Neurologic Changes and Depression

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KEYWORDS

• Major depressive disorder • Subjective cognitive impairment
• Mild cognitive impairment • Neurocognitive disorder • Neuropsychological testing
• Neuroimaging • Psychotherapy • Antidepressants

KEY POINTS

- The assessment of late-life depression with comorbid cognitive impairment can be challenging and requires a clear clinical history and a thorough medical and cognitive assessment.
- There are several neuropsychological changes associated with late-life depression, ranging from subjective cognitive complaints to mild cognitive impairment to dementia.
- Changes on neuroimaging and in several biomarkers (eg, apolipoprotein E e4 allele, beta-amyloid, tau, neurotrophins, and so forth) have been associated with late-life depression.
- Multiple psychotherapeutic techniques have been found effective in the treatment of late-life depression as well as holistic/nontraditional, pharmacologic, and brain-stimulation approaches.

INTRODUCTION

Late-life depression affects 3.0% to 4.5% adults older than 65 years in the United States.[1] For many older adults with depression, affective symptoms are accompanied by cognitive difficulties, which can range from subjective cognitive complaints to mild cognitive impairment (MCI) to dementia. Epidemiologic findings suggest that late-life depression may be a risk factor for dementia.[2,3] Given the relatively high prevalence of depression in older adults and a growing focus on modifiable risk factors for dementia, there is interest in better understanding the complex relationship between depression and cognitive impairment. This review focuses on individuals with unipolar depression without psychotic features with comorbid MCI or dementia. To align with the

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terminology used in earlier literature and within the *International Classification of Diseases, Tenth Revision* coding system, the authors use *Diagnostic and Statistical Manual of Mental Disorder* (Fourth Edition, Text Revision) (*DSM-IV TR*) terminology (ie, MCI and dementia) instead of the *DSM-5* terminology for neurocognitive disorders.

Clinical Assessment of Late-Life Depression with Comorbid Cognitive Impairment

Accurately diagnosing late-life depression can be challenging because of the wide variety of symptom presentations.[4] A few key points can guide the clinical evaluation of depression in older adults with comorbid cognitive impairment. Specifically, these are (1) receiving a detailed history from both the patients and their informants, (2) following patients longitudinally to monitor symptom progression, and (3) interviewing with potential reversible causes of cognitive impairment in mind (eg, substance use, metabolic problems, and so forth).

First, the most powerful diagnostic tool the clinician has is the clinical interview. Obtaining a detailed history from both the patients and their informants will be a critical piece to determine whether the patients have a primary mood and/or cognitive disorder. In certain cases, a detailed neuropsychological evaluation may be necessary to delineate cognitive and mood symptoms. Furthermore, neuropsychological testing is indicated when there are questions of multiple comorbidities, questionable self- or informant-report, and to establish a baseline in mild dementia and MCI cases. An accurate informant can be especially helpful, as many patients frequently experience anosognosia (lack of awareness due to neurologic disease) about their cognitive deficits or alexithymia (inability to describe one's feelings). Patients may also experience variations in their mood depending on the time of day (ie, diurnal variations); therefore, an informant may be helpful in mapping the overall mood.

Second, clinicians can follow patients' symptoms over time. This technique can be important in the diagnosis of more complex cases when it is difficult to determine whether patients' have primary cognitive disorder, primary mood disorder, or both. Clinicians should determine whether emotional and cognitive symptoms resolve, remain static, or progress over time. For example, if the cognitive symptoms worsen despite stable or improved mood, this would suggest a primary cognitive disorder. Alternatively, if the cognitive symptoms vary with emotional state, for example, worsening with increased emotional distress, this would suggest a primary mood disorder.

When patients present with both significant emotional and cognitive complaints, clinicians should aggressively treat the depressive symptoms first and then reassess cognitive symptoms after some resolution of the severe emotional distress. Literature has indicated that mild to moderate depression is best treated with a combination of antidepressants and psychotherapy.[5] However, the patients' cognitive capacity to engage in psychotherapy should always be considered. Electroconvulsive therapy (ECT) and other brain-stimulation therapies are generally reserved for severe or treatment-resistant cases.

Third, clinicians should always approach these complex cases considering potential reversible causes of the patients' mood and cognitive symptoms. One of the most overlooked, but easily reversible, causes of cognitive impairment in older adults is medication side effects. Specifically, research has shown that benzodiazepines, anticholinergics, opiates, non-narcotic pain medications (ie, tramadol), hypnotics, and antipsychotics have been associated with cognitive symptoms.[6] Substance use in older adults is frequently not explored thoroughly, particularly in regard to alcohol and cannabis use.[7] Finally, a thorough workup for late-life depression should also include a comprehensive laboratory workup, assessing hematologic, metabolic, toxic, and infectious contributions to cognitive and/or affective symptoms.

Risk Factors

The interactions between medical illnesses, depression, and cognitive impairments are typically multidirectional, making it difficult to distinguish causes of current symptom presentations. Men, Caucasians, and individuals with functional impairments were more likely to present with affective symptoms of depression in MCI and early Alzheimer disease (AD).[8] Cerebrovascular disease has been associated with both late-life depression and comorbid executive dysfunction.[9,10] Cognition and mood can also be impacted by other causes of organ failure, including chronic renal failure[11,12] and chronic obstructive pulmonary disease.[13,14]

SUICIDE AND COGNITION

The incidence of suicide among individuals aged 85 years and older in the United States is 17.8 deaths per 100,000 (compared with 15.0 deaths per 100,000 for those aged 65–84 years).[15] Although aging alone may increase the suicide risk, further research is needed to clarify the relationship between cognitive changes from aging and suicidality. The ventromedial prefrontal cortices, which are important in reasoning and decision-making, may become impaired in later adulthood[16] and consequently increase the risk for suicidality. This impairment may be further exacerbated by changes in social support, that is, depressed elders with suicide attempts tend to have greater difficulties socially.[17] Finally, many medical illnesses affecting older adults are often accompanied by comorbid depression and cognitive impairments, likely predisposing the affected older adult to suicidality.[11,18,19]

NEUROPSYCHOLOGICAL CHANGES IN DEPRESSION

Cognitive Aging

Cognitive aging is characterized by gradual changes in cognitive functioning associated with normal aging.[20] These changes can be variable between patients, are not secondary to a neurodegenerative illness or typically accompanied by functional decline, and generally accelerate in late life. Specific cognitive changes associated with aging include trouble with memory recall and executive dysfunction and slowed processing speed. In contrast, visuospatial skills, crystallized intelligence, and vocabulary knowledge remain stable.[21] Generally, good management of multiple health factors, including hypertension, diabetes, chronic obstructive pulmonary disease, and so forth, and psychiatric disorders (including depression and anxiety) can help mitigate some of the changes associated with normal aging.

Subjective Cognitive Impairment and Depression

Subjective cognitive impairment (SCI) refers to the perception of cognitive decline without evidence of deficits on objective measures.[22] Several cross-sectional studies on the relationship between subjective cognitive complaints and objective impairments on cognitive testing have shown conflicting findings, ranging from a positive correlation[23–25] to no association.[26] However, in longitudinal studies, subjective cognitive impairments have been associated with higher rates of incident cognitive impairment and dementia.[22,27–29] Of note, multiple studies have shown that subjective cognitive impairments are common in individuals with late-life depression, with ranges falling from 50% to 70%.[30,31] Interestingly, one prospective study showed that tau-mediated degeneration, but not beta-amyloid (Aβ) deposition, was significantly higher in patients with MCI compared with SCI.[32] At this time, although there seems to be compelling evidence of a relationship between SCI and depression, further research is needed to more fully understand the causal relationship between the two.

Mild Cognitive Impairment and Depression

MCI is characterized by cognitive complaints (per the patients, informants, or observed by a clinician), objective evidence of impairment, independence in functional abilities, and no impairment in social or occupational functioning.[33] The prevalence of depression in MCI varies widely, with population-based estimates ranging from 3.0% to 83.0%, with a median prevalence of 44.3%; alternatively, the prevalence of MCI in depression ranges from 30% to 50%.[34–36] For most individuals with late-life depression and comorbid cognitive impairment, the profile seems to be a dys-executive pattern[37] characterized by difficulties with working memory, set-shifting, planning, and response inhibition. This syndrome suggests that cerebrovascular disease affects white matter tracts in the fronto-striatal pathways, resulting in executive dysfunction and, potentially, the affective symptoms of depression. Additionally, studies have found that late-life depression is associated with a higher ischemic burden on structural MRI as well as impaired executive and memory functions.[38,39]

Dementia and Depression

Longitudinal studies have provided information on the cognitive trajectories of those with late-life depression. Potter and colleagues[40] found that baseline impairments in encoding and executive functioning in patients with depression seem to be risk factors for progression to dementia. However, this progression seems to be highly variable. Steffens and colleagues[41] found that in a large group of nondemented depressed older adults, at the 2-year follow-up approximately 25% had reverted back to normal cognitive functioning, 15% had progressed to dementia, and the remainder continued to display cognitive impairments without functional decline. Additional research has shown that although one would expect most individuals with late-life depression and MCI to progress to a vascular dementia, these vascular risk factors may simply serve to accelerate the AD process.[34,42]

BIOMARKERS

Apolipoprotein E, Beta-Amyloid, and Tau

Studies on various markers in neurodegenerative illnesses (ie, apolipoprotein E ε4 variant [*APOE* ε4], Aβ, and tau) and late-life depression have been variable. Regarding *APOE* ε4, there seems to be a significant relationship between depressive symptoms and *APOE* ε4 in regard to progression from MCI to dementia. Specifically, a longitudinal study showed that *APOE* ε4 carriers with depression were 4.4 times more likely to progress to AD compared with non-*APOE* ε4 carriers with depression.[43] Meanwhile, a cross-sectional study found no relationship between *APOE* ε4 status, depression, and cognition.[44] Further research on the relation between Aβ and *APOE* ε4 is mixed.[45–48] Finally, although the relationship between tau protein and late-life depression has not yet been clearly established, a longitudinal study indicated those with late-life depression and elevated cerebrospinal fluid total tau levels progressed differently from MCI to AD.[49,50]

Neurotrophins

Recent literature has indicated that individuals with late-life depression display a reduction of neurotrophins, including nerve growth factor, glial-derived neurotrophic factor, and brain-derived neurotrophic factor.[51–53] However, Arnold and colleagues[54] found that 2 neurotrophins specifically associated with neurogenesis, long-term potentiation, and response to ischemic injuries seemed to be increased in older adults

with depressive symptoms: vascular endothelial growth factor and hepatocyte growth factor (reflecting possible compensatory responses).

Hippocampal-Pituitary-Adrenal Axis, Insulin Pathway, and Inflammation

There is limited evidence suggesting that the hippocampal-pituitary-adrenal (HPA) axis and inflammation play a role in late-life depression with comorbid cognitive deficits. Although chronic distress has been associated with disruption in the HPA axis, research on this relationship with comorbid cognitive impairments has been variable.[54,55] Interestingly, literature has provided compelling evidence of hippocampal atrophy in individuals with severe depression and positive inflammation biomarkers.[56]

NEUROIMAGING AND ELECTROPHYSIOLOGY

Structural MRI

With structural MRI, changes in both white and gray matter have been associated with late-life depression and comorbid cognitive impairment compared with nondepressed older adults. In support of the vascular hypothesis, suggesting that cerebrovascular disease is a major contributor to late-life depression, longitudinal MRI studies have shown a correlation between the severity of depression and white matter ischemic changes.[57,58] Similarly, these white matter lesions, especially when concentrated in anterior periventricular regions, have been associated with comorbid executive dysfunction.

Gray matter changes seen in late-life depression may be part of the prodrome to AD. Hippocampal atrophy, a well-known feature of AD, has also been shown to be associated with a higher severity of emotional distress in nondemented individuals.[59] For individuals with MCI, depression was associated with reduced thickness of the entorhinal cortex, anterior cingulate cortex, and bilateral dorsomedial and ventromedial prefrontal cortices.[60–62]

Functional MRI

The connectome (how the brain functions as a system of multiple connected networks) and how pathophysiologic processes can disrupt the connectome are now major areas of research. Recent functional MRI studies suggest that structural lesions associated with late-life depression can also lead to the disruption of networks associated with the clinical features in late-life depression (eg, apathy and executive dysfunction). In one study, the cognitive control network and corticostriatal networks were shown to be linked to cognitive dysfunction (ie, executive impairments) in late-life depression.[63]

PET Imaging and Florbetapir Imaging

PET imaging studies provide conflicting information. Specifically, one study found that some patients with late-life depression and MCI showed a Pittsburgh compound B imaging pattern suggestive of AD,[64] whereas another did not replicate this relationship.[65] Research with an amyloid and neurofibrillary tangle binding agent (FDDNP) for individuals with MCI and depression found variable temporal and parietal lobe binding.[66,67] This finding was further confirmed by research coming from the Alzheimer's Disease Neuroimaging Initiative showing that lifelong depressive symptoms reliably predicted Aβ accumulation in patients with MCI.[68] These findings suggest that larger studies are needed to understand the complex PET imaging relationship between depression and cognitive impairment.

Electrophysiology Markers

Using electroencephalogram (EEG) technology, individuals with late-life depression have shown more slow-wave activity and prolonged $P300_a$ latencies, indicating decreased cerebral arousal and information processing.[69] Additional researching using a complex response inhibition task showed decreased event potential localized to the anterior cingulate cortex in depressed older adults.[70] Although not diagnostic, these EEG findings may help shed light on the cognitive deficits often reported by individuals with late-life depression.

PSYCHOTHERAPIES

Several evidence-based psychotherapies have been shown to be effective in the treatment of late-life depression, even in those with associated cognitive impairments. Psychotherapy should always be considered for individuals with MCI and early AD, especially, as older adults typically only show an adequate response in approximately 30% after a trial of a first-line antidepressant.[71]

Cognitive Behavioral Therapy

Cognitive-behavioral therapy (CBT) has become one of the more common treatments for a wide-range of disorders, including depression, posttraumatic stress disorder, anxiety, insomnia, and so forth. It is based on the assumption that maladaptive patterns of thought and behavior contribute to the development of emotional distress, such as depression. CBT focuses on breaking the links between dysfunctional cognitions, emotions, and behaviors. One recent meta-analysis[72] found that CBT and problem-solving therapy (PST) were more effective than other therapies in treating late-life depression. Furthermore, research has shown CBT to be effective even when applied to individuals with MCI.[73]

Interpersonal Therapy

Interpersonal therapy (IPT) concludes that the development of depressive symptoms is influenced by the relationships between patients and their significant others. For treatment, it combines techniques from supportive and psychodynamic therapies, focusing on interactions between the therapists and the patients, with the goal of generalizing positive interactions toward the patients' significant others. IPT has been shown to be effective in the treatment of treatment-resistant depression for younger to middle-aged adults,[74] although there are fewer studies in older adults. One study[75] showed that IPT, when modified to include patients' caregivers, was effective in reducing depressive symptoms in cognitively impaired individuals.

Problem-Solving Therapy

PST focuses treatment on everyday problems, with the goal of improving coping skills to prevent distress. The therapists work with the patients to identify problems, develop a set of possible solutions, decide on one of these solutions, and then implement the solution (assessing its success). Two meta-analyses[76,77] have shown that PST effectively treats late-life depression. Furthermore, these findings are supported by another meta-analysis indicating PST was more effective than several other psychotherapies.[72] In a multisite clinical trial of older adults with depression and executive dysfunction, problem-solving was shown to be more effective than supportive therapy in reducing depressive symptoms (persisting long after the 12 weeks of treatment).[78] Furthermore, late-life depression seems responsive to modified PSTs, including

primary care–based PST, problem adaptation therapy, and home-bound PST for individual with cognitive impairments.[79–81]

Reminiscence and Life Review

Based on Erikson's last stage of life span development focused on "meaning making," reminiscence and life review therapies were designed to treat psychological disorders in older adults. The life review is a systematic process structured around life themes, such as one's childhood, parenthood, work productivity, and so forth. For treatment, the therapists work with the patients to recall memories with the goal of focusing on positive life events and enhancing well-being. The life review process then focuses on developing a narrative of the person's life, evaluating events and reframing and integrating them. There are 3 meta-analyses that have shown reminiscence and life review therapies to be effective in treating late-life depression[72,82,83]; however, these data were complicated by the variations in how these therapies are applied.

HOLISTIC AND OTHER NONTRADITIONAL APPROACHES

Because of a variety of reasons, for many older adults, holistic and other nontraditional approaches for treatment of depression may be more acceptable than psychopharmacologic and psychotherapeutic approaches. First, as nontraditional treatments (eg, physical activity, art therapy, meditation, and so forth) have been used by many for non–mental health reasons, older adults may be more open to their use, especially if they have no history of psychiatric treatment. Second, older adults may find it easier to speak with their physicians about their physical symptoms than their emotional or cognitive complaints. Therefore, offering holistic and nontraditional treatments, which may benefit both physical and mental health, may be more acceptable. Third, as the mental health community has grown in the integration and study of nontraditional treatments, the authors have found that, although not easy to study, these approaches may offer unique benefits for the treatment of late-life depression.[84]

Physical Activity and Cognitive Training

Physical exercise has been shown to have a significant impact on both late-life depression and cognition. A systematic review by Mura and Carta[85] showed that most of the included studies showed reductions in depressive symptoms (with no other interventions used). Multiple studies have shown that exercise alone is equally effective, if not a powerful addition, to antidepressant medications.[86–88] Moreover, exercise has the potential to improve cognitive functioning in older adults as well. Particularly, executive functions, for example, planning, working memory, problem-solving, and so forth, seem to have robust benefits from aerobic exercise.[89]

There also seems to be some evidence that cognitive training may have some cognitive benefits in depressed older adults.[90,91] However, further research needs to be done to examine generalization from these effects to daily functioning.

Technological Interventions

Recent advances have allowed technological approaches to be combined with traditional treatments of mental health issues. Internet-based psychotherapies[92] and exergaming[93] can function independently or be further augmented with the use of mobile applications.[94] However, there is not yet compelling evidence for the effectiveness of these approaches with older adults.

Religion and Spirituality

With the increased importance of cultural competency in mental health research, the role of religious and spirituality practices has gained recognition for the treatment of late-life depression. For example, studies on the use of yoga and meditation have shown significant reductions in depressive symptoms in older adults.[95,96] However, the effects these practices have on cognition are not yet well known. Finally, research on the use of tai chi with older adults suggests improvements in depressive symptoms, physical functioning, and cognitive functioning as well as reductions in inflammatory C-reactive protein.[97,98]

Music, Art, and Dance Therapy

Various art therapies have been shown to have positive effects on both mood and cognition. Specifically, music therapy may improve depression and cognitive symptoms in older adults[99,100] and dance therapy has shown a significant effect on mood.[101,102]

Ketamine

Recent literature has indicated that ketamine, typically used as an intravenous anesthetic, has been shown to have rapid antidepressant efficacy in individuals with refractory major depressive disorder (MDD).[103] Moreover, initial studies have not shown there to be lasting neurocognitive deficits secondary to ketamine treatment 1 week after administration, although there is an initial slowing in processing speed.[104]

PHARMACOLOGIC APPROACHES

Antidepressants

Most of the recent literature on depression and cognition has focused on selective serotonin reuptake inhibitors (SSRIs) and selective serotonin-norepinephrine reuptake inhibitors (SNRIs). The results on SSRIs have been variable, depending largely on the medication being studied. Specifically, sertraline was indicated to improve episodic memory and executive functions,[9] whereas citalopram was shown to cause difficulties in response inhibition, verbal learning, and processing speed.[105,106] Alternatively, there seems to be more compelling evidence of cognitive benefits from SNRIs.[107,108] Alternatively, antidepressants with anticholinergic effects (ie, many tricyclic antidepressants) likely have detrimental effects on cognition.[109]

Cholinesterase Inhibitors and N-Methyl-D-Aspartate Antagonists

Research on the use of cholinesterase inhibitors for late-life depression and comorbid MCI are limited, with conflicting findings in terms of cognitive and mood outcomes. Interestingly, research on donepezil has shown varying results, from positive effects on depression[110,111] to no positive effects.[112] Memantine, an N-methyl-D-aspartate antagonist, has not been shown to have any efficacy as a treatment of comorbid MDD.[113–115]

BRAIN STIMULATION THERAPIES

Electroconvulsive Therapy

Although initially developed for the treatment of psychotic symptoms, ECT has been shown to be effective in the treatment of severe, treatment-resistant depression.[116] Although not fully understood, ECT is thought to release multiple neurotransmitters, including glutamate, noradrenalin, dopamine, and serotonin.[117,118] However, post-ECT cognitive adverse effects have been found. These effects tend to be time limited

and include disorientation after each ECT session and both anterograde and retrograde amnesia, which can persist for 1 to 6 months after the last session.[117,119] More subtle cognitive deficits have also been shown to be time limited and include decreases in processing speed, working memory, learning and memory, and executive functions.[120,121]

Other Brain-Stimulation Therapies

Rather than using an electrical current, transcranial magnetic stimulation (TMS) uses an electromagnet to stimulate brain regions. In one study, patients receiving repetitive TMS showed improvement in depressive symptoms, functioning, and cognitive performances.[122–124] Although not yet used to study late-life depression with comorbid depression, this intervention seems to be a promising area of future research.

Although deep brain stimulation (DBS) has been shown to be associated with successful outcomes for treatment-resistant depression, responses differ among studies, with 6-month success rates ranging from 41% to 66%.[125–128] Several DBS targets have been studied, including the subgenual cingulate region, subcallosal tracts, nucleus accumbens, ventral striatum, inferior thalamic peduncle, and habenula. At this time, there is not compelling evidence for cognitive benefits of DBS for patients with late-life depression and comorbid cognitive impairment.

SUMMARY

Although the understanding of the relationship between depression and cognition has grown significantly over the past several years, researchers continue to uncover more details regarding the complex interplay between these two factors. There have been several promising developments recently, especially with advances in neuroimaging and biomarker research. Additionally, although several therapeutic modalities have been researched for the treatment of late-life depression, many of them have been limited by factors, including providers' experience and/or treatment availability. Given the current literature, optimal assessment and treatment of older adults with depression should include multiple modalities, such as neuroimaging, genotyping, and risk factor burden calculations, to better understand the patients' prognosis and potential treatment response. Future research should then focus on more individualized treatments, pharmacologic and psychotherapeutic, for late-life depression in order to more effectively treat both cognitive and affective symptoms.

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