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# Depression in Older Adults: Is There Another Reason to Worry?

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The term *neuropsychiatric symptoms* describes behavioral or mood disturbances such as agitation, delusions, hallucinations, depression, and apathy. These symptoms are commonly found among patients with dementia and compound the patients' disability as well as the burden experienced by their caregivers.[1] Neuropsychiatric symptoms have not been part of the defining diagnostic criteria of dementia or mild cognitive impairment (MCI), and their characterization and importance in the presentation of MCI and potential conversion to dementia are just being established. Several recent studies have shown that neuropsychiatric symptoms are common and highly morbid in patients with MCI and are associated with greater impairment in global, cognitive, and functional measures.[1–4] Subjects progressing to dementia have a higher prevalence of psychopathology than subjects who remain stable or improve, and, thus, neuropsychiatric symptoms appear to be a predictor of progression to dementia alongside established factors such as apolipoprotein E ε4 carrier status, features of memory function, cerebrospinal fluid amyloid-β peptide (Aβ)/tau ratio, amyloid imaging, and magnetic resonance imaging volumetric measurements of the hippocampal formation.[5] Persistent neuropsychiatric symptoms and behavioral changes can also be present in the absence of patient- or caregiver-reported cognitive deficits, impairment in activities of daily living, and dementia—a syndrome termed *mild behavioral impairment*.[6] Many patients with mild behavioral impairment develop neuropsychiatric symptoms as the first indicator of impending dementia long before the occurrence of cognitive symptoms. This finding raises questions as to the pathophysiology of neuropsychiatric symptoms, but the symptoms most likely are consequences of damage to the brain from underlying brain disease.

In the United States, over 5.4 million people are living with dementia, a number that will roughly double every 20 years up to 16 million individuals by 2050.[7] Equally concerning is that nearly 5 million of the 31 million Americans who are aged 65 years or older are clinically depressed, and 1 million have major depression.[8] As one might expect from these figures, depression and cognitive disorders are the most common neuropsychiatric disorders in later life. Their co-occurrence most likely exceeds chance. Depression leads to multiple negative outcomes, including increased rates of morbidity and mortality.[9] Depressive disorders and affective symptoms are common among those with diagnosed dementia: the overall prevalence rate for major depression is approximately 20% among older adults with dementia, and the frequency of affective symptoms is roughly twice as great.[10] Across hospital- and population-based studies, about 34% of patients with MCI have depressive symptoms at the median.[11]

On balance, data suggest that the presence of depressive symptoms confers higher risk of developing both MCI and dementia and that late-life depression, MCI, and dementia could represent a clinical continuum. This association remains even in individuals in which depression occurred long before the onset of the cognitive disorder. A recent review by Barnes and Yaffe[12] presents epidemiologic data on dementia risk factors and estimates that, worldwide, 10% of Alzheimer's disease is attributable to depression, while, in the United States, the attributable risk is even higher at 15%.[12] Further support for the link between depression and Alzheimer's disease comes from Steinberg et al,[13] who found that older individuals who had less stress, anxiety, depression, and trauma, even in the face of tragic events or circumstances such as a life-threatening illness, were less likely to develop Alzheimer's.[13] Research from the Alzheimer's Disease Neuroimaging Initiative database supports a possible biological link between depression and dementia, as Chou et al[14] found that expansion of the ventricles was correlated with depressive ratings, while Lee et al[15] showed that the presence of depressive symptoms in subjects with MCI, compared to subjects with no symptoms or with other nondepressive neuropsychiatric symptoms, was associated with increased white matter atrophy.

We struggle with multiple issues surrounding this interface. First of all, the exact mechanism of the interconnect between depression and cognitive impairment remains obscure. Proposed mechanisms include depression as a psychological reaction to the awareness of gradual loss of abilities similar to other function-limiting medical disorders; depression unmasking incipient cognitive impairment; depression causing pathophysiologic changes in brain tissue; and depression as an early manifestation of a common neuropathological condition that will also result in cognitive decline over time.[16] There is still more to do to fully explore the true nature of this relationship. The critical question is how the presence of depression modifies the risk of developing MCI or progression from MCI to dementia. In this month's special section "Focus on Alzheimer's Disease and Related Disorders," Baba and colleagues[17] compare serum Aβ40 and Aβ42 levels, Aβ40/Aβ42 ratio, and other clinical factors between controls and inpatients with *DSM-IV* major depressive disorder (MDD) in 3 age groups: young (< 40 years), middle-aged (≥ 40 to < 65 years), and elderly

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(≥65 years). The serum Aβ40/Aβ42 ratio was significantly higher in MDD patients than controls in all age groups due to lower Aβ42 levels in the MDD cases. These results were independent of apolipoprotein E ε4 status. The findings suggest that Aβ metabolism is affected in depression, even in early-onset depression,[17] but still do not determine whether depression is a true risk factor for Alzheimer's disease rather than an additional consequence that arises from a common neuropathological process; the 2 hypotheses are in fact not mutually exclusive.

Many people develop neuropsychiatric symptoms as the first indicator of impending cognitive decline, making depressive symptoms a particularly robust predictor of dementia. Current diagnostic criteria for MCI and dementia do not list neuropsychiatric symptoms as cardinal features, and recently proposed research criteria for preclinical stage, MCI, and dementia due to Alzheimer's disease do not list neuropsychiatric symptoms as core clinical features. As a link between neuropsychiatric symptoms or depression and MCI/dementia becomes more apparent, the diagnostic criteria may need to adapt accordingly. The Baba et al[17] article published in this issue helps to support this association as it suggests that depression signals biomarker changes that are proposed to be a very early measure of neuronal injury in prodromal Alzheimer's disease. As the dementia epidemic is upon us, it will be extremely important to prevent even some cases. We do not fully know yet whether treatment interventions or risk modifications are helpful in the short or long run—this question is a grand challenge that urgently needs answers. As current pharmaceutical treatment of dementia provides only modest symptomatic improvement with limited impact on the underlying neuropathological process, risk reduction or early intervention—including depression identification and treatment—may be the most promising approach until we have effective disease-modifying agents.

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