Cognitive Impairment Associated With Depression in the Elderly

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Introduction

In the United States and worldwide, the group of people 65 years and older is the most rapidly growing population. By the year 2030, this older population is projected to be more than twice as large as it was in 2000, growing to 72 million in the United States (974 million worldwide) and comprising almost 20% of the total U.S. population.[1] The group of individuals 85 years and older is expected to expand especially rapidly until and after 2030 as the Baby Boomer generation ages.[1] With the increase in this population, the late-life health issues of depression and dementia will increase, calling for improved diagnostic and treatment approaches and a more complete understanding of the relationship between these disorders. Steven P. Roose, M.D., gathered experts in the fields of dementia and depression to discuss and address these issues. Their presentations offer insight into the complex relationship between cognitive impairment and depression and provide strategies that address these conditions.

Genetics of Alzheimer's Disease: Insights for Therapy

Richard Mayeux, M.D., M.Sc., stated that insights into genetic variants associated with Alzheimer's disease (AD) have led to the development of animal models of AD and have identified pathways with multiple targets primed for the development of treatments.

Gene Variants Involved in AD

Dr. Mayeux explained that the gene variants amyloid precursor protein (*APP*), presenilin, apolipoprotein E (*APOE*), and *SORL1* have been known to cause AD or susceptibility to it. All of these genes affect either the production or the processing of Aβ, which is the key to therapy. The protein tau is also involved in the processing of amyloid-β (Aβ), a relationship that has also been associated with AD.

APP *and presenilin.* The *APP* gene and presenilin 1 (*PS1*) and presenilin 2 (*PS2*) genes are mutations occurring in an autosomal dominant fashion that cause the disease to occur at very early ages, between 30 and 70 years. People with these mutations invariably develop the disease.

APP is a ubiquitous transmembrane protein, which generally undergoes proteolytic cleavage by α-secretase enzymes, forming a soluble *APP* α-secretase protein (APPsα), which is recycled and excreted.[2] A small portion of the APPsα (about 5%) undergoes proteolytic cleavage by β-secretase, forming the APP β-secretase protein (APPsβ), which is insoluble. APPsβ goes on to form Aβ, which is normally transported out of the cell and extracellular space. *SORL1* sorts *APP* into the recycling pathways, but if someone has less *SORL1*, *APP* is directed into the β-secretase cleavage pathway, increasing APPsβ production, then ultimately to the γ-secretase pathway to generate Aβ. Any mutation in *APP*, presenilin 1, or presenilin 2 affects the γ-secretase pathway, increasing the amount of Aβ. Amyloid-β is then converted to an oligomer, which may account for neuronal cell death and many of the cognitive and behavioral

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abnormalities seen in AD.[3] Dr. Mayeux explained that senile plaques, or accumulations of Aβ deposits, do not necessarily correlate directly with cognitive and behavioral abnormalities during life but rather indicate a secondary toxic process that changes the protein formation or structure.[3,4]

APOE. The *APOE* gene provides instruction for forming the protein apolipoprotein E (ApoE), and 3 different alleles of *APOE* (*APOE*E2*, *APOE*E3*, and *APOE*E4*) encode the 3 slightly different forms of ApoE (E2, E3, and E4). Of the 3 *APOE* alleles, *APOE*E4* normally occurs in about 25% of the population and increases a person's risk for AD.[5] Inheriting 1 copy of *APOE*E4* increases the risk for AD about 2-fold, but inheriting 2 copies increases the risk 5- to 6-fold.

ApoE is required for neuronal maintenance and repair and is upregulated in trauma, stroke, and oxidative stress. ApoE3 and ApoE2 effectively maintain and repair neuronal cells, but ApoE4 may be responsible for the negative effects that ApoE has on the central nervous system, including excess Aβ. Amyloid-β42 is a fibrillar form of Aβ and constitutes the basis of amyloid plaque. Dr. Mayeux noted that ApoE may also cause proteolysis and translocation of ApoE4 fragments in the cytosol, which is also toxic to nerve cells.

SORL1. The *SORL1* gene, which occurs in both the familial and sporadic forms (like *APOE*), may lead to the late-onset form of AD.[2] *SORL1* also affects the *APP* processing step. Normally, *SORL1* acts as a switch that determines whether *APP* goes into the Golgi secretory pathway for the recycling endosome process or into the late-stage endosomal pathways to form APPsβ, which goes on to create Aβ. People with the haplotype that is associated with AD make less *SORL1*, which interferes with the recycling step and causes a shift in which more of the β-secretase is created and subsequently the Aβ formation occurs. Dr. Mayeux suggested that this may be how *SORL1* affects AD risk.[2]

Tau. The protein tau forms the basis for neurofibrillary tangles, which occur secondary to generation of Aβ and may be diagnostic of AD.[6] Because tau protein holds together the microtubule system within the synapses, the phosphorylation of tau by an increase in Aβ destabilizes the microtubules. This impairs axonal transport and leads to a cycle of neuronal cell death, causing paired helical filaments called neurofibrillary tangles, which also increases neuronal cell death. Although neurofibrillary tangles are common in AD, mutations in the tau protein actually lead to frontotemporal dementia, not AD.[3] Aβ- and tau-mutant mice, which reflect both the senile plaques and the neurofibrillary tangles found in AD, show not only the pathology similar to human Alzheimer's patients but also learning problems and sub-behavioral problems, which provides an opportunity for researching how to treat this condition.

Therapeutic Strategies for AD

Dr. Mayeux stressed that improved treatment strategies for AD would have an important public health impact. In fact, one study[7] found that if an intervention could delay the onset of AD by 2 years, almost 2 million fewer cases would appear in the United States over the next 50 years. Even delaying the onset by 6 months could produce a remarkable reduction in the number of cases over the next 10 to 50 years.

APP *processing.* *APP* processing may be involved in creating 2 potential therapeutic targets for AD, amyloidogenic (producing Aβ, which is neurotoxic but degrades into inactive fragments) or nonamyloidogenic (producing soluble APPsα, which may be protective).[8] Dr. Mayeux explained that the *APP* processes may offer opportunities for therapeutic intervention.

β-Secretase inhibition. The inactivation of β-secretase (BACE1) may successfully reduce amyloid production, lowering the neurogenerative and behavioral deficits in *APP* transgenic mice.[9] Lentiviral vectors expressing silencing RNAs (siRNAs), which target BACE1, decrease Aβ and improve behavior. However, Dominguez et al.[10] found some problems with BACE1-knockout mice, which may challenge the safety of BACE1 inhibitors. For example, BACE1-knockout mice made almost no Aβ in neurons, but Aβ generation was not blocked in glia, and the number of glia in the brain was greater than the number of neurons. These mice also showed early mortality and small body size compared with their littermate controls. The surviving BACE1-knockout mice were treated with a siRNA, which did, in fact, decrease the amount of Aβ produced and improve behavior. BACE inhibitors are currently under development.[11]

γ-Secretase regulation. Another potential site of therapeutic intervention is γ-secretase, which is an important site for *APP* processing where the presenilins act in collaboration with other integral membrane proteins, nicastrin, Aph-1, and Pen-2.[12] Allosteric regulation of γ-secretase could selectively inhibit or modulate *APP* processing without interfering with Notch signaling, which could subsequently decrease the production of Aβ. Dr. Mayeux stressed that presenilin is required for the amyloid intracellular domain and for the processing of Notch; interfering with it entirely is harmful, and presenilin-knockout mice often die. Those mice that survive often have lymphocytic problems and intestinal damage. However, the drug flurbiprofen, a nonsteroidal anti-inflammatory agent, has been shown to alter the proteolytic cleavage of γ-secretase and decrease the amount of Aβ.[13] Flurbiprofen and its racemic form, r-flurbiprofen, have decreased the amount of Aβ in the brain in both human[14] and animal trials.[13]

α-Secretase activation. One alternative to β-secretase and γ-secretase inhibitors is α-secretase activation, which would prevent the release of the insoluble Aβ and would increase the

secretion of soluble *APP*. Existing drugs such as muscarinic agonists, the hormones estrogen and testosterone, statins, and protein kinase C activators activate the α-secretase pathway and may be a safer treatment for AD than some of the currently approved AD medications.[15,16]

The Aβ monomer may be a safe component, but toxicity occurs as it goes on to form oligomers, fibrils, diffused plaques, and plaques. Enzymes such as neprilysin,[17] insulin-degrading enzyme,[18] endothelin-converting enzyme,[17] and plasmin[19] have also been shown to interfere with some of these steps in the processing of Aβ, which is a positive step toward the treatment of AD.

Immunization. The mechanism of action behind the effects of Aβ immunization seems to be that Aβ antibodies activate microglial cells that clear Aβ.[20] Research[20–22] has demonstrated that Aβ can be rapidly processed from the brain to plasma, inhibiting the fibril formation and the cytotoxicity of nerve cells. One immunologic therapy for AD is an active synthetic form of Aβ. A review[23] of immunologic clinical trials reported that 6% of the patients who received this active vaccination developed meningoencephalitis. In some, it was fatal and led to halting the trial. A postmortem investigation of these patients found virtually no plaques; tangles were still present, but there was a slower rate of cognitive decline and some evidence of Aβ elimination. A passive vaccine, in which antibodies against Aβ42 are infused into patients, has been developed in response to the problems associated with the active vaccine.[23]

Lithium. Lithium has been discovered to be a potent inhibitor of glycogen synthase kinase (GSK), which is a major tau kinase. Preliminary studies[24,25] have shown that lithium and other available GSK-inhibitors may decrease the amount of tau in the brainstem. Dr. Mayeux noted that studies are underway to determine whether these agents could advance the area of treatment for AD.

Conclusion

Dr. Mayeux added that not all of the genes potentially involved in AD have been identified. A host of other genes identified in families have shown an involvement in the processing of Aβ, and some candidate genes that have been identified in case-control studies may also provide information about potential targets or pathways that are important in the treatment of AD.[26]

Dr. Mayeux concluded that the clinical applications of genetics to the treatment of AD are critical. One advantage to the study of genetics is that it homogenizes the disease, allowing clinicians to treat people with a common set of genes such as *APOE* or presenilin. Genetic knowledge would also allow clinicians to engage in either primary or secondary prevention and make risk-benefit assessments. A problem with genetic testing for late-onset diseases is that it will invariably involve genetic counseling and the ethical responsibility of stored DNA for the offspring of patients with AD. Nevertheless, the promise of genetic study is the prevention of these types of diseases in the future.

The Biology of Depression and Dementia

Depression and dementia can be difficult to differentiate in older people. Because the occurrences of both dementia and the cognitive symptoms associated with depression increase with age, patients often present with combined symptoms. Cognitive symptoms may be missed when mood symptoms are prominent at the initial presentation, and mood symptoms may be overlooked if cognitive symptoms are the chief complaint. Gary W. Small, M.D., said that depression and dementia share some underlying biological determinants and clinical correlates and that it is important to understand the biology of these conditions and their correlation to provide more effective interventions and work toward the broader clinical goal—to help patients live longer and maintain brain health.

Depression increases the risk for mild cognitive impairment (MCI)[27] and dementia[28] and can predict future cognitive decline in patients already experiencing a cognitive impairment.[29] The progression of cognitive symptoms leading up to an AD diagnosis is often accompanied by changes in behavior,[30] including social withdrawal, depression, paranoia, and anxiety. After the diagnosis of AD, depression continues to be a psychopathologic feature, in addition to aggression, agitation, wandering, and delusions.[31] These observations suggest that some late-life mood symptoms are an initial presentation of a neurodegenerative process.

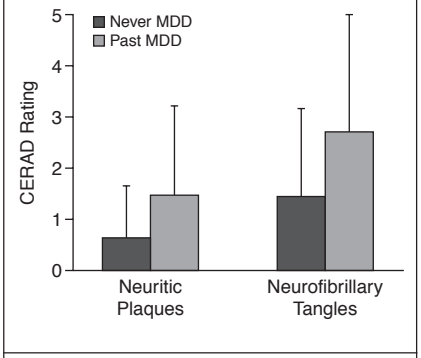
Neurodegeneration

In addition to mood changes, there are multiple other possible causes of and contributing factors to the neurodegeneration inherent in dementia. Dr. Small hypothesized that neurotransmitter deficits could be a possible cause because a decline occurs in cholinergic and other neuronal systems in AD and even with normal aging. In general, nerve transmission is reduced with aging, and a decline in brain circulation takes place. Age-related medical illnesses such as diabetes and hypertension can affect cognition as well, and neuroinflammation is also thought to be involved in neurodegeneration. Finally, abnormal brain protein deposits—amyloid plaques and tau neurofibrillary tangles—are a hallmark of AD, the main form of neurodegeneration in old age. These protein deposits build up even in normal aging, but they are considered central to the development of AD.

Neuroanatomy of Dementia and Depression

Positron emission tomography (PET) scans of glucose metabolism, which reflects synaptic activity, reveal consistent patterns of neuronal activity deficits specific to various types of illness.[32] Human behavior, including

Figure 1. History of Major Depressive Disorder and Alzheimer's Disease Pathology[a]



[a]Reprinted with permission from Rapp et al.[39] Abbreviation: CERAD = Consortium to Establish a Registry for Alzheimer's Disease.

executive dysfunction, disinhibition, and apathy, is regulated by the frontal-subcortical circuits in the brain; different disorders can cause dysfunction in the cortical area, the subcortical area, or both.[33] While AD and frontotemporal dementia are seen as causing cortical dysfunction, vascular dementia and depression are seen as causing both subcortical and cortical dysfunction.

Depression has been observed in patients with lesions in the frontal cortex and caudate nucleus, and reduced frontal and dorsolateral prefrontal metabolism has been found in depressed patients with a variety of neurodegenerative diseases, including Alzheimer's, Parkinson's, and Huntington's diseases.[33] Depression may also follow dorsolateral prefrontal as well as basal ganglia strokes.

Hippocampal Atrophy

Dr. Small reported that medial temporal atrophy, particularly involving the hippocampus, is associated with impaired memory function.[34] The rate of volume loss in the medial temporal regions often predicts future cognitive decline. Annual volume loss in the entorhinal cortex, the main neocortical input to the hippocampus that is responsible for the familiarity of input signals, is significantly greater in early AD compared with normal aging.[34]

Hippocampal volume is similarly reduced in patients with depression.[35,36] A study[37] of 38 women with recurrent depression in remission found a significant ($p = .0006$) inverse correlation between total hippocampal volume and days of untreated depression. The degree of atrophy is positively correlated with recurrence and longer duration of depression,[35,36] and volume changes may persist after remission of depression.[36]

Amyloid Plaques and Neurofibrillary Tangles

Although the accumulation of amyloid plaques and neurofibrillary tangles is characteristic of normal aging, their increased deposition is the neuropathologic evidence of AD. In patients with AD, there is a high density of plaques and a few tangles in the lateral temporal region; in the medial temporal region, there are a few plaques and a high density of tangles.[38]

A recent study[39] examined the role of major depressive disorder in AD pathology. Patients with AD and a lifetime history of major depressive disorder (MDD) had higher levels of hippocampal neuritic plaques and neurofibrillary tangles than patients with AD without a history of MDD (Figure 1). These results suggest that plaque and tangle deposition may not only relate to cognitive symptoms but also to depressive symptoms.

Physical Exercise and Stress in Dementia and Depression

Physical exercise can affect mood and the risk for dementia.[40] Exercise increases endorphins, the body's natural antidepressants, thereby improving mood, at least in the short term. Cardiovascular fitness is associated with greater parietal, temporal, and frontal cortical tissue,[41] and physically active adults have a lower risk for AD than inactive ones.[40]

Life stressors may lead to depression or anxiety and are associated with impaired memory and concentration, explained Dr. Small. Laboratory animal studies[42] show that chronic stress actually leads to adverse effects in the hippocampus—including disruption of synaptic plasticity, atrophy of dendritic processes, and compromise of neuronal survival of coincident insults—and consequently, impaired memory. In humans, the injection of the stress hormone cortisol impairs memory in otherwise healthy individuals.[43]

Genetic factors, specifically the serotonin transporter gene (5-HTT), affect the influence of stress on depression.[44] The 5-HTT gene has 2 alleles or forms—a short allele and a long allele. People with 1 or 2 copies of the short allele have a higher risk for depression and suicidality in the face of stressful life events than people with 2 copies of the long allele.[44]

Conclusion

Dr. Small ended by emphasizing that depression and dementia overlap clinically and in their underlying neuropathology and consequent neurodegeneration. Treatments developed for each condition have both cognitive and mood effects, and treatment of depression may prevent neurodegeneration and even enhance neurogenesis.[45] Further research elucidating the underlying biology is necessary to develop more effective treatments for both conditions.

The Role of Vascular Disease in Late-Life Depression and Dementia

K. Ranga R. Krishnan, M.D., discussed the role of vascular disease in leading to depression and cognitive impairment and dementia in later life. The geriatric population are at increased risk for hyperintensity, or lesions, in the brain's white and gray matter, or what Dr. Krishnan called *silent strokes*. When these strokes occur in certain critical regions of the brain, depression can result, as well as an increased possibility for the development of memory problems and dementia over time.

Vascular Disease and Depression

Vascular depression is associated with ischemic changes in the subcortical region of the brain, such that *vascular depression* may be more accurately named *subcortical ischemic vascular depression* (SIVD).[46] One study[47] developed a statistical parametric map of brain lesions in subjects with depression and nondepressed controls. After subtracting the lesions common to subjects without depression, researchers found that lesions in the medial orbital prefrontal cortex were associated with the occurrence of depression. Researchers also performed tests to determine if lesion location was associated with depression severity as rated by the 17-item Hamilton Rating Scale for Depression (HAM-D). A correlation was found between severity of depression and lesions in the medial orbital region of the brain. Lesions in the basal ganglia are also associated with SIVD.[48] The Cardiovascular Health Study,[49] which examined approximately 3660 people from 4 communities, found that people aged 65 years or older who had more large cortical white-matter lesions, small lesions in the basal ganglia, or more severe subcortical white-matter lesions were at higher risk of developing depressive symptoms.[48]

SIVD differs from other forms of depression[46]; patients with SIVD are typically older and experience a later onset of depressive symptoms, have less family history of mental illness, and have an increased incidence of risk factors for stroke, such as high blood pressure and diabetes, than other depressed patients. Patients with SIVD also experience more fatigue, retardation, memory problems, and functional impairment and tend toward less agitation and less loss of libido.

Impact of the progression of vascular disease on depression outcomes. Dr. Krishnan explained that vascular disease is generally progressive. One study[50] using magnetic resonance imaging (MRI) found a mean increase of 26.7% in white matter hyperintensity (WMH) volume at 2-year follow-up compared with baseline. The progression of vascular disease has a negative impact on the outcome of late-life depression. A 2-year study[51] of 133 patients with MDD and a mean age of 68.6 years measured response to antidepressant treatment as either "good" or "poor." The group with a good outcome had an 11.5% increase in WMH volume, while the group with a poor outcome experienced a WMH volume increase of 31.6% ($p = .01$). Change in WMH volume was found to be the factor most significantly associated with a poor outcome for depression during the course of the study ($p = .04$). In other words, according to Dr. Krishnan, the more the vascular disease progresses, the less likely it is that a patient will achieve or maintain remission from depression.

Treatments for vascular depression. Antidepressants can be used to treat SIVD. However, since progression of vascular disease is associated with a worse outcome for depression, a treatment that could modify the vascular disease might increase the likelihood of remission from depression.

One type of treatment that has been used for cerebrovascular disease is calcium channel blockers. Dr. Krishnan described a controlled, double-blind trial of nimodipine,[52] an L-type calcium antagonist, in which all patients ($N = 84$) were also treated with standard doses of an antidepressant. More patients receiving nimodipine plus an antidepressant achieved remission than those who received the inactive comparator (vitamin C) plus an antidepressant (45% vs. 25%, respectively), according to HAM-D scores. Among patients whose HAM-D scores dropped by 50% within the first 60 days, 7.4% of those taking antidepressants augmented with nimodipine had a recurrence versus 32% taking an antidepressant plus vitamin C. Similar results were found in another study by the same researchers,[53] in which all patients ($N = 101$) took fluoxetine plus either nimodipine or placebo.

Mlekusch and colleagues,[54] noting that people with vascular depression often have carotid atherosclerosis, attempted to determine if treating the atherosclerosis with placement of a carotid artery stent (CAS) would improve depressive symptoms. Prior to undergoing CAS, 33.6% of the test group had depressive symptoms. At 4-week follow-up after CAS, 9.8% of the test group had depressive symptoms ($p = .003$). The prevalence of depressive symptoms in the control group was not significantly affected (16.7% at baseline vs. 13.0% at follow-up).

Vascular Disease and Dementia

Vascular disease is also connected to cognitive deficits, memory problems, and the development of dementia. According to Steffens et al.,[55] silent strokes in the subcortical gray matter of the brain were associated with subsequent dementia. Vascular change can produce cognitive impairment and dementia through a variety of pathologies,[56] including a narrowing of the blood vessels, strokes, specific genetic malformations, or altered white-matter connectivity. Vascular dementia is the second most common form of dementia in the elderly, representing 15% to 20% of all cases worldwide.

Treatments for vascular disease and dementia. Because hypertension is a risk factor for vascular dementia in the elderly, researchers have wondered whether treating patients for hypertension would reduce the incidence of dementia. However, a meta-analysis[57] combining the results of 3 trials with over 12,000 patients found no evidence that treatment for hypertension lowers the incidence of cognitive impairment or dementia. More trials are needed because, in the available studies, dropout rates were high and control participants were also taking antihypertensive medication.

Aspirin is commonly prescribed as a treatment for vascular dementia.[58] Dr. Krishnan stated that, despite its widespread use, there is no conclusive evidence supporting aspirin as an effective treatment for cognitive impairment or dementia caused by vascular

disease.[58,59] Another commonly used treatment is folic acid, a B-complex vitamin, but, as with aspirin, trials have not demonstrated a significant beneficial effect on cognition in patients with vascular dementia.[60]

Nimodipine has also been considered as a possible treatment for vascular dementia. A review[61] found short-term cognitive benefits of nimodipine, but no benefits in activities of daily living, in patients with different forms of dementia (AD, vascular, or both); long-term study is needed.

The cholinesterase inhibitor donepezil[62] was researched in patients with dementia due to AD for up to 1 year and was associated with improvements in cognition and activities of daily living. A similar drug, galantamine,[63] was studied in patients with vascular cognitive impairment, but the 2 available trials had inconsistent results. One trial showed a significant advantage over placebo on cognitive measures, and one trial did not.

Memantine, a low-affinity antagonist of glutamate *N*-methyl-D-aspartate receptors, has also been studied in dementia. A review summarized results from trials in AD, vascular, or mixed dementia.[64] The small beneficial effect on cognition at 6 months was more apparent in patients with moderate-to-severe dementia than mild-to-moderate dementia.

Summary

Dr. Krishnan concluded that vascular disease is common as people age, and it is linked to depression, cognitive dysfunction, and their prognosis. Elderly patients with depression or dementia need vascular assessments and treatment. Specific treatments for dementia should be used, even when it seems that the dementia may be primarily vascular.

Course and Treatment of Patients With MCI

Memory loss is the most common neurologic symptom of aging. This MCI is believed to often represent a transitional stage between normal cognition and AD.[65] Davangere Devanand, M.D., explained that an older person will generally go through the stage of MCI before a diagnosis of AD is made, but all patients with MCI do not progress to AD or other forms of dementia.

Although MCI is a controversial topic with numerous definitions, the basic diagnostic criteria of MCI include memory complaints with objective cognitive deficits but without significant functional deficits that are consistent with AD or other dementia.[65] Objective cognitive deficits are rated by neuropsychological test scores 1.5 SD below age-adjusted norms.

Risk Factors and Early Markers of AD

Dr. Devanand related that many clinicians have difficulty estimating the prognosis for patients with MCI, especially in those who have relatively high scores on the Mini-Mental State Examination (MMSE). Accurate early diagnosis and knowledge of the prognosis may help with life planning and early treatment. Currently, researchers are trying to predict conversion from MCI to AD by examining risk factors and early markers. Risk factors include age and genetic factors. Early markers reflect part of the disease process and may help predict conversion to AD. These early markers include declining memory and executive function as measured by neuropsychological tests, functional impairment as reported by a caregiver, olfactory identification deficits, hippocampal and entorhinal atrophy as shown on MRI, parietotemporal blood flow and metabolism deficits as shown on single photon emission computed tomography (SPECT) or PET, presence of amyloid in amyloid-imaging PET scans, and abnormal concentrations of Aβ, tau, and phosphorylated tau in cerebrospinal fluid.

Predicting Conversion From MCI to AD

Although no individual risk factor or early marker has been shown to be strong enough to be the sole predictor of conversion from MCI to AD, Dr. Devanand asserted that combining markers may improve predictive if feasible accuracy.

Neuropsychological measures. Tabert and colleagues[66] attempted to identify the neuropsychological measures most predictive of conversion to AD. Over an average follow-up of 47 months, 40 of the patients with MCI had converted to dementia, with 39 of these patients having a clinical diagnosis of AD. Of the neuropsychological predictors examined, deficits in verbal recall examined by the Selective Reminding Test (SRT) and executive function deficits examined by the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Symbol Test best identified those patients likely to convert to AD. However, overlap between nonconverters and converters on these tests indicated that neuropsychological tests alone were not sufficient predictors of conversion.

Functional impairment. Although diagnostic criteria for MCI require that there be no significant functional impairment, many people with MCI have subtle cognitive deficits—not in basic activities of daily living but in complex tasks such as social cognitive tasks. In a study by Tabert and colleagues[67] using the Pfeffer Functional Activities Questionnaire (FAQ), self-reported functional deficits by patients with MCI were not predictive of conversion to AD, but functional impairment reported by an informant was significantly predictive of conversion to AD during follow-up. Items on the FAQ include tasks that require intact cognition, such as difficulty in writing checks or paying bills, shopping alone, heating water for coffee or tea and turning off the stove, and preparing a balanced meal. From a clinical perspective, questioning caregivers about the patient's daily functioning can be an important diagnostic tool.

Apolipoprotein E genotype. The *APOE*E4/*E4* homozygote genotype (inheriting an *APOE*E4* allele from both parents) is known to confer an increased risk for AD, particularly in patients above the age of 70 years.[68] The heterozygous *APOE*E4/*E3* form, in which an individual has one *APOE*E4* allele, confers a somewhat increased risk of AD and is fairly common, but the high-risk homozygous *APOE*E4/*E4* genotype is relatively rare in the general population. Additionally, many patients with the *APOE*E4/*E4* genotype do not convert to AD, and many who do convert to AD do not have it. Consequently, Dr. Devanand concluded that APOE genotyping cannot be recommended for widespread clinical use as a predictor of AD.[68,69]

Brain tissue atrophy. Evidence of medial temporal lobe atrophy on specially processed MRI scans can predict conversion to AD in nondemented elderly people and those with MCI.[70] Over time, patients with the smallest hippocampal and entorhinal volume are most likely to progress to AD.[70] However, general MRI centers do not yet have the technology for these types of scans; they are mainly available in academic clinical centers.

Olfactory identification deficits. The olfactory tract and bulb have early infiltration with neurofibrillary tangles in AD, so olfactory identification deficits are another important early marker. An olfactory identification deficit is difficulty in identifying a particular smell, not necessarily in smelling itself. In a study[71] of 90 patients with MCI who took the University of Pennsylvania Smell Identification Test (UPSIT) at baseline—a simple 40-item, multiple-choice, scratch-and-sniff test—patients who did not convert to AD after 2 years had a mean score of 32; those who did convert to AD had a mean score of 26 ($p < .05$). Some natural variability in people's ability to identify smells consequently decreases the value of the test as a lone predictor of conversion to AD.

Other markers using brain imaging. Regional cerebral blood flow deficits[72] (as assessed by SPECT) and metabolism deficits[73] (as assessed by PET) in the parietotemporal and posterior cingulate brain regions distinguish people with AD from controls. However, the predictive value for conversion to AD in patients with MCI has not been well established for these imaging tests; Dr. Devanand said that larger studies are needed. PET imaging of amyloid and tau is still in research development but is a promising predictor of conversion from MCI to AD.[38,75]

Several spinal fluid markers can be predictive of conversion to AD. A study by Hansson and colleagues[74] showed that the combination of pathologic concentrations of beta amyloid (Aβ42), total tau, and phosphorylated tau is a strong predictor of conversion from MCI to AD. If findings are replicated, some of these techniques may become widely used in clinical practice.

Combining Measures to Predict Conversion From MCI to AD

If no single diagnostic method can reliably predict conversion from MCI to AD, clinicians need to know which tests to use in combination for the best predictive value. Dr. Devanand reported results of a study[76] that used logistic regression to examine the predictive accuracy of 8 measures—age, 2 neuropsychological cognitive measures (WAIS-R Digit Symbol and SRT), a functional impairment measure (FAQ), olfaction test (UPSIT), *APOE* genotyping, hippocampal volume, and entorhinal volume. After logistic regression, 3 of the 8 measures were found to be insignificant: age, WAIS-R Digit Symbol, and *APOE* genotyping. In the 3-year follow-up period, 33 of 126 patients with MCI converted to AD. Sensitivity for 80% specificity was substantially greater for the combined 5 measures than for combined age and MMSE score, a commonly used predictive combination. Prior attempts[69,77] at combining predictors focused on age, memory, *APOE*E4/*E4* genotype, and hippocampal volume and had only moderate predictive accuracy. Examining the olfactory identification deficit, informant-reported patient functioning, and entorhinal cortex volume seems to strongly improve prediction of AD.

Treatment of MCI

If patients with MCI who will convert to AD can be recognized, treatment might be used for prevention. However, of the few studies of MCI treatment, most have been negative. The largest study[78] to date was a multicenter, double-blind study of 769 patients with amnestic MCI who received vitamin E, donepezil, or placebo for 3 years. The annual conversion rate from MCI to AD was 16%. Donepezil had a short-term benefit during the first year, which was lost with longer-term follow-up, and vitamin E was indistinguishable from placebo throughout the study. New amyloid agents are currently being used to treat AD but have not yet been tested in patients with MCI.

Conclusion

A large proportion of patients with MCI convert to AD. Diagnostic methods for predicting conversion to AD are improving markedly, but these methods seem to have the most value when combined. The usual combination is age plus MMSE scores, but neuropsychological testing, caregiver report of the patient's functioning, and olfaction testing can add to predictive accuracy. Dr. Devanand called for more research to find effective treatments for MCI.

Interactions Between Depression and MCI and Clinical Approaches

Roy Hamilton, M.D., M.S., began by reporting that depression occurs in 20% of patients with MCI.[79] Among the population aged 85 years and older, 25% suffer from comorbid depression

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and cognitive impairment; the prevalence of comorbid depression and MCI doubles every 5 years after age 70 years.[80]

A complicating factor in the diagnosis and management of patients with both depression and MCI is the overlap of each disorder's clinical presentation. Both syndromes can exhibit impairments in information-processing speed, attention and vigilance, working memory, visuospatial memory, executive function, and the ability to inhibit inappropriate behavior. In other words, often no clear phenotypic boundary exists between one syndrome and the other.

Possible Explanations for the Link Between Depression and MCI

Multiple lines of evidence suggest that depression and MCI are linked, but the nature of the interaction remains unknown. Dr. Hamilton reviewed some of the theories[81] that have been advanced to explain the interaction between depression and MCI. One possibility is that depression is a causal factor that induces long-term changes in the brain's neurochemistry, leading to injury and subsequent cognitive impairment. Another hypothesis is that depression and MCI share common risk factors such as specific genetic variants, demographic factors like age, or environmental factors. If common risk factors are predictors of both syndromes, the two would often co-occur in patient populations. A third hypothesis supposes that depression is a manifestation of early MCI. According to this model, cognitive deficits may be present but of insufficient severity to garner the attention of the patient or of family members. Instead, depression may emerge as the result of preclinical cognitive impairment, while clinically significant cognitive impairment may not become apparent for months or even years. The last possibility that Dr. Hamilton discussed was a stress-diathesis model. According to this theory, some patients may have a predisposition—genetic or otherwise—to develop cognitive impairment. In the presence of this existing susceptibility, the additional burden of depression leads these patients to manifest the symptoms of cognitive impairment. Evidence for this theory was found when Geda et al.[81] examined the interaction between the presence of the *APOE*E4/*E4* or *APOE*E4/*E3* genotype, depression, and MCI. A 5-fold increase in the risk for the development of MCI was found when either *APOE*E4* genotype and depression co-occurred in elderly patients ($p < .001$), as opposed to those with neither the genotype nor depression.

Dr. Hamilton stressed that these are not the only theories possibly explaining the relationship between depression and MCI and that it is not known if any of them are correct. Whatever the relationship between depression and MCI may be, the existing evidence demonstrates that the two conditions are inextricably linked. Therefore, clinicians must adopt a therapeutic approach that takes both mood and cognition into account.

The Impact of Depression on the Course of MCI

Evidence indicates that depression and MCI each impact the incidence and course of the other. A study[81] that followed 840 normal elderly adults in the primary care setting for a median duration of 3.5 years found that subjects who developed depression were more than twice as likely to develop MCI as patients who did not develop depression. Another study[82] followed a cohort of patients with amnestic MCI for a mean duration of 3 years. A little over a third of these patients were also depressed at baseline (36%). At endpoint, 52% of the total cohort had developed AD, which is consistent with the expected rate of progression from MCI to AD. While 32% of the nondepressed patients had developed dementia, 85% of patients with depression had developed dementia. Thus, depression more than doubled the risk of developing dementia in patients who already had MCI.[82] Dr. Hamilton emphasized that clinicians need to consider depression when treating patients with MCI because cognitive outcome is worsened by the presence of depression.

The Impact of MCI on the Course of Depression

Dr. Hamilton then described how the presence of cognitive impairment leads to a poorer initial and maintenance response to treatment for depression. Kalayam and Alexopoulos[83] found that elderly patients with prefrontal dysfunction experienced a delayed or poor antidepressant response. Cognitive test scores in patients whose depression had remitted with antidepressant treatment were similar to those of normal control subjects. In a controlled study[84] of depressed elderly patients being treated with citalopram, the presence of executive dysfunction was an independent predictor of low remission rates.

Cognitive impairment is also associated with poor ongoing response to antidepressant therapy. A study[85] of elderly depressed patients being treated with nortriptyline demonstrated that depressive relapse, recurrence, and residual symptoms were associated with executive dysfunction (but not with memory impairment). Thus, converging evidence indicates that the presence of depression worsens the course of MCI and that the presence of cognitive impairment worsens the course of depression. What remains to be answered is how patients with combined depression and MCI can be treated and how treatment of one condition affects the other.

Do Agents That Treat AD Also Treat MCI?

Dr. Hamilton stated that, because MCI is often associated with the subsequent development of AD, one might reason that the medications used to treat AD could be effective in the management of MCI. Acetylcholinesterase inhibitors are the mainstay of AD treatment, and investigators have attempted to determine whether this class of medication has utility in treating MCI. A large multicenter study[86] compared donepezil, vitamin E, and placebo,

using progression to a clinical diagnosis of AD over 3 years as the primary outcome measure. Researchers found an overall rate of conversion to AD of around 16% per year. Approximately three quarters of patients who developed AD were carriers of at least one *APOE*E4* allele. At endpoint, no significant difference was found in the rate of conversion to AD between patients treated with donepezil, vitamin E, or placebo.

However, the donepezil group experienced a significant reduction in conversion to AD within the first 12 months.[86] Among *APOE*E4* carriers, a reduced risk of conversion to AD was found in the first 24 months after initiation of donepezil treatment. Patients who were taking donepezil and who eventually converted to AD did so approximately 6 months later than those taking placebo. Vitamin E, by contrast, was not associated with a significant benefit at any time interval. Modest evidence points to beneficial effects of an acetylcholinesterase inhibitor at 1 to 2 years, but no evidence suggests a long-term benefit.

Treatment trials evaluating other acetylcholinesterase inhibitors have been even less encouraging. Rivastigmine and galantamine have both been found to be insufficiently effective in the treatment of MCI.[87]

Researchers have also investigated treatment for MCI with agents other than acetylcholinesterase inhibitors. Vitamin E and the nonsteroidal cyclooxygenase 2 inhibitor refocoxib were both insufficiently efficacious as treatment for MCI.[87]

Does Treating Depression Improve MCI?

Dr. Hamilton posed the question whether treatment for depression can improve cognition. Butters et al.[88] compared depressed elderly patients with cognitive impairment to those without cognitive impairment, as well as a control group. After antidepressant treatment, the cognitively impaired subjects demonstrated an improvement in cognition. However, even after improvement, these patients were still mildly cognitively impaired relative to both controls and the cognitively normal subjects,[88] suggesting that MCI persists even after remission of depression. One potential limitation of this study was that it did not differentiate treatment responders from nonresponders, so that response to antidepressant treatment could have been correlated with more significant improvements in cognition.

Another study[89] specifically looked at differences in performance between responders and nonresponders in patients with depression and MCI who were being treated for depression with sertraline. Across a battery of neuropsychological tests, only one domain of cognition, executive function, was significantly improved in patients who responded to treatment. Other cognitive domains, including memory, visuospatial organization, and language, showed little improvement with antidepressant treatment.

These studies suggest that antidepressant treatment has a marginal impact on cognition in patients with depression and MCI, and this impact seems principally restricted to certain measures of executive function. However, Dr. Hamilton noted, additional data suggest that even this conclusion might be overstating the case for cognitive improvements resulting from treatment of depression. For instance, a study[90] of change on cognitive measures in depressed patients who received treatment with either paroxetine or nortriptyline found improvement in the domains of executive function and verbal memory. However, this improvement paralleled that of control subjects who were not being treated, likely reflecting the effects of test-taking practice in both controls and patients. Thus, depressed patients' cognitive performance may not normalize in response to antidepressant treatment.

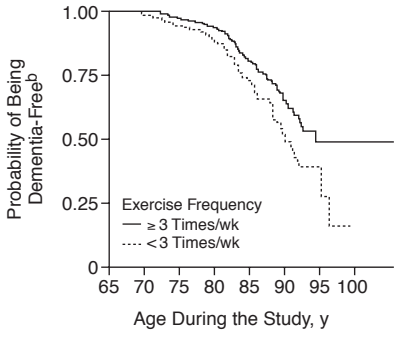
Treatment Strategies for Patients With Depression and MCI

Eliminating iatrogenic cognitive deficits. If pharmacotherapy for both AD and depression is ineffective at improving cognition in depressed patients with MCI, what can clinicians do to address the cognitive deficits for patients who present with this dual diagnosis? Dr. Hamilton suggested that clinicians first address any medication-induced impairments in cognition in the elderly. Investigators[91] have found one or more anticholinergic medications associated with deficits in several cognitive domains. Deficits in cognition in the elderly are often multifactorial, and alleviation of iatrogenic effects can have a significant overall effect on cognition. Patients with concurrent depression and cognitive impairment may be taking psychoactive medications that have prominent anticholinergic effects. Dr. Hamilton reported that besides anticholinergic agents, many other medications can negatively affect a patient's cognition, including narcotics, corticosteroids, anticonvulsants, dopaminergic medications, and sedative-hypnotics such as benzodiazepines. Clinicians need to consider the effects of polypharmacy and the inadvertent intellectual effects of certain medications when treating patients with depression and MCI.

Nonpharmacologic treatments. A comprehensive approach to treating cognitive deficits and depression should include consideration of nonpharmacologic therapies. One intervention receiving increasing attention is physical exercise. Evidence has demonstrated that regular, moderate exercise is associated with a lower risk for future development of dementia in healthy elderly subjects (Figure 2).[92] Physical exercise may also play a beneficial role in the management of depression.[93]

Rigorous mental activity has also been associated with improved cognition in the elderly. For example, epidemiologic research has established that a higher number of years of education confers a reduced risk of developing dementia.[94] A wide range of intellectually stimulating leisure activities, including but not limited to puzzles, reading, and musicianship, also confer a reduced risk of dementia.[95] Likewise,

Figure 2. Exercise Lowers the Risk of Dementia in the Elderly[a]



[a]Reprinted with permission from Larson et al.[92]
[b]Kaplan-Meier survival estimates.

mental stimulation in the form of social interaction is an important element in staving off depression in elderly populations.[96] Thus, remaining intellectually and socially active may prevent or lessen the impact of depressive symptoms and cognitive decline and should be encouraged as part of a comprehensive approach to treating older patients.

Summary

Depression and MCI commonly co-occur and exacerbate each other's course. Dr. Hamilton recommended that the assessment of patients with MCI and depression should be comprehensive and should include, but not be limited to, a thorough, formal assessment of affect and cognition. Neuroimaging should be performed to look for contributory focal lesions or changes consistent with a specific pattern of progressive cognitive decline. Cerebrovascular risk factors and other medical etiologies that contribute to decline in cognition should also be assessed, and clinicians should screen for anticholinergic and other medications that can contribute to altered cognition.

Pharmacologic management of MCI in patients with depression has thus far been disappointing. Cognitive impairment complicates treatment of depression, and antidepressant treatment often fails to resolve cognitive deficits. Regular aerobic exercise and intellectual and social engagement can potentially play a role in preserving cognition and preventing depressive symptoms. These nonpharmacologic measures should be recommended for patients who are able to engage in them. Dr. Hamilton concluded that systematic studies are needed to better define the characteristics of combined MCI and depression. Elucidating the interactions of these 2 conditions should aid the development of efficacious treatment regimens for patients with comorbid depression and MCI.

Drug names: citalopram (Celexa and others), donepezil (Aricept), fluoxetine (Prozac and others), flurbiprofen (Ansaid and others), galantamine (Razadyne), lithium (Eskalith, Lithobid, and others), memantine (Namenda), nimodipine (Nimotop and others), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil, Pexeva, and others), rivastigmine (Exelon), sertraline (Zoloft and others).

Disclosure of off-label usage: The chair has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

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For the CME Posttest for this ACADEMIC HIGHLIGHTS, see pages 1625–1627.

