Late-life life depression causes suffering to patients, disrupts their families, worsens the outcomes of medical illnesses, and increases mortality. It principally afflicts older adults with cognitive compromise and medical illnesses. The chronic stress of living with disability, social isolation, relocation, caregiving, and bereavement are common precipitants and/or consequences of depression in late-life.

Although safe and tolerated treatments have been developed, only one-third of depressed older adults achieve remission when treated with any of the available antidepressants. The reasons are complex and in part related to the cognitive and medical comorbidity and the social context of late-life depression. An additional complicating factor may be the setting in which depressed older adults receive care. Approximately two-thirds of patients with late-life depression are treated in primary care offices. The fast pace and the lack of advanced mental health expertise in the primary care setting combined with the complex clinical context of late-life depression often poses formidable challenges. Workforce shortages necessitate that geriatric and general psychiatrists serve as consultants and only treat the most difficult cases. Models of collaborative care in which primary care physicians work together with care managers and utilize psychiatric consultants in complex cases have satisfactory outcomes. Practice guidelines emphasize the need for a comprehensive psychiatric, cognitive, neurological, medical, and psychosocial assessment and the use of targeted sequential trials of antidepressants combined with psychotherapy. The article by Avari et al. outlines assessment procedures, indications for psychiatric referral, and treatment strategies for late-life depression as well as novel therapies currently under investigation.

An important clinical concern has been the relationship of depression to dementia. Recurrent depression is a risk factor for development of dementia in late life. Moreover, depressive syndromes and symptoms can be the first clinical manifestation of dementing disorders (prodrome), including Alzheimer’s disease, vascular dementia, and Lewy body disease. A syndrome once termed “pseudodementia” and thought to have a benign course has a high conversion rate to dementia. Mild neurocognitive disorder has been recognized by the DSM-V: Diagnostic and Statistical Manual for Mental Disorders, fifth edition (DSM-V) task force. It is characterized by modest decline from a previous level of function in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual motor, or social cognition). Mild neurocognitive disorder is a heterogeneous entity that includes a high number of patients in early stages of dementing disorders. However, it is unclear whether the mild cognitive impairment occurring in the context of late-life depression has high conversion rate to dementia since depression itself impairs cognition transiently. The article by Morimoto et al. discusses the relationship of late-life depression to dementing disorders and their implications for prognosis and treatment and outlines bedside examination and testing procedures for distinct cognitive domains.

Although the clinical context of late-life depression can pose diagnostic and treatment challenges, it offers a unique opportunity for investigating mechanisms of psychopathology and for developing
targeted treatments. Early studies of the Weill Cornell Institute of Geriatric Psychiatry documented that patients with late-onset major depression have less frequent family history of mood disorders, higher prevalence of dementing disorders, greater impairment in neuropsychological tests, higher rate of dementia development on follow-up, more neurosensory hearing impairment, greater enlargement in lateral brain ventricles, and more white matter hyperintensities. These studies also suggested that late onset depression includes a large subgroup of patients with neurological brain abnormalities. However, the early-versus late-onset description had limitations. Episodes of mild depression occurring in early life might have been missed and patients could be incorrectly thought to have late-onset depression. A percentage of patients with early-onset, recurrent depression might have died from cardiovascular disease or suicide and never reached late life (selective mortality). Early-onset depression does not preclude that an individual could develop depression due to neurological brain disease in late life. However, the most important limitation had been that age of depression onset could not offer a clear enough “window to the brain.”

The above concerns led us to focus on cognitive comorbidity of late-life depression. This strategy was opportune. When this work started, geriatric neuropsychology and cognitive neuroscience were already advanced, and if complemented by structural and functional neuroimaging, could identify some brain dysfunctions of late-life depression. In replicated studies, we documented that executive dysfunction occurring during late-life major depression was associated with poor or slow response to conventional antidepressants. Executive functions require integrity of fronto-striato-limbic networks, which participate in the regulation of mood. Structural neuroimaging studies showed that reduced volume of the anterior cingulate cortex (ACC), high volume of white matter hyperintensities, and microstructural abnormalities in frontal and frontal subcortical areas were associated with low remission rate of late-life depression treated with an selective serotonin reuptake inhibitor (SSRI) antidepressant. These observations were complemented by functional neuroimaging studies, which documented that depressed older patients who do not achieve remission after SSRI treatment had low functional connectivity within the cognitive control system (dorsal ACC to dorsolateral prefrontal cortex). Apathetic, depressed older patients had abnormal functional connectivity not only in the cognitive control system, but also in reward networks. Taken together, these findings suggest that executive dysfunction and its underlying abnormalities are central to the pathophysiology of a subgroup of late-life depression and influence its response to antidepressants. The article by Manning et al. summarizes the functional neuroanatomy of executive systems and their relevance to late-life depression. It also outlines clinical and neuropsychological assessment procedures and their neurobiological substrates.

Whereas most depressed older adults are treated with pharmacotherapy, effective psychotherapies have been developed for late-life depression. Practice guidelines recommend combination of psychotherapy with pharmacotherapy as the first-line treatment of late-life major depression, whereas psychotherapy alone is a first-line treatment in mild major depression. Interpersonal therapy and learning-based therapies such as cognitive behavioral therapy, problem-solving therapy, and behavior therapy have been found effective in depressed older adults without significant cognitive impairment and medical burden. Poor response of depression with executive dysfunction to pharmacotherapy was the impetus for a modification of problem-solving therapy (PST-ED) to address the cognitive limitations of depressed older patients with executive dysfunction. PST-ED was found more effective than supportive therapy. Problem adaptation therapy (PATH) was designed for patients with severe executive dysfunction. It combines problem-solving therapy with environmental adaptations and involves caregivers in treatment. Treatment models for depression have been developed for patients with chronic...
and acute medical conditions. The personalized intervention for depression in COPD (PID-C) was designed to mitigate treatment and rehabilitation adherence problems originating from lack of energy and demoralization. Ecosystem-focused therapy (EFT) was designed to address the psychosocial storm that disrupts patients’ lives and disorganizes their ecosystems.

Despite availability of efficacious psychotherapies, few depressed older adults receive psychotherapy. Streamlining of psychotherapies is a necessary first step for increasing the utilization of psychotherapies by the existing workforce. We have argued that neurobiological knowledge has reached the point of providing biologically meaningful behavioral targets, thus guiding the development of effective, simplified psychotherapies. This view is supported by the Research Domain Criteria (RDoC) Project and its workshops, which reflect the field’s consensus and recognize the readiness of neurobiology to guide research in treatment development. “Engage” is an example of such a streamlined therapy for late-life depression. It targets behavioral domains grounded on RDoC constructs using efficacious behavioral strategies selected for their simplicity. The article by McGovern et al. discusses psychotherapies for late-life depression in more detail.

This volume combines information directly related to the clinical care of depressed older adults with a discussion of aspects of pathophysiology serving for novel treatment development. Its articles do not offer a comprehensive coverage of the entire field of late-life depression and are influenced by the clinical and research work of its authors. Although biased, I hope that this volume will be both clinically valuable and also stimulate the readers’ interest, curiosity, and creative thinking in approaching a complex disorder that affects a large number of older adults.

**REFERENCES**


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