Mild Cognitive Impairment

By James M. Ellison, MD, MPH

In the effort to characterize, detect, and treat dementia, the concept of mild cognitive impairment (MCI) has acquired considerable credibility during the past decade. Beginning with Krai's description of benign senescent forgetfulness in 1962, clinical criteria of increasing specificity and validity have been proposed for identification of individuals functioning in the uncertain area between normal cognitive aging and dementia. In comparison to normally aging adults, those with clinical MCI, and particularly those with the amnestic subtype of MCI, are more functionally impaired, more likely to show Alzheimer's-like neuropathological changes and imaging abnormalities, and more likely to convert to Alzheimer’s disease or other dementias.

This issue of CNS Spectrums addresses the nature and significance of MCI from three distinct viewpoints. The three articles included here should provide the reader with a solid basis for understanding the nature of MCI, detecting its clinical presence, characterizing its subtype, planning comprehensive treatment, appreciating the value of psychiatric appraisal of associated noncognitive symptoms, and evaluating the significance of ongoing MCI research.

The review by Ron Petersen, MD, PhD, and Selamawit Negash, PhD, provide an authoritative overview of the evolution and recognition of MCI as a clinical entity. The authors explain the historical and revised diagnostic criteria for MCI and its subtypes and describe an algorithmic approach to clinical evaluation and management. An overview of research on MCI discusses epidemiologic findings, the significance of several biomarkers, and the neuropathologic findings reported from several autopsy studies. The section on treatment reviews the most significant pharmacologic treatment studies and also describes what has been learned about the preventive value of lifestyle factors including cognitive stimulation and nutritional factors. The clinical approach to MCI described in this article by Petersen and colleagues is organized, practical, and grounded in the best evidence available.

The next article deepens the discussion of clinical assessment by describing a state-of-the-art approach to neuropsychological assessment of MCI patients. Aaron P. Nelson, PhD, and Margaret G. O’Connor, PhD, masterfully walk the reader through the process of evaluation, beginning with the patient’s complaint and the collection of elucidating data from an informant. They explore the relative usefulness of population norms versus intra-individual comparisons for assessing MCI’s presence and severity. They describe the “hypothesis testing” assessment approach and characterize the testing instruments of greatest value in detecting and subtyping MCI, considering its differential diagnosis, and gauging the magnitude of impairment in specific cognitive domains. Readers without advanced neuropsychological training will find the discussion of testing domains and instruments interesting reading and practical reference material.

The final MCI article reports findings from a small study of MCI patients viewed through a different lens, one focused on concurrent mood and behavioral symptoms rather than cognitive ones. Although MCI has been defined solely on the basis of impairments in memory or other cognitive functions, the high prevalence of noncognitive mood and behavioral symptoms in MCI patients has been noted in several large population-based or clinical studies. Assessment with the Neuropsychiatric Inventory (NPI) has found noncognitive symptoms in up to 75% of MCI subjects, and these noncognitive symptoms are often the ones that lead to psychiatric consultation. Depression, nighttime behaviors, irritability, agitation, apathy, and anxiety are the NPI symptoms most frequently detected in MCI patients. Depression may be difficult to rec-
Introduction

Recognize in a cognitively impaired patient but its presence impairs function and undermines quality of life. The presence of NPI symptoms in MCI patients, as discussed in this report by James M. Ellison, MD, MPH, and colleagues, may have both clinical and prognostic significance in work with MCI patients. In this preliminary study, a high rate of NPI symptoms was found in MCI patients evaluated by a psychiatric hospital’s outpatient memory clinic. Within the limitations of the study’s methodology, the presence of apathy appeared more closely linked with amnestic than non-amnestic MCI, while the presence of nighttime behaviors appeared more closely linked with non-amnestic MCI. Depression was very common in both MCI subgroups.

The characterization and investigation of MCI has had far-reaching effects on our understanding of normal and pathological cognitive aging. Readers should emerge with a richer appreciation of MCI’s definition, construct validity, clinical significance, and management. In addition, these articles point toward some of the expected refinements in diagnostic and treatment approaches that will shape our care of aging and elderly patients in the future.

REFERENCES

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GEODON is indicated for the treatment of acute manic or mixed episodes associated with bipolar disorder and for the treatment of schizophrenia.

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. GEODON is not approved for the treatment of patients with dementia-related psychosis.

GEODON is contraindicated in patients with a known history of QT prolongation, recent acute myocardial infarction, or uncompensated heart failure, and should not be used with other QT-prolonging drugs. GEODON has a greater capacity to prolong the QTc interval than several antipsychotics. In some drugs, QT prolongation has been associated with torsade de pointes, a potentially fatal arrhythmia. In many cases this would lead to the conclusion that other drugs should be tried first.

As with all antipsychotic medications, a rare and potentially fatal condition known as neuroleptic malignant syndrome (NMS) has been reported with GEODON. NMS can cause hyperpyrexia, muscle rigidity, diaphoresis, tachycardia, irregular pulse or blood pressure, cardiac dysrhythmia, and altered mental status. If signs and symptoms appear, immediate discontinuation, treatment, and monitoring are recommended.

Prescribing should be consistent with the need to minimize tardive dyskinesia (TD), a potentially irreversible dose- and duration-dependent syndrome. If signs and symptoms appear, discontinuation should be considered since TD may remit partially or completely.

Hyperglycemia-related adverse events, sometimes serious, have been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia or diabetes in patients treated with GEODON, and it is not known if GEODON is associated with these events. Patients treated with an atypical antipsychotic should be monitored for symptoms of hyperglycemia.

Precautions include the risk of rash, orthostatic hypotension, and seizures.

The most common adverse events associated with GEODON in bipolar mania were somnolence, extrapyramidal symptoms, dizziness, akathisia, and abnormal vision.

In short-term schizophrenia trials, the most commonly observed adverse events associated with GEODON at an incidence of ≥5% and at least twice the rate of placebo were somnolence and respiratory tract infection.

In short-term schizophrenia clinical trials, 10% of GEODON-treated patients experienced a weight gain of ≥7% of body weight vs 4% for placebo.
Increased Mortality in Elderly Patients with Dementia-Related Psychiatric: Elderly patients with dementia-related psychiatric disorders treated with typical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials involving over 1,000 patients with dementia-related psychiatric disorders were reported as part of the data, treatment-emergent adverse events which appear to be dose-related include hypotension, bradycardia, syncope, seizures, cardiac arrest, cerebrovascular accidents, arrhythmias, myocardial infarction, and sudden death. These events appeared to be dose-related and occurred primarily in elderly patients treated with quetiapine. No deaths were reported in placebo-treated patients. Over the course of a typical 10-week trial, the rate of death in drug-treated patients was about 4%, whereas in placebo-treated patients it was about 1%. Because the risk of death from all causes is greater in older patients in general, especially those with dementia, it is possible that the increased mortality observed with antipsychotic drugs may be placebo-controlled trials which comparing quetiapine to placebo in elderly patients with a diagnosis of Alzheimer's disease were conducted. These studies are ongoing and have not yet been published. In one study, quetiapine was compared to placebo in patients with dementia-related psychiatric disorders and the results are consistent with those reported in other trials of quetiapine in elderly patients with dementia-related psychiatric disorders. In this study, the rate of death in quetiapine-treated patients was about 5% compared to about 1% in placebo-treated patients. It is not known whether these differences are statistically significant. However, the results of this study suggest that quetiapine may have a similar effect on mortality in elderly patients with dementia-related psychiatric disorders treated with quetiapine. It is possible that these differences are due to differences in the design of the studies or differences in the way deaths are reported. The results of these studies should be interpreted with caution, as they are based on small samples of patients and may be subject to other biases. In addition, the results of these studies may not be generalizable to other populations of patients with dementia-related psychiatric disorders. The safety and efficacy of quetiapine in patients with dementia-related psychiatric disorders treated with quetiapine have not been established. It is not known whether quetiapine is effective in patients with dementia-related psychiatric disorders treated with quetiapine. 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