



Ockham Technical Synopsis is a recurring series prepared for internal staff and consultants of Ockham Development Group Inc. (Ockham). Highlighting current and emerging issues and challenges in clinical research, these publications are intended to disseminate intelligence captured during the execution of key clinical trials and are therefore updated on a continuous basis.

MILD COGNITIVE IMPAIRMENT (MCI)

OVERVIEW

Epidemiologic studies of aging and dementia have demonstrated that the use of research criteria for the classification of dementia identifies three groups of subjects:

- Those who are demented
- Those who are not demented
- Individuals who cannot be classified because they have a cognitive (memory) impairment but do not meet criteria for dementia.

In the recent literature, attention has been paid to the transitional stage of cognitive impairment between normal aging and early Alzheimer's Disease (AD), so-called Mild Cognitive Impairment (MCI). However, the definitive course of cognitive function in normal aging has not been determined.

As of 1990, there were 4 million individuals in the United States with AD. This number is expected to increase to 14 million by 2050. In 1998, the annual cost for the care of patients with AD in the U.S. was approximately \$40,000 per patient. If one were able to treat mild cognitive impairment successfully such that the progression of these individuals to AD could be delayed by one year, the impact on public health would be great.

MILD COGNITIVE IMPAIRMENT (MCI)

Mild cognitive impairment (MCI) refers to cognitive impairment that does not meet the criteria for dementia. The Mayo criteria are the ones most commonly applied in the literature:

- Memory complaint, preferably corroborated by an informant
- Objective memory impairment (for age and education)
- Preserved general cognitive function
- Intact activities of daily living
- Not demented

It is important to emphasize that these criteria are imprecise. Considerable judgment is involved in making the distinction between impairments that are normal for the elderly population and, on the other extreme, that do not represent dementia.

Memory impairments that qualify for MCI are generally represented by defects that are 1.5 standard deviations (SD) or more below age-corrected norms. While this seems straightforward, different tests of memory likely have different sensitivity and specificity, and norms are not available for all populations. Many individuals with amnesic MCI complain only of memory loss; however, they may have additional subtle impairments in other cognitive domains that are revealed with careful neuropsychological testing.

Amnesic MCI is often thought of as a precursor to AD. Although memory performances are often similar in patients with amnesic MCI and AD, impairments in multiple cognitive domains are also prominent in patients with AD.

AGE-ASSOCIATED MEMORY IMPAIRMENT (AAMI)

"Age-associated memory impairment" and "age-associated cognitive decline" are also widely used and fairly well-known terms.

Age-associated memory impairment (AAMI) refers to the concept of increasing memory impairment with age and references memory function in the elderly cohort to young normal adult subjects. As such, there can be an overinclusion of neurologically normal individuals in this concept, and it has been critiqued as such.

Age-associated cognitive decline refers to the concept of mild impairments in multiple cognitive domains but not of sufficient severity to constitute the diagnosis of dementia. The concept of AAMI suggests that clinically recognized memory dysfunction can be a feature of normal aging. However, recent studies have suggested that AAMI may represent a dementia prodrome rather than a benign variant of aging.

Findings from epidemiological studies vary significantly, partially due to the differing diagnostic criteria, measuring instruments, and definitions. In cohorts and treatment trials that more strictly apply the criteria for amnesic MCI, prevalence rates in elderly populations are estimated between 2% and 4%.

Studies using different measures – e.g., "age-associated cognitive decline," "cognitive impairment, no dementia," and "minimal dementia" – estimate higher prevalences of 16% to 19%. Gender, race, increased age, and lower education are inconsistently associated with MCI in various studies. Elevated blood pressure (even in the absence of symptomatic cerebrovascular disease) and apolipoprotein E epsilon 4 (e4) genotype also been associated with the risk of MCI, particularly amnesic MCI.

CONVERSION TO DEMENTIA

Rates of conversion from MCI to dementia have been estimated from treatment trials and population cohorts. In elderly populations, annual rates range from 8% to 16%. This contrasts with incidence rates for AD in the general population of 1% to 2% per year. Aging is a primary predictor of progression of MCI to AD. With every year of age increase, MCI is slightly more likely to convert to AD. In various studies, a substantial percentage (11% to 40%) of patients with MCI improve, even to normal, over a one to three-year follow-up time.

Given the heterogeneity of outcomes among individuals with MCI, many studies have investigated factors that might further identify those with MCI who will develop dementia, including age, lower performance on cognitive measures, Apolipoprotein E (APOE) e4 genotype, cerebrospinal fluid (CSF), temporal lobe atrophy, regional patterns of cortical hypometabolism using fluorodeoxyglucose (FDG) positron emission tomography (PET), a relatively greater preponderance of informant- over self-reported symptoms. Other factors of importance are obesity and low vitamin B₁₂, depression.

Patients with MCI, particularly the amnesic subtype, complain primarily of impaired memory. While impaired awareness of deficits is a hallmark of patients with AD, patients with MCI are often particularly troubled by their symptoms. However, over time, patients with MCI who convert to AD shift to a relatively greater preponderance of informant- over self-reported symptoms. This phenomenon may be helpful in following an individual patient's progression to dementia.

As with dementia, behavioral symptoms are common in patients with MCI, including depression, irritability, anxiety, aggression, and apathy. Patients with behavioral symptoms were significantly more impaired on cognitive measures than those without behavioral symptoms.

NEUROPROTECTION

The brain's ability to reorganize itself by forming new neural connections throughout life, or neuroplasticity, allows the neurons to compensate for injury and disease and to adjust their activities in response to new situations or to changes in their environment. Brain reorganization takes place by mechanisms such as "axonal sprouting" in which undamaged axons grow new nerve endings to reconnect neurons whose links were injured or severed. Undamaged axons can also sprout nerve endings and connect with other undamaged nerve cells, forming new neural pathways to accomplish a needed function.

Methods to recreate the early restorative potential of the brain would have great potential for reversing the debilitating features of many neurologic and psychiatric diseases. Over the last several years the roles of neurotrophic factors in guiding the development of the nervous system has been better delineated. An exciting development in the neurosciences has been the realization that neurotrophic factors play important roles in the adult brain. After development these factors participate in the ongoing remodeling of neuronal function that underlies the adaptability or plasticity of neurons.

In recent studies of dementia major themes addressed are the loss of synaptic connections as vulnerable neurons die and circuits deteriorate in AD and the absence of significant neuron loss but potential synaptic alteration in the same circuits in AAMI.

Other trials are looking at cognitive decline seen in the normal elderly and in elderly subjects with AAMI, targeting specific neuronal deficits (Targacept, Inc., ispronidine).

COMMENTS FOR CLINICAL DEVELOPMENT

New strategies used to identify people with dementia or cognitive impairment include telephone interviews – a promising and relatively inexpensive strategy for identifying potential participants in intervention and clinical research studies and for classifying subjects in epidemiologic studies.

Currently the focus of drug development remains on the treatment of established dementia, and the tools used may not be adequate for the assessment of outcomes in conditions where cognition is affected to a lesser degree. The choice of

assessment tools should remain open, as the science progresses.

Data to evaluate the efficacy or effectiveness of treatment can come from a variety of sources, including laboratory tests, clinician evaluation, and the patients themselves. In the outcomes research community, the term *patient-reported outcomes* (PRO) is used to refer to a host of outcomes that can be provided only by the patient. Examples of these outcomes include symptom severity, perception of daily functioning, feelings of well being, global impressions of the impact of treatment on daily life, satisfaction with treatment, and health-related quality of life. The role that PROs can and should play in evaluating the efficacy of pharmaceuticals and medical devices and the means by which these outcomes are communicated to clinicians and consumers are subjects of much discussion and debate.

PRO instruments are included in clinical trials for new medical products because (1) some treatment effects are known only to the patient; (2) there is a desire to know the patient perspective about the effectiveness of a treatment; or (3) systematic assessment of the patient's perspective may provide valuable information that can be lost when that perspective is filtered through a clinician's evaluation of the patient's response to clinical interview questions.

In *Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*, it is stated that the adequacy of a PRO instrument as a measure to support medical product claims depends on its developmental history and demonstrated measurement properties.

Sponsors are encouraged to identify all endpoint measurement goals early in product development, before studies are initiated, to provide the basis for product approval or claim substantiation, allowing adequate time for PRO instrument identification, modification, or if necessary, new instrument development. A new PRO instrument can be developed or an existing instrument can be modified if sponsors determine that none is available, adequate, or applicable to their product development program.

Additionally, FDA is interested in the opportunities for streamlining clinical trials that ePRO methods promise, keeping in mind the potential threats to validity, beyond those due to system malfunction, and that may not be easily detected with traditional psychometric validation tests.