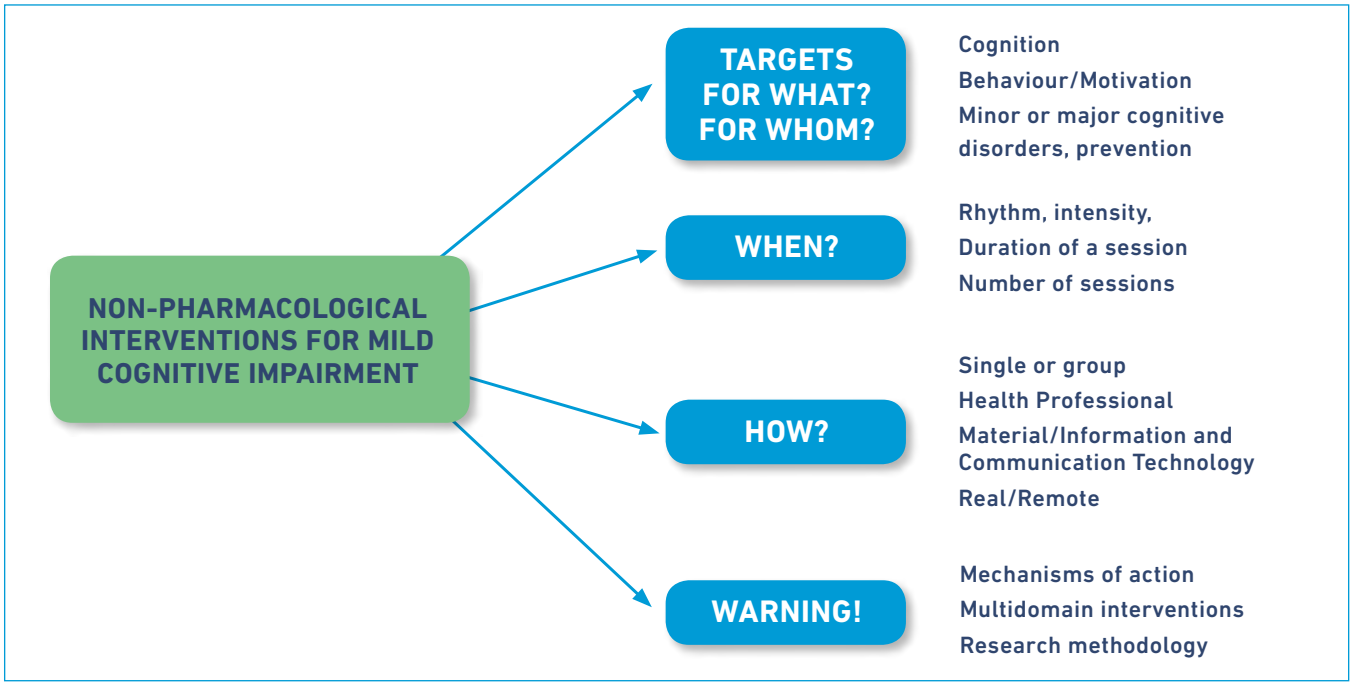
By way of conclusion, the authors indicated that there is very little consistency in the outcome measures used in randomized clinical trials for non-pharmacological interventions in MCI and mild dementia. Interestingly, they add this comment: *«the prevalence of cognitive measures found in this study suggests that researchers are including such measures because there is an expectation to do so. Researchers should be clear on the theory behind how their intervention creates change and use the appropriate outcome measures».*

The effectiveness of non-pharmacological interventions **cannot be ascertained** because the validation methods are unsuitable/have not been adapted, and, in addition, cognition is not necessarily the right target. This must be taken into account now, when the advent of new technologies will be likely to lead to even more heterogeneous non-pharmacological interventions than in recent decades.

Outlook/characteristics of non-pharmacological interventions

To clarify the therapeutic use of non-pharmacological interventions, the characteristics listed in Figure 1 should be considered.

Figure 1. - The therapeutic use of non-pharmacological interventions.



The first key factor in a successful intervention is to choose an appropriate clinical target, and cognition is not the only possible one. One of the most popular ways to perform non-pharmacological interventions is by using a workshop, defined as an activity allowing several individuals to work together and share an activity, a theme. In the field of mental health, workshops have been used for a long time at treatment level (occupational therapy, reminiscence), albeit also for prevention (memory workshop)

As part of the ongoing AGAP (Art and GAme Project http://www.innovation-alzheimer.fr/agap/) a survey carried out in a group of experts indicates that, with regard to the overall objectives of workshops, the stimulation of emotion and the stimulation of motivation in goal-directed behaviours and cognitive activity are considered to be equally important targets. This is important, because mild behavioural symptoms, and more particularly affective dysregulation and decreased motivation, are frequent in MCI[10,11]. In fact, participant motivation is a core element in the establishment and success of a non-pharmacological intervention. The results of a study testing the efficacy of a web application for cognitive training[12] in people with neurocognitive disorders indicated improvements in attention and motivation only for patients who used the application regularly.

Serious ExerGames (SeG) promote cognitive simulation with physical activity in a positive emotional context. The results of the first pilot usability study with XTorp – a serious exergame stimulating physical and cognitive activity in a positive emotional context[13] –suggest that this SeG represents a usable and enriched environment for healthy subjects and people with MCI and Alzheimer´s Disease.

In a multicentre study[14], the use of a therapeutic video game with motion capture improved neuropsychiatric symptoms, and more particularly apathy. Similarly, the use of board games in family or with professional caregivers can further emotional stimulation and promote social interactions https://www.game-in-lab.org/projets/projet-cab/

The choice of target is evidently important irrespective of whether the non- pharmacological intervention is intended for people with minor or major cognitive disorders.

This is also true in preventive interventions.

The second key factor for success is to determine the characteristics of the intervention (the 'dosage') in advance, in terms of:

- The intensity and proportion of the different activities offered during a session. This includes controlling the amount of time dedicated to social interaction - present in most of the non-pharmacological interventions - and the time dedicated to activities corresponding to multiple domains, such as physical and cognitive stimulation.
- The duration of a session
- The number of sessions per week
- The total number of sessions and total intervention duration are some of the key characteristics for an effective intervention.

The third key factor concerns human interactions and technical/technological aspects. Depending on the objectives and the type of intervention, the first decision to be made is evidently whether the sessions should be individual One patient and one clinician or whether it is more appro-

Table 1: Summary of a Strengths, Weakness, Opportunities, Threats (SWOT) Analysis of Using ICT for MCI non-pharmacological intervention[15]

STRENGTHS	WEAKNESS
• Can facilitate reproducibility and standardisation (contents and automatic follow-up) • Increased ecological validity, can place a patient in a 'reality-like', albeit more controlled setting • Possibility of recording patient activity and treatment adherence automatically, longitudinally and remotely, online or offline; • Possibility of recording and analysing several "indirect" data items (voice, movements, etc.) • Adaptation to the user (e.g., impairment type and level, personal interest) • Increased variety of activities, and easy content adaptation (themes, ergonomics) to increase engagement • Can stimulate attention and other cognitive processes in a controlled environment • Can increase motivation, curiosity, immersion and positive emotions • Useful for long training sessions, making it possible to extend patient activity at home • Cost-effectiveness (e.g., tablets, actigraphy) • Permanent presence of a therapist not required • Can be used for group stimulations	• Time-consuming setup (for some devices) • Poor understanding (and fear of not understanding) of the technology • Need for patient and staff training • Expensive equipment (e.g., VR headsets) • Absence of human contact (risk of reducing the opportunities of social interaction) • Possibility of poor engagement/interest • Games potentially not appropriate for participant's cognitive profile and culture • Lack of generalisation to patient's environment (activities far removed from reality) • Side effects such as hallucinations, loss of sense of reality (e.g., for Virtual Reality) • Risk of accidents (e.g., risk of falls, increased sleep disturbances) • Risk of addiction • Low standardisation
OPPORTUNITIES	**THREATS**
• Emerging advances in technology • Good accessibility for users, also remotely (at home or in remote clinical facilities) • Increasing number of seniors commonly using ICT • Could help to reduce barriers in access to care in middle- and low-income countries with limited access to neuropsychiatric centres • Usable on a large scale • Can be used trans-diagnostically • Can facilitate training sessions for therapists	• Long and expensive technical development, difficult to modify • Low user ICT experience • Cognitive/behavioural fundamentals of the classical therapies are not fully reproduced • Insufficient research evidence of effectiveness, risk and impact. • Absence of cross-cultural validation • Unrealistic belief that ICT can remedy everything • Digital divide

priate to arrange sessions with several patients in the form of an interactive workshop.

It is important to choose a person with the most suitable professional skills for the activity or activities proposed as the caregiver/facilitator/therapist for the sessions. In some cases, the practitioner can also be provided with specific training in the techniques and procedures of the intervention before the sessions begin. In fact, sometimes several caregivers are needed to be able to hold the session (e.g. for a workshop).

The materials used in non-pharmacological interventions are very variable and depend on the clinical target.

For several years now, Information and Communication Technologies (ICT) have played an increasingly more important role in the assessment of cognition and behaviour[15]. The use of ICT is also very appropriate in therapeutic interventions[16]. Table 1[15] summarises a SWOT analysis performed to evaluate the use of ICT in patients with cognitive and motivational disorders.

The COVID pandemic also highlighted the potential importance of ICT in facilitating the delivery of non-pharmacological interventions. Are remote sessions possible? Can these sessions take the form of workshops? How will this new type of interaction be tolerated by seniors? These are some of the questions currently being asked and which, in the context of the AGAP project, will lead to recommendations on the use of these technologies in non-pharmacological interventions.

Finally, in order to maximise the intervention's effectiveness, it is crucial to assess the mechanisms of action of the non-pharmacological intervention, recommend non-pharmacological interventions with a high level of scientific evidence, reduce symptomatic interventions and promote lifestyle interventions. In this regard, multi-domain interventions[17] can also be useful.

Non-pharmacological lifestyle interventions such as cognitive training, physical exercise, diet and vascular risk monitoring could improve or maintain cognitive functioning in at-risk elderly people from the general population[18]. Multi-target interventions may be a more rational choice for a multi-factorial entity, such as MCI. Lifestyle modifications need to be tailored to the subject's specific characteristics and include mental, physical and social activity. They should include symptomatic pharmacological treatment and changes in nutrition[19].

Conclusions

Non-pharmacological interventions are not alternative medicine, and very often complement pharmacological treatments. In reality, it is a type of fully-fledged care whose interactions with other treatments must be known.

At research level, there is still a major degree of debate about the methodologies that seek to prove their effectiveness and it is not clear that they should be modelled exactly on those used for pharmacological treatments. It is important to review the level of scientific evidence and the mechanism of action of non-pharmacological interventions, as discussed in the first part of this article. Activities of interest to the patient must be clearly identified[20]. In fact, the most effective non-pharmacological treatments were those tailored to each subject's interest, because a generic approach to activities will probably fail to bring about positive changes in many patients[21]. Therefore, non-pharmacological interventions can and should be personalized for MCI as well. This is one of the causes that explain why studies on non-pharmacological interventions are not "methodologically sound", precisely because they are heterogeneous. In this regard, non-pharmacological interventions are at the forefront of the current trend to promote personalised medicine.

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PHARMACOLOGICAL TREATMENTS FOR MILD COGNITIVE IMPAIRMENT

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Background:

Mild cognitive impairment (MCI) is a prodromal stage for dementia; it is referred to as the transitional stage between the earliest changes of cognition in normal aging to fully developed Alzheimer's disease (AD)[1]. This stage is of particular interest for therapeutic interventions due to the potential ability to prevent further cognitive decline[1].

The diagnosis of MCI has been based on the following clinical criteria: (1) evident change in cognition, (2) impairment in one or more cognitive domains greater than expected for their age, (3) normal activities of living, (4) normal general cognitive function, (5) and not demented[2,3]. MCI can present with deficits in memory, as well as in language, attention, visuospatial and executive functions[3]. Individuals with MCI can be subdivided as amnestic MCI (aMCI) and non-amnestic MCI (naMCI)[4]. Classification as aMCI is defined by the presence of memory impairments in one or multiple domains (e.g., visual or verbal memory)[3,4]. Similarly, a non-amnestic classification is based on the presence of subclinical impairment in one or more non-memory tasks (e.g., attention, working memory)[3].

Risk Factors and Predictors for MCI

The pathophysiological mechanisms underlying MCI are highly heterogeneous[5]. Consistent with this, many risk factors have been identified for MCI, including those considered modifiable and non-modifiable[6]. Non-modifiable risk factors include genetic factors and demographic characteristics, such as age or sex. Modifiable risk factors include level of education, cardiovascular and vascular risk factors[6,7]. Measures of brain atrophy using neuroimaging tools are well-established predictors of progression from MCI to AD. The accumulation of brain Aβ protein is thought to precede the appearance of initial cognitive changes, while structural changes on MRI appear later[8]. In individuals with MCI, amyloid positive subjects have a greater chance of progression to AD compared to those who are amyloid-negative[8].

The purpose of this review is to identify and summarize the existing literature on the current pharmacological interventions for MCI, with the emphasis on those that measure cognitive outcomes or conversion to dementia. These interventions include those that target risk factors for MCI and those that are potentially disease-modifying.

Methods

Systematic reviews and meta-analyses that evaluated pharmacological interventions that have been studied in MCI were included where possible. A broad search of the Medline, PubMed and PsycINFO electronic databases and the Cochrane library was conducted. The database search was supplemented by searching clinical trial registry websites, Google Scholar, and the reference lists of relevant papers. Searches were carried out using the following key words: Mild cognitive impairment, mild cognitive dysfunction, mild cognitive decline, pre-dementia, cognitive dysfunction, pharmacological, drug therapy, medication, clinical trial, clinical study.

Table 1. Inclusion and Exclusion Criteria

INCLUSION	EXCLUSION
The complete text was available	Contained natural health supplements
Published in English	Contained non-pharmacological interventions
Researched in a MCI or pre-dementia population	Did not describe cognition as an outcome
Primary outcomes were cognitive performance or a risk factor for cognitive decline	Did not describe risk factors for cognitive impairment and/or MCI as an outcome

Titles and abstracts were reviewed to determine eligible studies and full-text articles were examined to match the search inclusion and exclusion listed in Table 1.

Pharmacologic interventions include cognitive enhancers, those targeting risk factors and those that target the underlying neuropathology of Alzheimer's disease.

Cognitive enhancers

CHOLINESTERASE INHIBITORS

Cholinesterase inhibitors (ChEIs) act by inhibiting the acetylcholinesterase enzyme, which degrades acetylcholine, a major neurotransmitter. The inhibition of acetylcholinesterase enhances cholinergic neurotransmission across the synaptic cleft. While three ChEIs, donepezil, rivastigmine and galantamine, are currently approved for Alzheimer's disease, their potential benefits for memory deficits in MCI have also been evaluated[9-11].

Donepezil, rivastigmine and galantamine[12] have been assessed for MCI as summarized in 3 recent reviews. Russ and Morling assessed the efficacy, safety and tolerability of ChEIs for MCI in adults over time (16 weeks to 3 years) and found little evidence that ChEIs affect progression to dementia in MCI[10]. Possible limitations of that review included the definition and diagnostic criteria of MCI used and the lack of differentiation between amnestic and naMCI[10]. Another systematic review examined the efficacy and safety of donepezil, rivastigmine, galantamine and the NMDA receptor antagonist memantine, which is also approved for AD. The results demonstrated that none of these agents reduce progression to dementia and that there was no improvement in cognition or function among MCI patients using any of these cognitive enhancers[13]. The most recent systematic review conducted in 2019 found that while ChEIs did not improve cognitive function in MCI patients, they were associated with a lower incidence of progression to dementia. However, the clinical benefit may be limited, because the effect size of ChEIs for the progression from MCI to dementia is small (RR = 0.76, NNT = 20)[14].

The Cognition Platform Study is an ongoing clinical trial that uses a repeated high-frequency computerized cognitive assessment to evaluate the effects of donepezil on visual learning and short-term memory in participants at risk of AD. They hypothesize that participants receiving donepezil will score higher than participants receiving placebo. The Multiple Dose Trial of donepezil is a second study evaluating the safety, tolerability and pharmacokinetics of the daily dose of donepezil in MCI patients or mild-to-moderate AD patients.

To date, there is no evidence showing that ChEIs benefit cognition in MCI. ChEIs are associated with an increased risk of side effects. Reviews conducted hitherto have found that the use of ChEI in MCI was associated with greater rates of discontinuation, with increased adverse events such as gastrointestinal symptoms, dizziness, headache, insomnia, muscle cramps and weight loss compared with placebo[10,13,14].

NICOTINE

Nicotine binds to the presynaptic nicotinic acetylcholine receptors in the brain and facilitates the release of various neurotransmitters known to be involved in cogni-

tive processes such as memory and attention[15]. Two clinical trials testing the use of 15 mg transdermal patches in MCI patients showed an improvement in cognitive performance after 6 months[15,16]. Limitations of both studies include the small sample size and the lack of populations with a smoking history, whereby the results may not be extrapolated to a general population[15,16]. In conclusion, transdermal nicotine is a relatively safe treatment for patients with MCI with minimal adverse effects. Future clinical trials with larger populations and long-term follow up are recommended to investigate its effects on cognition in prodromal dementia populations.

LEVETIRACETAM

Levetiracetam is of interest in aMCI for its ability to target hippocampal memory loss[17-19]. Animal models of age-related memory loss have indicated that elevated hippocampal activation in C3 regions of the brain is correlated with episodic memory impairment[19,20]. This is supported by clinical research in aMCI patients in whom greater hippocampal activity has been found in the dentate gyrus/CA3 (DG/CA3) regions, suggesting a similar brain dysfunction[20].

A prospective, open-label study of levetiracetam in MCI, dementia and AD patients found an average improvement of 2.2 points (SD=3.0, p=0.01) in global cognition and an average of 4.3 points (SD=6.4;P=0.02) in the ADAS-cog after 12 weeks of treatment[17]. This was aligned with results from a placebo-controlled single-blinded study in aMCI patients receiving low-dose levetiracetam (125mg BID) which attenuated DG/CA3 activation and significantly improved performance in the three-choice memory task, suggesting a therapeutic response[20].

In the studies mentioned above, the rate of adverse effects was below 17%, which were commonly reported as fatigue, headache and dizziness[17,18]. We conclude that levetiracetam is a drug with low adverse effects and a potential treatment for cognitive decline in elderly individuals with MCI.

Pharmacological Interventions Targeting Risk Factors

ANTIDEPRESSANTS

In patients with MCI, the prevalence of depression is 32%[21], and those with depressive symptoms present an additive risk for progression to dementia[22]. Antidepressants may be beneficial in MCI due to their potential neuroprotective effects by lowering Aβ formation, increasing neurotrophic factor and promoting neurogenesis via an increasing proliferation of hippocampal neurons[12,23].

The findings regarding the effects of antidepressants on cognition in older adults are mixed. A large retrospective study found that both depressed and non-depressed antidepressant users had a higher incidence of dementia compared to non-users, with the highest risk found with tetracyclic antidepressants and the lowest risk with selective serotonin reuptake inhibitors (SSRI) and tricyclics[24]. They concluded that antidepressant medication is a potential risk factor for dementia independent of any effect of the actual depression. However, since that study utilized secondary data, causality between the use of antidepressants and the development of dementia could not be determined[24]. Similar results were found in a systematic review and meta-analysis of 18 longitudinal studies[14,25], a meta-analysis of 5 observational studies[26] and another meta-analysis of 5 studies[22]. Chan et al. concluded that the use of antidepressants has no protective role against cognitive decline in elderly individuals and could be associated with greater risks of developing dementia and MCI among individuals with depression[25]. This is similar to other reviews which suggest a significantly increased risk of dementia with antidepressant therapy, specifically with patients before the age of 65 and with those on monoamine oxidase inhibitor therapy compared to those on tricyclic or SSRI therapy[22,26].

Recent trials have yielded promising results for the use of antidepressants and improved treatment outcomes in patients with MCI. Bartels et al. studied the impact of SSRI treatment on cerebrospinal fluid (CSF) biomarkers, cognitive status and progression from MCI to AD in individuals with aMCI or early AD. The results showed that long-term SSRI treatment (longer than 4 years) in MCI patients with a history of depression was associated with delayed progression to AD of approximately 3 years compared with short-term SSRI treatment, treatment with other antidepressants or none[27]. More recently, Sheline et al. studied the effect of SSRI treatment dose and duration on CSF AB levels in cognitively normal adults[28]. Escitalopram (either 20 or 30

mg) for 2 weeks or 8 weeks was associated with decreased CSF AB42 levels[28]. A study conducted in 2020 also found that long-term antidepressant use was associated with a lower incidence of development of dementia compared with short-term treatment. More specifically, treatment with tricyclic antidepressants or escitalopram was associated with a lower incidence of dementia[27]. An ongoing study is exploring the use of duloxetine (a selective serotonin and norepinephrine reuptake inhibitor) in improving cognition in MCI patients, although the results are not yet available.

There is a complex relationship between depressive disorders and neurocognitive disorders; further evidence reviewing the use of antidepressants and their influence on cognitive function is needed[29]. The limitations of those studies include unclear time of initiation of antidepressant use, severity of depression, the types of depression scales used and the effect of using different classes of antidepressants. More multicenter trials with larger sample sizes and a longer duration of follow-up should be conducted to determine the efficacy, safety and tolerability of using antidepressants in patients with cognitive impairment. Long-term antidepressant use may be effective in delaying AD in patients with naMCI or non-APOE4 carriers, and these findings should be replicated in future trials[12]. Current studies are evaluating combined therapies in order to modulate multiple drug targets as a strategy to better address AD pathology.

ANTIDIABETICS

Diabetes mellitus (DM) is a risk factor for dementia and cognitive impairment. Insulin resistance, the key finding defining DM, is also found in individuals with reduced cognitive performance[30,31]. While intravenous (IV) insulin administration can improve memory in subjects with AD, the use of intranasal (IN) insulin is an attractive therapeutic approach due to its less invasive route of administration and effective delivery to the brain, bypassing the blood-brain barrier[30].

A recent meta-analysis of 306 studies in MCI or AD found that with IN insulin treatment (10, 20, 40 IU) compared to placebo, there was an improvement in verbal memory tested by means of the story recall task and word list recall tasks[31]. This is aligned with a subsequent systematic review conducted in 2020 in a similar population[32]. There are 3 main modulators of IN insulin response: ApoE4 status, type of insulin, and dosage[31-33]. Rapid-acting insulin is thought to be more advantageous than regular insulin, although the data are still inconsistent, and it is less efficacious in ApoE4-positive individuals[31]. Regular IN insulin was beneficial for ApoE4-negative patients, while IN detemir, a long-acting form of insulin, improved delayed recall performance in ApoE4-positive patients[30,31]. Long-acting IN insulin can be safely administered to subjects with cognitive dysfunction and has had beneficial effects on cognition, more specifically verbal memory and visuospatial performance in MCI and mild AD patients[31,34]. The dosages of IN insulin are unclear. Higher dosages of IN insulin (40 IU compared to 20 IU) showed significant beneficial changes in cognitive performance in one study[34], whereas in others, 20 IU of IN insulin yielded an improvement in cognitive performance[30,35]. The differences in results could be due to the varying dosages and lengths of IN administration, the lack of longitudinal assessments, specifically the use of IN insulin as a chronic intervention, as all the studies measured short-term effects (approximately 8 weeks).

Of the thiazolidinediones (TZD), which are used for diabetes, rosiglitazone has neuroprotective effects against the neuronal insulin resistance induced by Aβ proteins, whereas pioglitazone improves cognition in memory-impaired animal models[33]. Rosiglitazone produced promising results[36], although larger trials reported poor results and it was withdrawn due to cardiovascular risks[32,33,38]. Clinical studies and a meta-analysis of pioglitazone showed improved verbal memory, global cognition and CBF in mild AD and MCI diabetic patients[32,33,39]. The poor results of TZD could be due to the lack of brain bioavailability, as CNS penetration is limited by efflux transporters[32]. The limitations of the findings include small sample sizes and sample differences among studies[32,33,39]. Larger blinded clinical trials involving patients with and without diabetes are needed to confirm the results.

Metformin has been shown to have neuro-protective benefits by activating the AMPK pathway in neuronal stem cells *in vivo*[33,40] and to decrease cognitive decline and the risk of developing dementia in MCI indviduals[32,41]. Furthermore, it is thought to lower BACE1 activation and the

production of Aβ[40]. In contrast, a case-control study showed that long-term use of metformin, but not other antidiabetic drugs, was associated with a greater risk of AD progression[42]. Similarly, a study in an Australian population found that the use of metformin led to greater cognitive dysfunction[43]. These results do not provide a definite conclusion, although they do encourage further research in larger populations and in placebo-controlled clinical trials.

The literature currently highlights the potential benefits of some antidiabetics as a therapeutic approach to prevent cognitive decline, specifically in areas of verbal memory, although definitive research is lacking.

ANTIHYPERTENSIVES

Hypertension is associated with an increased risk of age-related cognitive decline and dementia[44], and antihypertensive use is associated with a reduced risk of dementia[45-47]. Hypertension has been more strongly associated with naMCI compared to aMCI[48]. There is evidence pointing towards the neuroprotective benefits of antihypertensive therapy, specifically calcium channel blockers (CCB) and renin–angiotensin system (RAS) blockers, which could reduce the incidence and progression of cognitive decline[50].

A recent systematic review found no protective effects of antihypertensive medications in MCI[50]. However, a pilot study in 2017 demonstrated the protective effects of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in improving amyloid-β (Aβ) clearance from the brain to the blood, indicated by higher plasma Aβ levels[51]. They found an association between ACE inhibitor use and higher plasma AB42 levels. Individuals with aMCI, probable AD dementia and mixed probable AD/vascular dementia had elevated Ab42/Ab40 ratios, which could be indicative of increased clearance of Ab42 from brain to blood[51]. Although the trial in question looked promising, further controlled trials are necessary to determine the therapeutic effects of ACE inhibitors in improving AB42 clearance, thereby protecting cognition.

Recent trials have examined the influence of several types of antihypertensives on the risk and progression of dementia. In 2013, the Gingko Evaluation of Memory study in participants with MCI or no cognitive impairment found that in MCI participants only diuretic use was associated with a reduced AD dementia risk[52]. A 2016 review found that a small number of studies reported mixed data and varying results with regard to ARBs[44]. In 2019, Wharton et al. found that fewer participants converted from MCI to AD when on RAS medications and exhibited fewer neurofibrillary tangles compared to those on non-RAS medications. They suggested that antihypertensive medications acting via the RAS system may have the potential to reduce AD risk[53]. The most recent meta-analysis included short and longer-term follow-up periods while adjusting for the duration of the use of antihypertensive medication. The findings did not provide evidence that supported one class of antihypertensive medication over the other[54]. However, that review was not specific to the MCI population and included other dementia populations.

In conclusion, antihypertensive medications may reduce the risk of cognitive decline and progression to dementia. However, there are still conflicting results on the type of medications that may be most beneficial. The data obtained hitherto present methodological limitations, as patients using antihypertensive medications may differ from those not using any medication, thereby leading the association between drug use and the progression of dementia to be underestimated. Inconsistencies with previous or current exposure to antihypertensive treatments, treatment duration and the lack of a consistent classification of hypertension constitute major limitations[44,49,52]. The management of hypertension with antihypertensive medications may deliver major health benefits through the protection of cognitive function[45]. However, current evidence does not suggest the use of one antihypertensive medication over the other.

STATINS

Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase enzyme[55], catalyzing the rate-limiting step of cholesterol synthesis[56]. Their primary function is to lower cholesterol levels in the blood and inhibit enzymatic reactions that can cause amyloid deposition and plaque formation[55]. Pre-clinical studies have suggested a link between cholesterol metabolism and accumulation of Aβ peptide[57].

Several meta-analyses have examined the role of statins in cognitive impairment and dementia. An early re-

view found a reduced risk ratio for all-cause dementia, AD, or MCI, and suggested a neutral effect of statins in cognitive outcomes[58]. They found that statins have protective effects for incident MCI[58]. A Cochrane review published in 2016 concluded that statins given to elderly individuals at risk for vascular disease could not prevent dementia or cognitive decline[56]. A 2018 review showed that patients without baseline cognitive dysfunction but who used statins had a significantly reduced risk of developing all-cause dementia, AD and MCI, but not vascular dementia[55]. Their study concluded that statins may protect against cognitive decline in prodromal stages[55]. However, that review only included observational studies, hence the results could be susceptible to bias and confounding.

Currently, there are 4 studies actively recruiting in MCI populations. The first one evaluates the effect of atorvastatin on brain vessel reactivity and CBF in patients with MCI. The PREVENTABLE trial is a multicenter, randomized, placebo-controlled study in elderly adults without cardiovascular disease or dementia given 40 mg of atorvastatin or matching placebo over 5 years. Another study in aMCI patients aims to examine the effects of 60 mg of simvastatin on Clinical Dementia Rating-Sum of boxes (CDR-SOB) score, compared to placebo. Lastly, the DEPEND trial will be developing an algorithm to examine individualized dosing of probucol, a cholesterol-lowering drug, as an agent to increase the availability of APOE in the CSF of cognitively intact older persons at risk of AD.

ANTI-AMYLOIDS

The deposition of Aβ peptide occurs up to 20 years earlier than the onset of symptoms[59] and is assumed to play a role in the pathology of cognitive decline in AD[60,61]. Extracellular senile plaques, which consist mainly of Aβ peptides, are thought to lead to neuronal dysfunction and neuronal death in the hippocampus, leading to memory decline[62,63]. Anti-amyloid drugs can decrease Aβ production (beta-secretase and gamma secretase inhibitors) or increase Aβ clearance in the brain (anti-Aβ monoclonal antibodies)[64].

β and γ-secretase inhibitors have been investigated in MCI and mild dementia[60,65]. BACE1 is a β-secretase enzyme that catalyzes the rate-limiting step in Aβ synthesis. The AMARATNH and DAYBRREAK-ALZ clinical trials in MCI and mild AD dementia patients found that while lanabecestat was well-tolerated among patients, it did not slow cognitive or functional decline compared to placebo[66]. γ-secretase inhibitors can reduce the production of $A\beta_{42}$, without reducing overall Aβ levels or altering Notch processing[60]. Of the γ-secretase inhibitors, avagacestat was shown to worsen cognition in prodromal AD patients[64]. γ-secretase inhibitors may increase risk of adverse events such as skin cancers, gastrointestinal symptoms and infection[67].

Preclinical studies that involve combination therapy are currently being conducted. A study using BACE1 inhibitor with a monoclonal antibody (mAb) in transgenic mice found that the combined treatment enhanced the anti-amyloid effect by reducing the amount of amyloid plaque in the brain[68]. There are currently no human trials studying the combination therapy approach in MCI[59].

MONOCLONAL ANTIBODIES

mAb contain specific antigen-binding sites that can recognize different forms of Aβ and inhibit the enzymes that produce the peptide from the amyloid precursor protein (APP)[63]. Evidence in AD suggests the potential for lowering phosphorylated tau protein in the CSF[69] and reduction in brain amyloid[70], particularly in APOE4 carriers[69].

In the "SCarlet RoAD" 2-year phase III trial in prodromal AD patients, subcutaneous gantenerumab showed a reduction in Aβ, hyperphosphorylation of tau and neuronal dysfunction measured by PET[70]. However, the trial was terminated on account of futility[70]. Similarly, data from the "EMERGE" and "ENGAGE" phase III trials did not show any clinical benefits from the aducanumab treatment in MCI and mild dementia patients[71]. The ENGAGE trial showed no cognitive benefits in contrast to placebo, at both low and high doses, whereas the EMERGE trial demonstrated a significant improvement using a higher dose[72]. The differences in these trials could be due to outliers, and the removal of the latter rendered the results of both studies more consistent[71,72]. The EMERGE findings underscore the need for longer follow-up, larger sample sizes and higher doses[71,72].

In conclusion, mAb are a novel therapeutic intervention of interest due to their ability to target AD pathologies. Larger clinical studies with larger doses and longer-term

follow-up are needed to provide more data regarding the clinical efficacy of mAb in MCI, either alone or in combination with anti-tau or other medications.

Conclusion

In summary, pharmacological treatments with potential symptomatic and/or disease-modifying benefits in MCI have been studied. While the control of risk factors has the greatest body of evidence to date, as yet there are no treatment options specifically approved for MCI. A large part of the existing literature is limited by methodological issues which include heterogeneity in treatment duration, the assessment scales used and the outcomes of interest. With the emerging interest in MCI as a treatment target and the use of biomarker-defined populations, future research should provide further clarification on current and novel therapies.

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NEUROKETOTHERAPEUTIC STRATEGIES FOR COUNTERING MILD COGNITIVE IMPAIRMENT

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1. Background

The transitional state between cognitive changes in normal aging and Alzheimer's disease (AD) is known as mild cognitive impairment (MCI)[1] The relative risk of MCI patients converting to AD within five years is about 3.0[2], although it varies according to the criteria used to define MCI. This transitional state has been the subject of intense research in the last 20 years. The etiology of MCI presents multiple facets, one of which is deteriorating brain energy metabolism (brain energetics and mitochondrial dysfunction).

I) BRAIN ENERGY CONSUMPTION IN MCI

a) Brain glucose metabolism

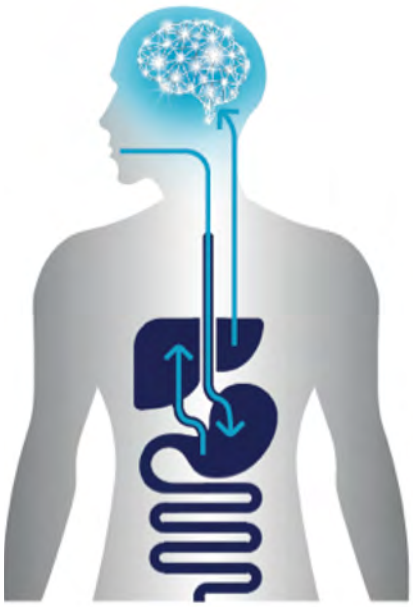
The brain has a high energy requirement relative to its weight, i.e. 20%-23% of whole body energy requirements[3]. In vivo positron emission tomography (PET) imaging studies have clearly established that MCI is already characterized by lower brain glucose uptake[4-7]. Lower gray matter glucose uptake has been extensively reported to precede cognitive impairment. Indeed, brain glucose hypometabolism is present up to 30 years before any cognitive symptoms present in individuals at high risk for AD, including presenilin-1 (PSEN1) mutation carriers[8], apolipoprotein E4 (ApoE4) carriers[9-10], and individuals with type 2 diabetes[12,13] or a familial history of AD[14-15]. A chronic presymptomatic brain glucose deficit could therefore contribute to the development of MCI.

In MCI, lower brain glucose uptake is present specifically in the posterior cingulate cortex and is also commonly reported in medial temporal lobe regions, including the hippocampus and entorhinal cortex[4,6,16]. White matter glucose deterioration is also evident in MCI and specific to limbic fascicles (or tracts)[7,17]. Lower brain glucose uptake in these brain regions clearly seems to be linked to the earlier onset of AD, i.e. impaired episodic memory. Therefore, brain energy (glucose) deficit was recently targeted in several clinical trials as a therapeutic strategy for MCI[18]. Brain energy rescue strategies in MCI include improving mitochondrial function[19] and brain insulin signaling[20,21], as well as ketogenic therapies, the latter being the main topic of this review[22,23].

b) Brain ketone metabolism

Under normal circumstances, about 95% of adult brain energy requirements are met by glucose[18,24]. During glucose deprivation, such as fasting or very low carbohydrate ketogenic interventions, ketones can supply as much as or more fuel to the brain than glucose. In prolonged fasting, ketones can supply ≥60% of the brain's energy requirements[25]. The two ketones that are taken up by the brain are acetoacetate and its reduced form, beta-hydroxybutyrate (βHB). In glucose deprivation conditions, ketones are synthesized from fatty acids in the liver and become available in the circulation for brain uptake by monocarboxylate transporters. Astrocytes also have the capacity to synthesize ketones and provide this energy substrate to the neuronal compartment[26] (Figure 1). Unlike in adults, in infants, sustained ketosis is common for several months after birth, as ketones act as essential brain fuels[27] and are the primary substrates for myelin synthesis[28].

Figure 1. Mechanism of action of kMCT.



Several ketogenic interventional studies have reported a strong positive correlation between plasma and brain ketone levels in animal models[29-30], healthy humans[31-33] and MCI/AD patients[17,34]. Brain ketone uptake is a direct function of arterial ketone concentration[33,35]. Brain energy metabolism can be assessed using in vivo PET imaging and various radiotracers, notably ^{11}C-acetoacetate[33] or ^{11}C-beta-hydroxybutyrate[36] (for ketones) and ^{18}F-flurodeoxyglucose (for glucose). Brain ketone uptake and utilization was shown to be similar in older adults compared to younger persons[37] and in MCI and AD patients compared to cognitively healthy elderly subjects[6,38].

Therefore, the brain's capacity to utilize ketones (rate of uptake) does not appear to be reduced during healthy aging or MCI, whereas whole brain glucose uptake is decreased by approximately 12% in MCI and by 18% in mild-to-moderate AD[18]. The brain metabolic deterioration associated with MCI thus appears to be specific to glucose and does not involve ketones. Rescuing brain energy deficit by providing ketones as an alternative fuel is an emerging therapeutic strategy for aging-associated cognitive decline[18] and has shown promise in several randomized controlled trials (RCT)[39-41]. Indeed, encouraging results involving ketogenic interventions that improve cognition in MCI [22,42] and AD[43-45] were published recently. In this review, we will present kMCT (ketogenic medium chain triglycerides) interventions in MCI and AD patients and will briefly discuss other ketogenic therapies investigated hitherto.

2. Neuroketotherapeutic interventions to rescue brain energy in MCI

I) MECHANISMS OF ACTION FOR COGNITIVE IMPROVEMENT

Cognitive improvement has been observed with a ketogenic intervention within hours of the dose being taken[46-47], suggesting that it is subsequent to brain energy rescue. Indeed, the cognitive benefits of kMCT supplementation and other ketogenic therapies can be attributed to improved brain energy status, since ketones act as an alternative source of energy, bypassing the chronic glucose deficiency in brain cells. Indeed, glycolytic gene expression is significantly impaired in the neurons, astrocytes and microglia of post-mortem AD brains, whereas the ketolytic pathway appears intact in these cell populations[48]. Therefore, when ketones are provided, ketolysis increases acetyl-CoA and ATP availability in the brain, thus providing energy for synaptic transmission and action potential propagation along

axons[49]. Ketones are also precursors for the synthesis of myelin, constantly remodeled throughout life[49], and are thus potentially associated with improved processing speed in kMCT clinical trials[42,44].

In addition to these effects on brain energy metabolism and structure, the neuroprotective role of ketones is becoming increasingly more recognized[50]. Indeed, in vitro and animal studies show that ketones increase - 1) protection against oxidative stress[51], 2) brain inhibitory/excitatory neurotransmitter ratio (GABA/glutamate)[52], and 3) brain-derived neurotrophic factor (BDNF) expression[53], 4) reduce apoptosis[50] and 5) preserve hippocampal long-term potentiation[54]. Ketones also have anti-inflammatory effects in animal models[55] and humans[56].

II) IMPACT OF A KETOGENIC DIET

Nutritional ketosis can be safely achieved by means of a ketogenic diet, i.e. a very-low-carbohydrate, very-high-fat diet. The ketogenic diet is an effective alternative treatment for refractory epilepsy in children. Five RCT evaluating the impact of a ketogenic diet in MCI and/or AD have been conducted to date and are included in Table 1. Their duration was 6 to 12 weeks, and the degree of ketosis induced by ketogenic diets in MCI and AD appears to be slightly higher than with kMCT (blood βHB ~0.9 mM; Table 1). Improved cognitive function was reported in these trials; three out of five RCT showed an improvement in memory in MCI and AD patients[23,57,58]. One RCT showed improved daily function and quality of life in AD[59], whereas the last one did not report cognitive or functional outcomes[60].

III) IMPACT OF COCONUT OIL

The daily intake of coconut oil for the potential treatment of AD has also been investigated. Two RCT reported significantly improved cognition after daily consumption of coconut oil (Table 1)[61,62], although these findings need to be reproduced, since the longest RCT (6-month intervention) did not show a benefit[63]. Blood ketones or their association with cognitive improvement were not reported in these trials. Any possible beneficial effect of coconut oil on cognition in MCI is unlikely to be ascribable to ketones, because the C8 and C10 concentration in coconut oil is too low to increase plasma ketones in humans[64]. C8-rich kMCT supplements are much more efficient in improving brain energy status than coconut oil.

IV) IMPACT OF KETOGENIC-ORAL NUTRITIONAL SUPPLEMENTS (KMCT)

The most studied approach to inducing mild nutritional ketosis in humans is oral kMCT supplementation, and most of the clinical trials involving ketogenic interventions in MCI and AD patients investigated the effect of kMCT supplements (Table 1). The kMCT are fatty acids of 6 to 12 carbons in length. They are mostly absorbed through the portal vein and are therefore transported more rapidly to the liver, beta-oxidized and transformed into ketones than long-chain fatty acids. In infants, brain ketone[65]. requirements are ensured through the continuous delivery of kMCT through breast milk. When breastfeeding stops, there is no further dietary source of kMCT, with the exception of coconut oil and palm kernel oil, which contain 10%-15% kMCT in the form of octanoic acid (C8) and decanoic acid (C10). Fractions of C8 and C10 can be extracted from coconut oil and concentrated to produce kMCT oil supplements. Based on plasma ketones response, C8 is more ketogenic than C10 and much more ketogenic than dodecanoic acid (C12)[66]. Emulsifying kMCT[67] or consuming them without a meal increases their ketogenic effect[64]. Compared to a very low carbohydrate ketogenic diet, kMCT supplements are easier to integrate in the daily routine, and better adherence and a longer supplementation period can be achieved.

a) Clinical data

Ten clinical trials with kMCT supplementation in MCI and/or AD have been reported (Table 1). One study using a ketogenic diet combined with kMCT[43] was included, since kMCT intake represented ~30% of energy intake, thus contributing substantially to ketosis. Mild ketosis was achieved in these ten trials; maximal blood βHB levels were between 0.10 and 0.61 mM. A significant positive correlation was also found between the maximal blood ketone level achieved and the daily oral

Table 1. Studies using ketogenic therapies in populations with mild cognitive impairment and/or Alzheimer's disease.

Intervention	Design	Population (completers)	Treatment (duration)	Blood βHB (maximal)	Cognitive domain/ Test with improvement*	Reference
kMCT	RCT - crossover	aMCI (n=5) AD (n=15)	C8, 40 g (1 dose)	0.61 mM	ADAS-Cog (global) (in ApoE4-)	Reger et al. 2004
	RCT - parallel	AD (n=140)	C8, 20 g/d (n=77) or placebo (n=63) (12 weeks)	0.39 mM	ADAS-Cog (global)	Henderson et al. 2009
	1 arm trial	AD (n=22)	C8, 20 g/d (12 weeks)	0.25 mM	No improvement	Ohnuma et al. 2016
	RCT - parallel	AD (n=16)	C8, 20 g/d (n=14) or placebo (n=2) (45 days)	N/R	N/R	Torosyan et al. 2018
	1 arm trial	AD (n=11)	C8C10, 30 g/d (1 month)	0.46 mM	N/R	Croteau et al. 2018
	1 arm trial	AD (n=6)	C8, 30 g/d (1 month)	0.57 mM	N/R	Croteau et al. 2018#
	RCT - crossover	AD (n=20)	C8C10, 20 g (1 dose)	0.47 mM	No improvement	Ota et al. 2019
	1 arm trial	AD (n=16)	C8C10, 20 g/d (12 weeks)	0.11 mM	Verbal memory and processing speed	Ota et al. 2019†
	RCT - crossover	AD (ApoE4 -/-) (n=46)	C8C10, 17 g/d or placebo (4 weeks)	0.09 mM	ADAS-Cog (memory, language, praxis, attention, and global scores)	Xu et al. 2020
	RCT - parallel	MCI (n=39)	C8C10, 30 g/d (n=19) or placebo (n=20) (6 months)	0.54 mM	Episodic memory, language, executive function and processing speed	Fortier et al. 2019
	RCT - parallel	MCI (n=83)	C8C10, 30 g/d (n=44) or placebo (n=39) (6 months)	0.40 mM	Episodic memory, language and executive function	Fortier et al. 2020‡
	RCT - parallel	AD (n=332)	C8, 20 g/d (n=172) or placebo (n=160) (6 months)	0.27 mM	QOL-AD subject score	Henderson et al. 2020
KD + kMCT	1 arm trial	AD (n=10)	KD (46±27g CHO/d) + kMCT C8C10, 21-42 g/d (12 weeks)	0.52 mM	ADAS-Cog (global)	Taylor et al. 2018

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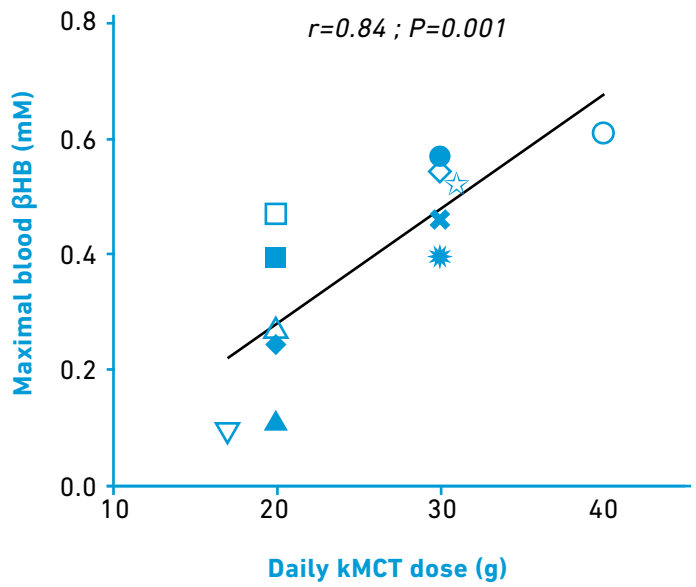
KD	RCT - parallel	MCI (n=23)	KD (34±18g CHO/d) (n=12) or HCLF (n=11) (6 weeks)	N/R	Verbal memory	Krikorian et al. 2012
	RCT - parallel	MCI or mild AD (n=14)	KD (30-50g CHO/d) (n=9) or HCLF (n=5) (12 weeks)	N/R	Memory composite score (at week 6)	Brandt et al. 2019
	RCT - crossover	MCI (n=11)	KD (<20g CHO/d) or HCLF (6 weeks)	N/R	N/R	Nagpal et al. 2019
	RCT - crossover	MCI (n=9) SMC (n=11) with pre-diabetes	KD (40±99g CHO/d) or HCLF (6 weeks)	0.93 mM	Memory performance	Neth et al. 2020
	RCT - crossover	AD (n=21)	KD (6 % CHO by weight) or HCLF (12 weeks)	0.95 mM	ADCS-ADL, QOL-AD	Phillips et al. 2021
CCO	RCT - crossover	AD (n=44)	40 mL/d (n= 22) or placebo (n=22) (3 weeks)	N/R	MEC-WOLF test$	Yang et al. 2015
	RCT - crossover	AD (n=22)	60 mL/d (n=8) or placebo (n=14) (6 months)	N/R	No improvement	Chan et al. 2017
	RCT - crossover	AD (n=44)	Mediterranean diet + CCO 40 mL/d or placebo (3 weeks)	N/R	Episodic, temporal orientation and sematic memory	de la Rubia Orti et al. 2018

** Test/cognitive domain is named if there was significant improvement.*
 # Croteau et al. 2018 1-month supplementation (C8+C10) was followed by a 4-week washout period and a second 1-month trial (C8).
† Ota et al. 2019 single administration was followed by a longitudinal open-label 12-week trial.
‡ Fortier et al. 2020 extended the recruitment from Fortier et al. 2019 by adding 44 participants.
$ The MEC-WOLF test is the Mini Examen Cognoscitivo (Spanish adaptation of the Mini-Mental State Examination).
Case reports (Farah et al. 2014; Newport et al. 2015) were not included as well as Rebello et al. 2015 due to very small sample size (n = 2/ group).

Abbreviations: RCT, randomized controlled trial; MCI, mild cognitive impairment; AD, Alzheimer's disease; βHB, beta-hydroxybutyrate; C8, caprylic acid; C10, capric acid; CHO, carbohydrates; HCLF, high-carbohydrate low-fat diet; KD, ketogenic diet; kMCT, ketogenic medium chain triglycerides; SMC, subjective memory complaints; aMCI, amnestic mild cognitive impairment; ADAS-Cog, Alzheimer's disease assessment scale-cognitive subscale; ApoE4, apolipoprotein E4; N/R, not reported; ADCS-ADL, AD Cooperative Study - Activities of Daily Living; QOL-AD, Quality of Life in AD; CCO, coconut oil.

dose of kMCT (from 17 to 40 g/day; Figure 2). The mean daily kMCT dose was 26 g, which on average would have generated a mild ketosis of about 0.40 mM (blood βHB) in MCI and AD patients. A recent meta-analysis including five of these RCT also concluded that kMCT significantly increased blood βHB levels (weighted mean differences = +0.355) compared to placebo[39]. No clinically significant changes in body weight or body mass index were observed in the ten clinical trials with kMCT supplementation (Table 1). Blood cholesterol and/or triglycerides increased compared to baseline in three of these clinical trials[22,34,45], although they remained within the clinical reference range. Other cardiovascular risk factors (blood pressure and electrocardiograms) were unchanged after kMCT supplementation in these trials. Blood glucose[22] and insulin[34] were also higher after supplementation in one trial but remained within the clinical reference range. One trial also reported increased renal function blood markers in a few patients, although these changes were not considered clinically significant by the investigators[68]. No other changes in plasma metabolites or hematology were reported in these trials.

Figure 2. Linear relationship between the daily dose of ketogenic medium chain triglycerides (kMCT) and maximal blood beta-hydroxybutyrate (βHB) in MCI and AD. Linear regression equation: Y = 0.01988X - 0.1283; slope significantly non-zero (P = 0.002). kMCT were given as single or multiple doses. ▽Xu et al. 2020; ▲Ota et al. 2019 (12 weeks); ◆Ohnuma et al. 2016[76]; ■Henderson et al. 2009; □Ota et al. 2019 (1 dose); ✹Fortier et al. 2020; ✖Croteau et al. 2018 (C8+C10); ◇Fortier et al. 2019; ●Croteau et al. 2018 (C8); ☆Taylor et al. 2018; ○Reger et al. 2004; △Henderson et al. 2020.



b) Improvement in brain energy status

Fortier et al.[42] conducted a RCT, called BENEFIC – the Brain ENErgy Fitness, Imaging and Cognition trial – with kMCT supplementation in MCI over 6 months (30 g/day). They evaluated the impact of a kMCT supplement on brain energy status using PET imaging. They assessed the global (whole brain) and gray matter metabolic rate of ketone (acetoacetate) and glucose. Post-intervention whole brain ketone uptake more than doubled, as it also did in the whole cortex, four lobes (frontal, temporal, parietal and occipital) and sub-cortical nuclei. In this same trial, using diffusion MRI (magnetic resonance imaging) and tractography, white matter fascicles were reconstructed and also investigated. The 6-month kMCT supplementation in MCI improved white matter energy supply, with an almost 3-fold increase in ketone uptake[17]. The increased ketone uptake was present in all the white matter fascicles assessed, including the fornix (Figure 3), the core fascicle of the limbic system. The increase in plasma ketones over this 6-month period correlated significantly with changes in global white matter or gray matter ketone uptake (Figure 4A). In terms of cognitive outcomes, processing speed improved after the 6-month kMCT supplementation. Improvement in processing speed composite Z-score and individual tests were associated with the increased gray matter (Figure 4B) and white matter ketone uptake both globally (Figure 4C) and in individual fascicles[17]. In contrast to memory, language and executive function, the composite Z-score for processing speed was the only one associated with improved brain ketone metabolism[42]. The reported improvement in processing speed may be attributed to ketones acting as an important neuronal energy substrate, but also as a precursor to myelin, thus preventing demyelination associated with progression to AD.

Figure 3. The fornix of a representative MCI participant before (Pre) and after (Post) 6 months of ketogenic medium chain triglyceride (kMCT) supplementation in the BENEFIC randomized controlled trial. The fornix is a white matter fascicle that is part of the limbic system; it connects the hippocampi to the mamillary bodies. Streamlines are colored according to their ketone (acetoacetate) metabolic rate (µmol/g/min). The fornix had a 3.2-fold increase in mean ketone uptake post-intervention, the highest increase in ketone uptake among the fascicles analyzed.

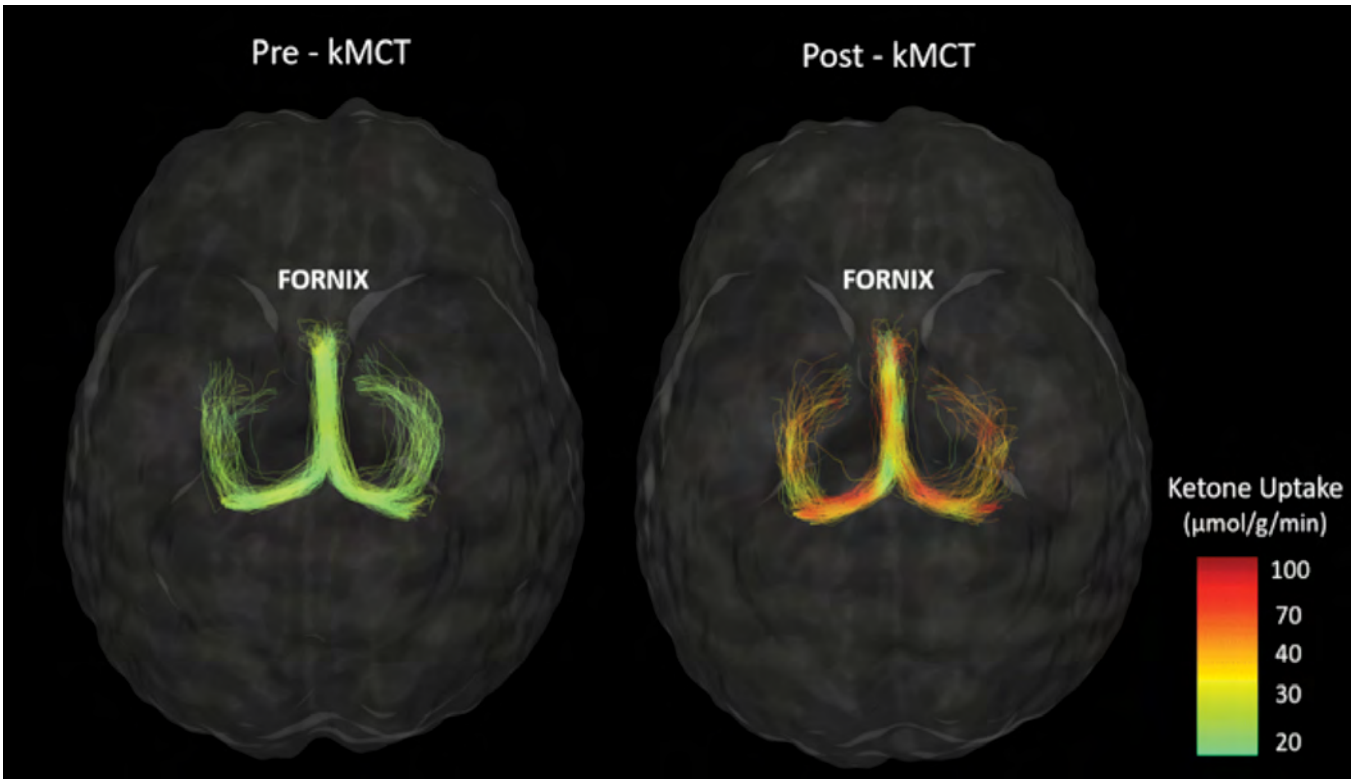
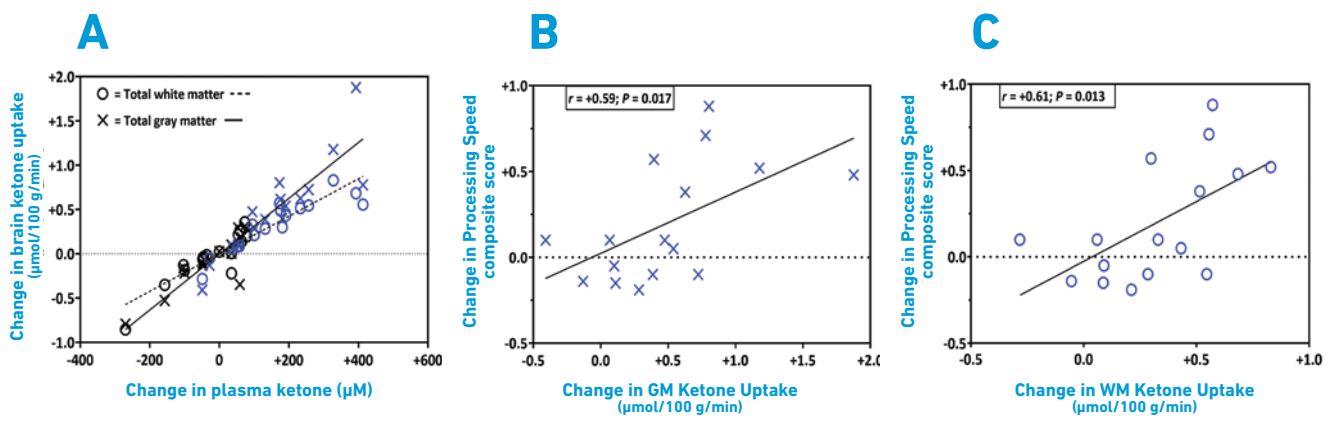


Figure 4. Associations of brain ketone metabolism in MCI participants over a 6-month period of ketogenic medium chain triglyceride (kMCT) supplementation during the BENEFIC randomized controlled trial[17,42]. (A) Scatter plot of the association between the change in plasma ketone (acetoacetate) and the brain total white matter (WM) ✕; r = +0.96; P <0.0001) or total gray matter (GM) ketone uptake (◯; r = +0.94; P <0.0001). The placebo (black) and kMCT (blue) groups were included in the statistical analysis. Improvement in processing speed (composite Z-score) in the kMCT group was positively associated with the increase in ketone uptake in the global gray matter (B; r = +0.59; P = 0.017) and global white matter (C; r = +0.61; P = 0.013).



In mild-to-moderate AD, a daily kMCT supplementation for 45 days also presented an increase in cerebral blood flow in specific regions, notably the temporal cortex, in ApoE4 non-carriers[69]. A one-month kMCT supplementation (30 g/day) in mild-to-moderate AD patients also led to a considerable increase in whole brain and gray matter ketone uptake, as assessed with PET imaging[34]. In contrast to ketones, gray and white matter glucose uptake remain unchanged after kMCT supplementation in MCI and AD[17,34,42]. Thus, a daily intake of 30 g of kMCT significantly improved global brain energy status in cognitively impaired elderly adults. Considering that whole brain glucose uptake is generally decreased by approximately 12% in MCI compared to healthy elderly[39], the kMCT treatment reduced global brain energy deficit by 4% in MCI[42], leaving a smaller energy gap (8%) after kMCT treatment.

c) Improvement in cognitive function

Six of the ten clinical trials with kMCT supplementation included in Table 1 reported a significant improvement in cognitive performance. Most of them also reported improved performance on the Alzheimer Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) in AD patients (change from baseline ranging between -1.7 and -5.3 points). A four-point change on the ADAS-Cog over 6 months is regarded as clinically meaningful in AD[70]. Several cognitive domains (memory, language, praxis and attention) assessed in the ADAS-Cog also showed significant improvement in AD patients[45]. The ADAS-Cog is less suitable for assessing cognitive changes in MCI, but significant improvements were reported in this population in several cognitive tests assessing episodic memory, language, executive function and processing speed following 6 months of kMCT supplementation[22,42]. Three of the six trials reporting cognitive improvement found that increased blood βHB was positively associated with cognitive changes in memory[22,46], executive function[22,42], processing speed[42], language[22,42] and ADAS-Cog scores[68]. A recent meta-analysis including four of the RCT listed in Table 1 also concluded that kMCT significantly improved cognition in a combined measure (ADAS-Cog combined with the Mini-Mental State Examination; weighted mean differences = -0.289) in MCI and AD[39]. Case reports involving a prolonged daily intake of kMCT in AD patients also showed a great improvement in cognition - ADAS-Cog[71] and Montreal cognitive assessment (MoCA)[72]. These encouraging results imply that at least a proportion

of the dysfunctional brain cells are energy (glucose)-starved but not yet dead, with ketones improving cognitive function by restoring or rescuing their energy status. A daily dose of 17 g of kMCT was sufficient to observe a significant positive effect on cognitive outcomes in AD patients[45]. However, much higher daily doses are probably needed to fully compensate for brain glucose deficit in MCI[42]. Giving kMCT as a single dose also significantly improved cognition in MCI and AD[46]. A daily intake of kMCT for only four weeks resulted in a significant improvement in four cognitive domains (memory, language, praxis and attention) in AD patients[45]. Nevertheless, daily intake over a prolonged period may be required to continuously restore the fuel supply to brain cells and maintain prolonged cognitive benefits.

d) Impact of ApoE4

The ApoE4 polymorphism is a major risk factor for the development of late-onset AD. Some of the RCT evaluating kMCT supplementation included in Table 1 suggest that ketogenic interventions might be less effective for brain function in individuals carrying the ApoE4 gene. Some trials reported that although maximal blood βHB was similar between carriers and non-carriers, ApoE4 carriers did not have improved cognitive performance (ADAS-Cog)[46,68] or regional cerebral blood flow[69] in MCI or AD. Fortier et al.[22] reported that fewer cognitive domains were improved after kMCT supplementation in MCI ApoE4 carriers vs non-carriers. However, most clinical trials were not adequately powered to assess the effect of ApoE4 status, so additional research is needed to determine how the ApoE gene may mediate βHB efficacy.

e) Safety

Providing kMCT in doses of up to 1 g/kg/day acutely or daily over several months has a robust safety record in all the species studied, including humans[73]. Of the ten clinical trials (Table 1), only one reported severe adverse events in ~1% of patients (gastrointestinal effects)[74]. Gastrointestinal adverse effects, mostly diarrhea and abdominal or stomach discomfort, albeit also reflux, nausea, bloating and constipation, were reported in seven of these ten trials. Most adverse events were transient and dose-related. Strategies such as splitting the total daily dose into multiple doses help to control gastrointestinal side effects and increase patient compliance. Xu et al.[45] reported no gastrointestinal adverse events in AD patients when kMCT were consumed three times daily. Concurrent aerobic exercise potentially increases the ketogenic effect of kMCT in MCI and AD. Indeed, a synergic effect between kMCT and aerobic exercise on blood ketones was recently shown in older women with or without pre-diabetes[75].

3. Conclusion

Neuroketotherapeutic strategies for countering MCI are relatively simple and effective ways of moderately increasing blood ketones in older people. The consumption of kMCT is safe both for healthy adults and older people with cognitive decline. Encouraging results from several clinical trials in which MCI or AD patients consumed kMCT supplements point to a significant improvement in outcomes in several cognitive domains. Improved cognition after kMCT supplementation is partly attributable to increased brain ketone uptake, the brain's main alternative fuel to glucose. Indeed, bypassing the chronic brain energy (glucose) deficit in MCI by providing ketones as an alternative fuel improves global and regional brain energy status. The clear implication is that at least a part of brain dysfunction is due to energy (glucose)-starvation that could be bypassed or possibly reversed. Considering these promising results, and the ineffectiveness of current potential therapies for MCI, rescuing brain energy (glucose) deterioration with ketogenic supplements such as kMCT is now a promising neurotherapeutic strategy for aging-associated cognitive decline.

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