New Concepts for Prevention and Treatment of Late-Life Depression

Old people and their families know well that the golden years are tarnished by pain, ill health, and disability. Several years have been added to the last part of life during the last century. The longevity of 85-year-old men has increased by over 20%. However, an important question has been, Are these "good years" and for whom? Vaillant and Mukamal address directly this question with their study of successful aging.

Successful Aging

Vaillant and Mukamal conceptualize aging as a life stage with three dimensions: decline, neutral change, and development. While usually underemphasized, positive personality changes, such as tolerance, regulation of affect, and ability to appreciate different points of view, occur with aging and can contribute to successful adjustment and high quality of life. Citing the Berlin Aging Study, Vaillant and Mukamal point out that elderly individuals do not have more psychiatric disorders than younger adults, they do not see themselves as sick even when they take three to eight different medications, their fear of death declines, and their spirituality and serenity increase.

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The study of successful aging followed a cohort of male students at Harvard University and a cohort of core-city youth for 60 years or until death. A unique asset of this study is that it addresses selective mortality of the most vulnerable members of the group. Death and disability occurred about 10 years later in the Harvard cohort than in the core-city cohort. While the impact of socioeconomic level on mortality and disability has long been known, an encouraging finding is that education had a protective effect even in the core-city cohort. The link of education to socioeconomic level is almost unavoidable. However, improving education to the extent allowed by each socioeconomic stratum may have a positive impact on quality of life and longevity.

An important contribution of the Vaillant and Mukamal report is the identification of predictors of successful aging that can be under the individual's own control. The absence of alcohol abuse and of cigarette smoking before the age of 50 years were predictors of successful aging in both study groups. In the Harvard cohort, socially isolated men at 75–80 years of age were four times as likely to have been alcohol dependent at age 50, 14 times as likely to have been heavy smokers, and twice as likely to have engaged in little exercise than nonisolated 75–80-year-old men. The pathways by which alcohol abuse and smoking affect mental and physical health are unclear, but a common mechanism may involve the vascular system. Finally, a stable marriage and adaptive defenses were also predictive of successful aging, subjective satisfaction, and objective mental health, although these effects may not have been independent of tobacco and alcohol abuse. While marriage, adaptive defenses, and tobacco and alcohol abuse may not be under the full control of an individual, they still indicate areas on which one may wish to work.

Among factors outside the individual's control, only depression before the age of 50 years was a significant predictor of mortality, medical morbidity, and sadness during late life. Ancestral longevity, parental social class, and unhappy childhood had no sig-

nificant effect. The impact of depression is impressive, especially since individuals who were chronically ill and disabled were excluded from these comparisons. It is unclear whether and to what extent the depressed subjects of the study of successful aging were treated. However, the association of depression with poor outcomes in late life suggests that there is a need for studies of the long-term effects of successful antidepressant treatment. It is equally important to examine contributors to late-life depression, as depression promotes mortality, medical morbidity, and disability (1).

The Stress-Vulnerability Model in Geriatric Depression

In their article, Ormel et al. report on contributors to late-life depression and initiate a sophisticated dialogue on the stress-vulnerability model. The model, first introduced by Brown and Harris (2), postulates that vulnerability factors interact with stressful life events and lead to depression. This interaction may occur in at least two ways. Vulnerable individuals may expose themselves to life circumstances and generate stressful events that promote depression. Therefore, vulnerability to depression is mediated by stressful life events. Moreover, vulnerable individuals may be more prone to develop depression when exposed to stressful life events than persons with lower vulnerability, so that vulnerability enhances the impact of stressful life events in contributing to depression.

Stressful life events are frequent in the elderly, and so is innate and environmental vulnerability. More than 50% of the subjects with major depression or subsyndromal depression and about 25% of the normal comparison subjects in the study group of Ormel et al. had had at least one stressful life event within a 3-month period. More than 60% of the depressed subjects had either a trait vulnerability, expressed as a high level of neuroticism, or vulnerability related to their life circumstances (long-term difficulties), e.g., poverty, chronic illness in the family, caregiver burden.

Neuroticism and long-term difficulties were shown to increase the impact of even mild stressful life events in promoting depression. Moreover, neuroticism and long-term difficulties increase the risk for depression in elderly persons even in the absence of stressful life events. The effect of neuroticism is stronger in individuals with a prior history of depression. These observations are relevant both to major depression and to mild subsyndromal cases and suggest that elderly persons with high neuroticism levels and/or long-term difficulties are a target for sharply focused studies of early intervention.

Unfortunately, stressful life events are part of late life. They are not caused by the older persons themselves, even those with high neuroticism levels and long-term difficulties, as Ormel et al. observed. Prevention of late-life stressful events may not be feasible. However, early identification of depression, psychosocial or pharmacological interventions, and vigilant follow-up are options that can be used in settings where elderly persons receive care.

Most elderly patients receive mental health care in primary care settings (3) and often do not follow through when referred to mental health specialists (4). However, depression is recognized in only a small fraction of elderly primary care patients (3), and an even smaller fraction of those identified receive appropriate antidepressant treatment (5). Educational approaches have not been helpful because the major impediment to recognition and treatment of depression is the limited time of general practitioners. Several major studies are under way to evaluate the effectiveness of specialized physician extenders in improving the recognition and treatment of geriatric depression in the general practice office. However, even if effectiveness is demonstrated, it is unclear whether these professional services would ever be used, as currently no insurance carrier reimburses the cost of such services. If physician extenders actually prove effective in recognizing and treating depression, our field needs to work for their implementation, as most depressed elderly patients are treated at the general practice office.

Striatofrontal Dysfunction in Geriatric Depression

Neuroticism may be one of the expressions of innate vulnerability but not the only one. Brain abnormalities may also increase vulnerability to depression. Nebes et al. report that white matter hyperintensities (WMHs) in deep white matter, but not in periventricular white matter, were associated with greater depressive symptoms. The relationship of WMHs and depressive symptoms was especially strong in individuals with an apolipoprotein E-4 (APOE-4) allele. The most prominent depressive symptoms of patients with subcortical WMHs were impaired motivation, concentration, and decision making. While other explanations are possible, the clinical profile of these patients suggests that striatofrontal dysfunction caused by subcortical WMHs is an important contributor to these symptoms.

The relationship of striatofrontal dysfunction to depression is supported by structural and functional neuroimaging findings as well as neuropathological findings. In depressed elderly patients, subcortical WMHs are common (6) and are associated with executive dysfunction (7), perhaps resulting from disruption of the anterior cingulate and the dorsolateral striatofrontal circuits. Stroke of the basal ganglia is associated with a high rate of depression (8). Positron emission tomography studies have demonstrated hypometabolism in both the dorsolateral (9) and anterior cingulate (10) pathways. Finally, neuropathological studies in depression have shown abnormalities in neurons and glia in both the dorsolateral cortex (11) and the anterior cingulate cortex (12).

Recent studies link striatofrontal dysfunction to the course of geriatric depression. Executive dysfunction, the neuropsychological expression of striatofrontal impairment, was found to predict poor or slow antidepressant response in depressed elderly patients receiving adequate antidepressant pharmacotherapy (13). Moreover, poor or slow antidepressant response was predicted by psychomotor retardation and prolonged latency of the P300 average evoked potential, functions requiring integrity of striatofrontal circuitry. Finally, executive dysfunction in late-life major depression was shown to be associated with early relapse, recurrence, and residual depressive symptoms (14). WMHs are associated with executive dysfunction (7) and were found to predict chronicity of geriatric depression (15). Hypometabolism of the rostral anterior cingulate was reported in treatment-resistant depression (16); integrity of the anterior cingulate is required for successful performance of some executive functions. Taken together, these findings suggest that striatofrontal dysfunction is part of the mechanisms perpetuating late-life depression.

The relationship of striatofrontal dysfunction to geriatric depression and its course opens a number of treatment possibilities. Drugs modifying the neurotransmitters participating in striatofrontal pathways, e.g., dopamine, acetylcholine, and opiates, are candidates for such studies (17) and are available for human use. These include dopamine D_3 receptor agonists and cholinesterase inhibitors, as well as opiate receptor agonists and antagonists. Similarly, agents that can change executive dysfunction, e.g., modafinil, may be studied as potential antidepressants. A major potential contributor to striatofrontal dysfunction may be ischemic brain damage caused by cerebrovascular disease. This assertion is supported by the findings of Nebes et al. and by the clinical, neuroimaging, and neuropathological findings of others (18). Vaillant's and Mukamal's observation that smoking and drinking contribute to poor mental health in late life offers additional support to the vascular depression hypothesis, as tobacco and alcohol affect the vascular system. Beyond a continued campaign against smoking and excessive drinking, agents used for prevention and treatment of cerebrovascular disease may become the first primary-prevention intervention for a psychiatric disorder after appropriate experimentation. Finally, psychosocial interventions focused on the interactions among depression, decreased motivation, and impaired decision making may interrupt the downward spiral of behavioral deterioration of elderly patients by remedying some of these disabilities.

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