Depression and Cognition in the Elderly

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Abstract

This review provides an overview of the relationship between depression and cognition in the elderly, with an emphasis on psychotherapies and nonpharmacologic approaches. We first review the clinical presentation of late-life depression and comorbid cognitive impairment, as well as the epidemiology and risk factors for cognitive impairment in late-life depression and the temporal relationship between depression and cognitive impairment. Next, we discuss the salient topic of elderly suicide and cognitive impairment. We then touch briefly on the neuropsychological deficits, biomarkers, and neuroimaging findings in late-life depression with comorbid cognitive impairment. We then focus most of this review on psychotherapies and nontraditional treatments for late-life depression with comorbid cognitive impairment and examine what evidence, if any, exists of the cognitive and functional benefits of these treatments. Finally, we examine the cognitive effects of pharmacologic treatments and brain stimulation therapies.

Contents

INTRODUCTION

Late-life depression affects about 3.0–4.5% of adults 65 and older in the United States (Eden et al. 2012). Many depressed older adults often complain of cognitive symptoms, which range from normal cognitive aging to mild neurocognitive disorder to major neurocognitive disorder (dementia). Epidemiologic findings also suggest that late-life depression may be a preventable risk for dementia (Byers & Yaffe 2011, Steenland et al. 2012). Given the relatively high prevalence of depression in older adults and the growing focus on preventable risk factors for dementia, recent studies have begun to probe the complex relationship between depression and cognitive impairment. In this review, we focus on older adults who experience unipolar depressive symptoms without psychotic features [such as those with major depressive disorder (MDD) without psychotic features, subsyndromal depression, or depression with insufficient symptoms] and conjointly experience cognitive symptoms consistent with mild neurocognitive disorder (Am. Psychiatr. Assoc. 2013) or mild cognitive impairment (MCI). We do not discuss in depth the very complex relationship between late-life depression and dementia or treatments for dementia with comorbid depression

MDD: major depressive disorder

MCI: mild cognitive impairment

because these topics have been reviewed elsewhere (Byers & Yaffe 2011). Finally, in this article we continue to use the traditional terminology (particularly MCI) instead of the DSM-5 terminology for neurocognitive disorders given that this is the terminology used by most investigators.

Clinical Assessment and Management of Late-Life Depression with Comorbid Cognitive Impairment

Recognizing late-life depression itself can be challenging because of the wide variation in presentation (Blazer 2003). The clinical presentation, diagnostic interview, and workup of late-life depression have been discussed in detail elsewhere (Blazer 2003). Here, we focus on a few key points that may be helpful for the clinical evaluation of depressed older patients with comorbid cognitive impairment. The keys to making an accurate diagnosis of late-life depression with comorbid cognitive impairment are (*a*) obtaining detailed histories from patients and their informants; (*b*) following patients longitudinally, which can be useful in diagnosing more complex cases; and (*c*) being vigilant about the possibility that substance use and iatrogenic causes may contribute to patients' cognitive symptoms, since these may be reversible causes.

First, obtaining a detailed history from patients and their informants can be helpful to diagnose whether the patients have primary mood or cognitive disorders. There are no laboratory or neuroimaging tests that definitively diagnose late-life depression. Similarly, in the absence of available neuropathologic confirmation, the most effective clinical diagnostic tools of cognitive deficits are clinical history (including collateral from a reliable source) and examination, and, when appropriate, referral for a detailed neuropsychological evaluation. Informants can be especially helpful in giving a more accurate picture about patients' functioning. Patients frequently experience anosognosia about their cognitive deficits or alexithymia, so their collateral sources may give more detailed descriptions about cognitive deficits and mood symptoms. Patients may also experience diurnal variations in their depressive symptoms, and depending on the time of the medical appointment, they may appear better than they are during the rest of the day.

Second, following patients longitudinally can sometimes be useful in diagnosing more complex cases when clinicians are trying to decide whether the patient has a primary mood disorder, a primary cognitive disorder, or both. Clinicians should focus on whether patients' initial presentations are more consistent with depressive or cognitive symptoms. The longitudinal relationship between depressive and cognitive symptoms can also be helpful to the diagnosis. If cognitive symptoms worsen as depressive symptoms progress, this suggests the presence of a primary mood disorder. If cognitive symptoms worsen despite relatively stable depressive symptoms, this suggests a primary cognitive disorder. Clinicians should not feel pressured to make a definitive diagnosis and identify a treatment when they are uncertain about the diagnosis, unless there are emergent symptoms such as suicidality or severe psychotic symptoms (such as not having sufficient oral intake or being aggressive toward others) that are endangering the patients' immediate well-being. Longitudinal data from a second visit may bring up important historical points that patients may not feel comfortable sharing on the first visit.

Given the complexity of some of these cases, it may not always be possible to immediately distinguish whether patients have a primary mood or a primary cognitive disorder. In these more challenging cases, clinicians may wish to consider aggressively treating depressive symptoms first, and then reassess cognitive symptoms to determine whether they have resolved, persisted, or progressed. In general, we recommend initially treating mild to moderate mood symptoms with antidepressants and/or psychotherapy. The ability of the patient to participate in psychotherapy, however, will depend on many factors, including whether the patient is cognitively intact enough to participate. Electroconvulsive therapy (ECT) and other brain stimulation therapies are generally

ECT: electroconvulsive therapy

reserved for treatment-resistant, severe, or life-threatening cases. Improvement in mood is more likely to result in noticeable subjective and functional improvement. On the other hand, no Food and Drug Administration (FDA)-approved drug therapies exist for MCI.

FDA: Food and Drug Administration

MOCA: Montreal Cognitive Assessment

Third, clinicians should be vigilant about the possibility of potentially reversible causes of patients' mood and cognitive symptoms. Medications are probably one of the most overlooked but easily reversible causes of cognitive impairment. Benzodiazepines, anticholinergics, opiates, other types of pain medications, hypnotics, and antipsychotics may cause cognitive symptoms. A recent report from the Institute of Medicine estimated that about 5.6 to 8 million older adults experienced a mental health and/or substance use disorder (Eden et al. 2012). However, substance use in older adults is frequently not explored enough, particularly with regards to alcohol consumption and cannabis use (Blank 2009).

Readily available clinical tools for the assessment of late-life depression include the Geriatric Depression Scale (both the shorter 15-item and the longer 30-item one) (Sheikh and Yesavage 1986) and the Patient Health Questionnaire-9 (Spitzer et al. 1999). The Center for Epidemiologic Studies Depression Scale is another scale that has been mostly used in the research setting, especially community settings, but may also have clinical utility (Radloff 1977). All of these depression-screening tools are available both on paper and online. Interview questions to assess insight into cognitive and behavioral changes include "Does she behave in a way without regard to the outcome and/or embarrassment to herself or other?" or "Does he minimize problems with his thinking or performance on everyday tasks without being aware of it?"

Cognitive screens for MCI and early dementia can help to detect the subtle cognitive deficits that co-occur with depression and to identify individuals who may benefit from neuropsychological consultation to further characterize their cognitive deficits. The Mini-Mental State Examination (MMSE) has been one of the most popular screens, but it may not detect more subtle impairment in executive functioning or cognitive impairment in highly educated individuals. The Montreal Cognitive Assessment (MOCA) has not been validated in large population studies of patients with late-life depression, but given the relatively high prevalence of comorbidity of MCI and early dementia with late-life depression, the MOCA can probably pick up subtler cognitive deficits compared to the MMSE (Nasreddine et al. 2005). Even with a normal MOCA score, however, subtle impairment in executive functioning (particularly in individuals with high cognitive reserve) may go undetected. Other screens that may probe more deeply into executive functioning include the QUICK EXIT (Campbell et al. 2014) and the Frontal Assessment Battery (Dubois & Litvan 2000).

Various scales are also available to measure functional impairment. The World Health Organization Disability Assessment Schedule 2.0 is a widely used measure and is available as one of the online assessments in DSM-5. It has been used in populations who are aging and have MCI (Kowal et al. 2010, Sosa et al. 2012). Other commonly used measurements include the SF-36 and its shorter version SF-12, which are generic measures that capture both physical health and mental health and are not designed for any particular population; and the Functional Assessment Questionnaire, which primarily captures impairment in independent activities of daily living and is used by the Alzheimer's Disease Research Centers.

Epidemiology and Risk Factors

The prevalence of depression in MCI ranges very widely. The population-based prevalence ranges from 3% to 83%, with a median prevalence of 44.3% in hospital-based settings and 15.7% in population-based settings. Conversely, the prevalence of MCI in depression ranges from about 30% to 50% (Bhalla et al. 2009, Reinlieb et al. 2014, Yeh et al. 2011).

As the population rapidly ages with a growing number of chronic medical illnesses, clinicians face the challenge of treating the triad of medical illness, depression, and cognitive impairment. The interactions between medical illness, depression, and cognitive impairment can be bidirectional, which can make it difficult to distinguish cause and effect. Apostolova et al. (2014) found that males, Caucasians, and those with functional impairment were more likely to have affective symptoms (including depression and apathy) in MCI and early Alzheimer's disease (AD). Vascular risk factors have long been associated with late-life depression with comorbid cognitive impairment, as reflected in the concept of depressive executive dysfunction syndrome (Sheline et al. 2010). Higher vascular burden in the context of late-life depression has been associated with a lower likelihood of improvement in working memory and executive functioning (Barch et al. 2012). Conversely, depressive symptoms also adversely affect the cognitive trajectory of those with coronary artery disease and diabetes (Freiheit et al. 2012, Sullivan et al. 2013).

AD: Alzheimer's disease

Studies have also shown that diseases affecting other organ systems may affect mood and cognitive symptoms. Cognitive impairment in chronic renal failure has been associated with both depression and cognitive deficits in attention, memory, processing speed, and executive functioning (Elias et al. 2013), and depression may further exacerbate deficits in processing speed and executive functioning in chronic hemodialysis patients (Agganis et al. 2010). Some studies suggest that chronic obstructive pulmonary disease may also be associated with depression (Bratek et al. 2014, Doyle et al. 2013); and growing evidence suggests that chronic obstructive pulmonary disease is associated with MCI, particularly nonamnestic subtypes, although the strength of this relationship may be related to the duration and severity of the chronic obstructive pulmonary disease (Singh et al. 2014).

SUICIDE AND COGNITION

The rate of suicide among people 85 and over in the United States is 17.8 deaths per 100,000 people, which is the second highest among all age groups, whereas those 65 to 84 years old have a suicide rate of 15.0 deaths per 100,000 people (Am. Found. Suicide Prev. 2012). These statistics support the argument that older adults, particularly white men, may inherently be at higher risk for suicide due to aging alone (Conwell et al. 2011), though it is depression that usually causes suicide. The ventromedial prefrontal cortices, which are important for reasoning and decision making, may become impaired even in older adults with normal cognition. Compared to younger adults, older adults with normal cognition have difficulty set-shifting their selections toward advantageous outcomes on a reward task, and in a study they were found to be more vulnerable to deceptive advertising on a real-world task (Denburg et al. 2007). Therefore, if a suicide attempt is seen as a deficit in reasoning and decision making, older adults, independent of any mood disorder and/or clinically significant cognitive impairment, may be at higher risk for suicide.

Attempted suicide may also reflect difficulties with social and cognitive processing in older adults with late-life depression and comorbid cognitive impairment. Compared to nonsuicidal depressed elders, depressed elders with suicide attempts have greater difficulties socially, as measured by social problem solving, social networks, and interpersonal relationships (Szanto et al. 2012). Furthermore, both older adults who attempt suicide and older adults who have suicide ideation but no suicide attempts have executive functioning deficits (Szanto et al. 2014). There may also be different risk factors for those with high-lethality versus low-lethality suicide attempts, although further studies will be helpful to confirm these initial findings.

Dombrovski et al. (2013) described two different neuroimaging patterns of suicide attempters during a reward learning task. The first type was impulsive suicide attempters who had blunted modulation of paralimbic structures in response to expected reward, and the second type was

depressed suicide attempters who had a weak signal in the thalamocorticostriatal region in response to unpredicted rewards and a maladaptive response to punishment. In a study testing whether individuals preferred a larger delayed monetary reward or a smaller immediate monetary reward, older individuals who made high-lethality suicide attempts preferentially selected larger delayed rewards over small immediate ones, compared to older individuals with low-lethality suicide attempts (Dombrovski et al. 2011). These neuroimaging studies suggest that the etiologies behind high- versus low-lethality suicide attempts may be different; the maladaptive sense of punishment causing high-lethality suicide attempts may be due to depression, whereas the need for immediate gratification causing low-lethality attempts may be more related to impulsivity.

MRI: magnetic resonance imaging

Certain types of medical illnesses, such as end-stage renal disease and cerebrovascular risk factors, can be accompanied by comorbid depression and cognitive impairment, which in turn may predispose older people suffering from such illnesses to suicidality (Agganis et al. 2010, Chan et al. 2007, Kurella et al. 2005). Given that these medical illnesses have well-recognized psychiatric comorbidities and comorbid cognitive impairment, interventions in the primary care setting that target suicidality in these populations may be beneficial. Studies suggest that interventions such as the availability of a depression care manager in conjunction with medication management may have significant utility for depressed older individuals with cognitive impairment (Bogner et al. 2007, Steffens et al. 2006). Additional studies will be beneficial to determine whether or not these interventions may be useful for decreasing suicidal ideation not only in older adults with medical disorders, comorbid cognitive impairment, and suicidal ideation but also in the larger population.

NEUROPSYCHOLOGICAL DEFICITS

A comprehensive review of the literature regarding neuropsychological deficits in late-life depression is beyond the scope of this review, and we strongly encourage readers to peruse other reviews that have elegantly covered the complex relationship between late-life depression and cognitive impairment (particularly dementia) (Byers & Yaffe 2011, Koenig et al. 2014, Morimoto & Alexopoulos 2013). Here we mainly focus on themes that are relevant in later sections about neuroimaging and treatment approaches (Byers & Yaffe 2011, Koenig et al. 2014, Morimoto & Alexopoulos 2013). Executive functioning has been used to describe various higher-order cognitive functions, including working memory, set-shifting, planning, and inhibitory control, and impairment of executive functioning is considered to be one of the classic signs of cognitive impairment in late-life depression. The depression executive dysfunction syndrome hypothesis suggests that cerebrovascular disease affects critical white matter tracts in the frontostriatal pathways, which results in the impairment of various cognitive functions, including executive functioning. Although impairment in multiple cognitive domains (including verbal and nonverbal memory and visuospatial functioning) has been observed, impairments in processing speed and executive functioning appear to be the core deficits that mediate deficits in the other domains (Morimoto & Alexopoulos 2013, Sheline et al. 2006).

Studies have tried to distinguish cognitive profiles for early-onset depression (defined as depression with initial onset before 60–65 years of age) and late-onset depression (defined as depression with initial onset usually around 60–65 years of age). One study of 60 geriatric inpatients found that late-onset depression was associated with higher ischemic burden, as quantified by magnetic resonance imaging (MRI), and impairment of executive functioning and verbal and nonverbal memory (Salloway et al. 1996). In a larger study of older adults with late-life depression who had comorbid impairment in executive functioning, subjects with late-onset depression were more impaired on measures of verbal learning and memory than subjects with early-onset depression (Mackin et al. 2014b).

Longitudinal studies of cognitive trajectories of patients with late-life depression have been important in the characterization of cognitive outcomes. Baseline impairment in memory and executive functioning deficits in depressed patients appear to be risk factors for progression to dementia (Potter et al. 2013). Although there may be a bidirectional relationship between depression and dementia, the cognitive outcomes of subjects with late-life depression and comorbid cognitive impairment are highly variable. In a study examining 201 nondemented depressed older subjects with cognitive impairment, at the two-year follow-up about 25% reverted back to normal cognition, 15% progressed to dementia, and the remainder had persistent cognitive deficits but were not demented. Despite the well-established relationship between vascular disease and late-life depression, most of these cases progressed to AD rather than vascular dementia (Steffens et al. 2009). Bhalla et al. (2009) also found that amnestic MCI (particularly multidomain) and possible or probable AD in the elderly with remitted depression were the predominant forms of MCI and dementia, respectively. Although one might expect vascular dementia to be the predominant form of dementia, these data suggest that vascular risk factors in the context of late-life depression may simply accelerate the AD process (Koenig et al. 2014).

As discussed earlier, treatment resistance (particularly to traditional psychopharmacologic approaches) in late-life depression remains a challenge. Impairment in executive functioning is a classic hallmark of poor responders to psychopharmacologic interventions (Sneed et al. 2010), and it may persist even after treatment (Baba et al. 2010). In fact, older individuals with either subjective or objective impairment in executive functioning may respond more poorly or slowly to citalopram than to placebo (Manning et al. 2013, Sneed et al. 2010). Baseline impairment in other cognitive domains (including verbal memory and processing speed) has also been associated with poorer response to psychopharmacologic intervention at one-year follow-up (Story et al. 2008). Mackin et al. (2014b) proposed that impairment of verbal memory in late-onset depression may also present significant clinical implications for psychotherapeutic interventions that require learning of new procedures, but this hypothesis requires further exploration.

In summary, several major themes have emerged from the neuropsychological literature examining late-life depression with comorbid cognitive impairment. First, late-life depression has been traditionally associated with impairment in executive functioning, processing speed, and psychomotor speed. A number of studies, however, have also shown deficits in other cognitive domains such as episodic memory, processing speed, and visuospatial functioning, but a more careful, detailed characterization is needed to better understand the pathways. Second, the long-term outcomes of these cognitive deficits in the context of late-life depression vary widely, from complete to partial resolution, to persistence despite treatment, to progression despite treatment. Third, neuropsychological evaluation may be one of many valuable tools that may help characterize the likelihood of treatment response before a trial of treatment is attempted and to determine patients' response after the trial is completed. On the whole, the phenotypic heterogeneity of late-life depression with comorbid cognitive impairment suggests that this disorder may exist on a continuum, with varying degrees of severity and potential for recovery.

BIOMARKERS

APOE, Beta Amyloid, and Tau

APOE: apolipoprotein E

Aβ: beta amyloid

Due to the overlap between late-life depression and cognitive impairment, a number of studies have examined the relationship between various markers in neurodegenerative disorders: apolipoprotein E (*APOE*) ε4 variant, beta amyloid (Aβ), and tau. The results have been variable. Köhler et al. (2010b) found that depressive symptoms and the presence of the *APOE* ε4 allele contribute

independently to cognitive decline. Mackin et al. (2013) found that individuals with MCI and subsyndromal depressive symptoms were more likely to have a positive *APOE* ε4 genotype compared to individuals with MCI alone. Likewise, Irie et al. (2008) found that in men who were depressed, depression increased the risk for dementia. Moreover, *APOE* ε4 carriers with depression were 7.1 times more likely to progress to AD compared to non-*APOE* ε4 carriers with depression, who were only 1.6 times more likely to develop AD (Irie et al. 2008). Bogner et al. (2009) found that there was no relationship between *APOE* status and depression (most notably, thoughts of death or suicide) with cognitive impairment. A more extensive study showed that plasma Aβ42 levels independently predicted late-onset depression and AD development in subjects who had never been depressed or did not have current cognitive impairment, suggesting a common biological etiology for these two conditions (Blasko et al. 2010). However, Metti et al. (2013) did not find a relationship between plasma Aβ42 levels and depression; they found, however, that a low plasma Aβ42/Aβ40 ratio was associated with an increased risk of incident depression in individuals carrying the *APOE* ε4 allele, suggesting a complex interaction between depression, Aβ levels, and *APOE*. Sun et al. (2009) found that lower plasma Aβ42 levels and higher Aβ40/Aβ42 ratios were associated with depressed older adults, independent of *APOE* genotype.

Tau proteins are microtubule-associated proteins that are important for axonal transport and cell shape and play a significant role in neurodegenerative disorders. Hyperphosphorylated tau depositions (neurofibrillary tangles) are a common pathological feature of AD. Mutations in microtubule-associated protein tau result in tau protein aggregations and have been associated with frontotemporal dementia with parkinsonism linked to chromosome 17. A relationship between the tau protein and late-life depression has not been clearly established. One study suggested that those with MCI who converted to AD differed from those with late-life depression in that they had elevated cerebrospinal fluid of total tau and phosphorylated tau levels (Schönknecht et al. 2007). In an autopsy of subjects without cognitive impairment, brainstem tangles were associated with higher depressive symptoms, whereas in subjects with cognitive impairment, brainstem tangles were associated with fewer depressive symptoms (Wilson et al. 2013).

Neurotrophins

The role of neurotrophins in late-life depression continues to be investigated. Several studies of subjects with late-life depression report a deficiency of neurotrophins, including nerve growth factor, glial-derived neurotrophic factor, and brain-derived neurotrophic factor (Diniz et al. 2012, 2013; Erickson et al. 2012). Arnold et al. (2012) examined the cohort from the Alzheimer's Disease Neuroimaging study, comprising individuals affected with subsyndromal depressive symptoms and whose cognitive status ranged from normal to MCI to mild AD. Interestingly, they found that vascular endothelial growth factor (involved in angiogenesis and neurogenesis) and hepatocyte growth factor (involved in long-term potentiation and response to ischemic injury) were increased in older patients with depressive symptoms. The authors proposed that the neurotrophin differences seen in this study might reflect potential compensatory responses.

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

Chronic stress, depression, and post-traumatic stress disorder have been associated with disruption of the hypothalamic-pituitary-adrenal axis. This disruption, in turn, may result in increased glucocorticoid levels and development of insulin resistance. Köhler et al. (2010a) did not find any relationship between cortisol levels and persistent cognitive deficits in late-life depression. On

the other hand, Arnold et al. (2012) found that depressive symptoms in a cohort of older adults whose cognitive status ranged from normal to MCI to probable AD were positively correlated with higher levels of insulin polypeptides and pregnancy-associated plasma protein A. Pregnancy-associated plasma protein A modulates the insulin pathway through its cleavage of insulin-like growth factor–binding proteins.

Chronic stress has also been associated with inflammation, and earlier studies have examined the role of inflammatory biomarkers in late-life depression and cognition. Depression in early to midlife may include cognitive symptoms associated with inflammation and hippocampal atrophy (Frodl et al. 2012). Repeated severe episodes of depression have also been associated with hippocampal atrophy (Sapolsky 2000). However, the study of the role of inflammation in late-life depression and comorbid cognitive impairment is still in its early stages.

In summary, there is only at best some modest evidence that pathways associated with neurodegenerative disorders, inflammation, and the hippocampal-pituitary-adrenal axis may play a role in late-life depression with comorbid cognitive impairment. More comprehensive studies with larger populations are needed to confirm some of these initial promising findings. One important unanswered question is whether a set of plasma or cerebrospinal fluid biomarker diagnostic profiles could facilitate the diagnosis/prognosis of those subjects with late-life depression who have or are more likely to develop cognitive impairment.

NEUROIMAGING AND ELECTROPHYSIOLOGY

Structural MRI

The vascular hypothesis suggests that cerebrovascular disease is a major contributor to the development of late-life depression. The burden of white matter lesions secondary to cerebrovascular disease is higher in depressed older adults. MRI studies of subjects with late-life depression have shown a correlation between severity of depression and white matter hyperintensities, which are primarily structural changes from cerebrovascular disease (Krishnan et al. 2004, Taylor et al. 2013); similarly, white matter lesions in the bilateral superior longitudinal fasciculus, right fronto-occipital fasciculus, and left uncinate fasciculus are associated with executive dysfunction in late-life depression (Sheline et al. 2008). Furthermore, compared to older adults with only MCI, older adults with both late-life depression and MCI have higher rates of white matter atrophy in the bilateral frontal, temporal, and parietal regions (Lee et al. 2012).

A number of studies have found changes in gray matter in late-life depression, suggesting that late-life depression may be a prodrome to AD. Hippocampal atrophy has been associated with higher severity of depression in nondemented individuals (Taylor et al. 2014). In older individuals with MCI, depression was associated with reduced thickness of the entorhinal cortex and higher rates of atrophy in the anterior cingulate cortex (Zahodne et al. 2013). Interactions between late-life depression and amnestic MCI were associated with smaller volumes throughout the gray matter, including the bilateral dorsal anterior cingulate cortex, right hippocampus, and bilateral dorsomedial and ventromedial prefrontal cortices (Xie et al. 2012).

Structural imaging may also have some potential utility for predicting treatment response in late-life depression with cognitive impairment. Alexopoulos et al. (2008) found that microstructural white matter damage throughout the brain (including multiple frontal regions) was associated with poorer antidepressant response. Marano et al. (2015) found that after citalopram treatment, depressed patients with larger volumes of gray matter in the frontal areas showed better performance in verbal memory and verbal fluency.

Table 1 Networks affected in late-life depression

Network	Components	Functions	Associated deficits in late-life depression
Default mode network	Medial prefrontal cortex Posterior cingulate cortex Precuneus Medial temporal lobe	Internal monitoring Autobiographical memory retrieval Future planning Theory of mind	Persistent negative rumination
Cognitive control network	Dorsolateral prefrontal cortex Dorsal anterior cingulate cortex Posterior parietal cortex	Decision making Working memory Task switching	Attention and working memory impairments Slowed processing speed
Affective/frontolimbic cortex	Amygdala Subgenual anterior cingulate cortex Hypothalamus Orbitofrontal cortex Nucleus accumbens	Emotional processing Motivation of behavior	Apathy
Corticostriatal circuits	Loop 1: Dorsolateral prefrontal cortex → dorsolateral caudate nucleus → globus pallidus (lateral dorsomedial part) → thalamus (ventral anterior nucleus part) → thalamus Loop 2: Lateral orbitofrontal cortex → ventromedial caudate nucleus → globus pallidus (medial dorsomedial part) → thalamus (medial ventral anterior nucleus part) Loop 3: Anterior cingulate cortex → ventral striatum → globus pallidus → thalamus (medial dorsal nucleus, posteromedial part)	Loop-specific mediation of motor, executive control, or emotional behavior Reward processing	Apathy Anhedonia

Source: Tadayonnejad & Ajilore (2014).

Functional MRI

Several key themes have emerged from functional MRI studies of late-life depression that may revolutionize our current understanding (particularly diagnosis and treatment) of late-life depression. First, we now better understand late-life depression as a disruption of particular networks. Previous models had characterized late-life depression as the result of structural lesions, but more recent functional MRI studies have helped us to understand which networks may be disrupted in late-life depression. These networks include the default mode network, the affective/frontolimbic network, the cognitive control network, and the corticostriatal networks (Tadayonnejad & Ajilore 2014). **Table 1** describes the major functions and anatomical components of these networks. Second, it has been proposed that certain observed clinical features (such as apathy and executive dysfunction) may be localized to the disruption of certain networks. For example, the cognitive control network and corticostriatal networks have been linked to cognitive dysfunction in late-life depression. Third, a better understanding of these networks may be helpful in our comprehension of treatment response or lack of response to both medications and therapy. In one study, resting functional connectivity of the cognitive control network predicted low remission rates after a therapeutic trial of escitalopram (Alexopoulos et al. 2012). In another study, Thompson et al.

(2015) observed patterns of activation and deactivation in the frontal lobes during functional MRI on the Wisconsin Sorting Test that predicted response to cognitive behavioral therapy; however, performance on the Wisconsin Sorting Test itself did not predict response to cognitive behavioral therapy, suggesting that functional MRI provides additional valuable data that are not available from neuropsychological assessment alone.

FDDNP: 2-(1-{6-[(2-[fluorine-18]fluoroethyl)-(methyl)amino]-2-naphthyl}ethylidene)-malononitrile

PET Imaging

One study found that in some patients with late-life depression and MCI, Pittsburgh compound B imaging showed a pattern suggestive of AD (Butters et al. 2008), although another study did not find any relationship between patients who had remitted late-life depression and Pittsburg compound B results (Madsen et al. 2012). In a study looking at binding by 2-(1-{6-[(2-[fluorine-18]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile (FDDNP) to amyloid plaques and neurofibrillary tangles, depressive symptoms in MCI subjects were associated with increased lateral temporal binding, whereas depressive symptoms in cognitively normal subjects were associated with increased medial temporal binding (Lavretsky et al. 2009). On the other hand, Kumar et al. (2011) found that compared to healthy controls, subjects with late-life depression and minimal cognitive impairment had higher [18F]FDDNP binding in the posterior cingulate and lateral temporal regions. These differences in binding suggest that the pathophysiology behind the development of depressive symptoms with comorbid cognitive impairment may possibly be different from that of depressive symptoms with normal cognition, but larger studies are needed to clarify which regions are affected.

Electrophysiologic Markers

A few studies have examined the utility of EEG and other electrophysiologic markers such as event-related potentials in late-life depression. Köhler et al. (2011) found that compared to nondepressed older subjects, subjects with late-life depression had more slow-wave activity and prolonged $P300_a$ latencies, which suggested that the depressed subjects had decreased cerebral arousal and information processing. In another study that examined cognitive control as measured by response inhibition on a more demanding variant of the Go/No-Go task, the N2 component of the event-related potential was significantly decreased in subjects with late-life depression as compared to nondepressed older adults. This deficit was localized to the anterior cingulate cortex, which strongly suggested that late-life depression was associated with a frontal inhibitory deficit (Katza et al. 2010). Another study found that deficits in preattentive auditory processing in late-life depression were associated with poorer semantic fluency and higher levels of functional disability; interestingly, this impairment of preattentive auditory processing was localized to the temporal but not the frontocentral area (Naismith et al. 2012).

In summary, neuroimaging and electrophysiological studies have transformed our understanding of cognitive impairment of late-life depression. Various neuroimaging modalities have indicated that several networks are responsible for comorbid cognitive impairment in late-life depression. Although the clinical guidelines for the assessment of late-life depression with cognitive impairment do not require neuroimaging, these recommendations may change as neuroimaging may start to play a greater role in the characterization of late-life depression, particularly with regard to the disruption of networks leading to cognitive impairment. Neuroimaging and electrophysiological studies may also help to predict which individuals have a higher likelihood of responding to psychotropics and psychotherapies for late-life depression. The evidence for the

utility of electrophysiologic biomarkers in late-life depression with comorbid cognitive impairment is promising, but more detailed and larger studies will be needed to confirm these initial findings.

PSYCHOTHERAPIES

Although clinicians often do not view older adults with cognitive impairment as candidates for psychotherapy, several effective evidence-based psychotherapies have been developed over the years to target this population. Many older depressed adults do not respond to antidepressants, despite multiple trials of different medications; are reluctant to take them because of cost, stigma about taking psychotropics, or concern about polypharmacy; or are not able to tolerate psychotropics due to their side effects. Even when older patients take an antidepressant, the rate of an adequate response is about 50% after an optimal trial of first-line antidepressant, and psychotherapies can be used as an adjunct treatment to alleviate residual symptoms (Lenze et al. 2008). Time-limited therapies for late-life depression have become popular because of the reimbursement limitations imposed by insurance companies and the financial and physical burden of traveling to appointments. Some therapies, particularly cognitive behavioral therapy, have also been adapted to address other symptoms such as insomnia and psychosis. Due to limited space, we focus mostly on therapies that are geared towards older people with depression, particularly on therapies that have been modified for those with comorbid cognitive impairment.

One of the most common psychotherapies is supportive therapy. The purpose of supportive therapy is to build the therapeutic alliance and the patient's self-esteem through an empathic, nonthreatening approach. Supportive therapy is often used as a comparator in psychotherapy trials, and a number of studies suggest that specialized, time-limited psychotherapies may be superior to supportive therapy. Nevertheless, supportive therapy is still valuable as an intervention for late-life depression for several reasons. First, supportive therapy does not require specialized training and materials, and therefore it remains quite popular among mental health clinics as a first-line therapy. Second, psychotherapy trials have shown that supportive therapy is feasible in depressed older individuals with executive dysfunction (Areán et al. 2010) and can be modified to be used in homebound individuals with depression and comorbid cognitive impairment (Kiosses et al. 2010). Third, one study suggested that supportive therapy may even improve information processing speed by ameliorating depressive symptoms; however, this type of therapy did not affect executive functioning, verbal learning, and memory in older adults with late-life depression and executive dysfunction (Mackin et al. 2014a).

Reminiscence therapy, in which older adults use storytelling as a means of reducing depressive symptoms, is based on Erikson's developmental theory, according to which the final stage of psychosocial development is accompanied by feelings of either integrity or despair. The goal of therapy is to assist the individual as she/he seeks purpose and meaning in life before death. There are various types of reminiscence therapy, including structured and unstructured approaches. Several studies have shown that reminiscence therapy can be utilized in demented populations, but its utility in patients with late-life depression and comorbid MCI has not been well studied.

Cognitive behavioral therapy was developed by Dr. Aaron Beck in the 1960s to treat depression, and it has subsequently been modified to treat a wide range of disorders including anxiety, insomnia, post-traumatic stress disorder, psychosis, substance use, personality disorders, and obsessive-compulsive disorder. In cognitive behavioral therapy, patients are taught how to identify the connections between their thoughts, feelings, and actions, and they learn skills to more effectively manage their emotions. Patients learn to identify cognitive distortions such as catastrophizing or black-and-white thinking, which encourages them to adopt a more realistic viewpoint. In addition, the cognitive behavioral therapist helps patients to identify and engage in activities

that are enjoyable and valuable to them. Patients are strongly encouraged to try out these new skills and behaviors outside of the therapy sessions and to use the therapist as a coach and advisor in implementing changes. A few studies have examined the use of modified cognitive behavioral therapy in patients with dementia, but only one small study of cognitive behavioral therapy in patients with MCI suggested that group cognitive behavioral therapy (modified to include both patients with MCI and their caregivers) had high attendance rates, increased patients' acceptance of cognitive deficits, and possibly improved marital satisfaction (Joosten-Weyn Banningh et al. 2008). In addition, one study suggested that older depressed people with cognitive complaints experienced improved depressive symptoms from cognitive bibliotherapy, in which patients learn cognitive behavioral therapy skills from a book (Scogin et al. 2014). Additional studies may be helpful to determine the utility of cognitive behavioral therapy in patients with MCI.

Interpersonal therapy for depression was developed by Drs. Klerman and Weissman and focuses on interpersonal functioning. Like cognitive behavioral therapy, it is usually time-limited (usually 12–16 weeks), but unlike cognitive behavioral therapy, there is no homework component and depression is seen as a medical illness (which often appeals to older people who may view depression as a stigmatizing illness). The therapy is based on identifying interpersonal problems and then working through these problems via a behavioral/educational approach. A modified version of interpersonal therapy for cognitively impaired individuals was developed because depressed individuals with cognitive impairment (MMSE $< 27/30$) were having difficulties with identifying problems to focus on in therapy and with retaining the psychotherapeutic process to build on previous sessions (Miller et al. 2007). The main differences between traditional interpersonal therapy and interpersonal therapy for cognitive impairment are the involvement of the caregiver to help the patient recognize the role transition and the use of specific techniques that address role conflicts related to caregiving. One study found that subjects with lower cognitive functioning who received paroxetine and monthly maintenance interpersonal therapy for 2 years had a significantly longer period until recurrence (41 weeks) compared to standard clinical care (Carreira et al. 2008). Curiously, this effect was not observed for individuals who were cognitively normal, which suggests some possible benefits for individuals with cognitive impairment, although further studies will be needed to confirm this finding.

Problem-solving therapy is probably one of the most carefully studied time-limited therapies designed for late-life depression and comorbid cognitive impairment, particularly for older adults with depression and comorbid executive dysfunction. Problem-solving therapy is based on the idea that depressed people are ineffective problem solvers; through a structured approach, problem-solving therapy teaches depressed people how to solve problems more effectively and, as a consequence, how to better manage their daily lives and improve their mood. Problem-solving therapy is usually administered over a 12-week course and includes the following sessions: psychoeducation about how depression affects problem-solving skills; creation of a problem list; and instruction according to a 7-step problem-solving approach. This 7-step problem-solving approach includes: recognizing the problem, deconstructing the problem into concrete steps, defining the target outcome, generating multiple possible solutions, choosing the optimal solution, deciding when and how to implement the solution, and verifying the effectiveness of the implemented solution. Like cognitive behavioral therapy, problem-solving therapy also focuses on behavioral activation, especially during the first five weeks, but then switches its focus to problem-solving skills, which makes it different from cognitive behavioral therapy. Problem-solving therapy differs from interpersonal therapy in that interpersonal therapy focuses on how patients are interacting with others, whereas problem-solving therapy focuses on developing problem-solving skills.

In a multisite clinical trial of 221 older adults with depression and executive dysfunction that compared problem-solving therapy and supportive therapy, problem-solving therapy was shown

to reduce depressive symptoms and to reduce disability at the end of 12 weeks of treatment. The effect on disability persisted 2 months after therapy was terminated and was more pronounced in patients who had greater cognitive impairment. This effect on disability appears to be mostly related to problem-solving therapy's efficacy for reduction of mood symptoms (Alexopoulos et al. 2011). There does not appear to be any difference between problem-solving therapy and supportive therapy on cognitive symptoms; those who had improved depressive symptoms also had improved information processing speed, but no effects were seen for executive functioning, verbal learning, and memory (Mackin et al. 2014a). PROMISE-D is an ongoing randomized controlled trial to examine whether problem-solving therapy, cognitive behavioral therapy, or enhanced treatment as usual is more effective for patients with late-life major or minor depression who also have at least one comorbid chronic health problem (Sharpe et al. 2012). The outcomes will include executive function, rumination, and emotion regulation.

Problem-solving therapy has also been modified for other settings. The IMPACT study compared problem-solving therapy in primary care versus community-based psychotherapy in older depressed adults. Compared to older adults who received community-based psychotherapy, older adults who received problem-solving therapy in primary care had fewer depressive symptoms and better functioning at 12 months, but there were no differences between the two groups at 24 months (Areán et al. 2008). There was no characterization of cognitive impairment in this study, so the utility of problem-solving therapy in primary care for depression and comorbid cognitive impairment cannot be determined. Problem adaptation therapy is another modified version of problem-solving therapy that accommodates the patient's home environment using environmental adaptation tools and caregiver participation. One preliminary study in homebound older individuals with cognitive impairment (including MCI and early dementia) compared 12 weeks of home-delivered problem adaptation therapy with home-delivered supportive therapy, and it showed that problem adaptation therapy was more efficacious at decreasing depression and disability at 12 weeks compared to supportive therapy (Kiosses et al. 2010). Interestingly, baseline overall cognitive impairment or executive impairment was not associated with the efficacy of either type of psychotherapy, nor did it moderate effects on depression or disability. Further studies will be needed to confirm the utility of problem adaptation therapy.

Technology-based psychotherapies are another promising area to increase accessibility to mental health services, particularly in rural areas where travel times are long and provider availability is limited. Tele-problem-solving therapy was shown to be a well-accepted and efficacious psychotherapy modality to treat depression in depressed, low-income homebound adults, but this study excluded patients with dementia and focused on a younger population (50 to 64 years old) (Choi et al. 2014). One small study showed that Internet-based cognitive therapy in older depressed adults was feasible and resulted in mood improvement symptoms (Dear et al. 2013). Both these findings will need to be replicated in larger studies and tested in patients with comorbid cognitive impairment. Mobile health, in which mobile phone applications (apps) are used for mood monitoring, behavioral interventions such as smoking cessation and weight loss, and delivery of therapies, may become an important tool for mental illness treatments (Donker et al. 2013b). Although no studies have shown whether apps can ameliorate mood and cognitive symptoms in late-life depression with comorbid cognitive impairment, mobile health has tremendous potential to change our current models of face-to-face psychoeducation and psychotherapy. Some potential directions include the development of apps to combine depression treatments with computerized cognitive training to address cognitive deficits or prevent cognitive decline for those at higher risk of decline; another example would be the development of psychoeducation tools for caregivers, especially children of older depressed adults who may have work and childcare responsibilities and may be unable to attend appointments in person.

In summary, many types of psychotherapies have been used in older adults with depression, but only three have been specifically modified to address cognitive impairment in depressed older adults: interpersonal therapy for cognitive impairment, problem-solving therapy, and problem adaptation therapy. Ongoing work to develop and test technology-based and home-based psychotherapies will be important to increase access for older adults who may have been excluded from psychotherapy due to physical restrictions. Problem-solving therapy has probably the strongest evidence for depression and comorbid cognitive impairment; and the observed improvement in disability is most likely mediated by its relief of depressive symptoms. Little effect on cognition, other than improvement of information processing, was observed. On the whole, this evidence suggests two possible (and not mutually exclusive) possibilities: (*a*) these psychotherapies target pathways that mediate the affective component but not the cognitive component of late-life depression; or (*b*) these cognitive deficits result from a pathway that is distinct from that of late-life depression. We found little to no evidence for family-based psychotherapy or psychodynamic psychotherapy in individuals with late-life depression and comorbid cognitive impairment. Given the frequency of comorbid depression and cognitive impairment, and the continued importance of psychotherapy for the treatment of depression, this area is ripe for future study.

HOLISTIC AND OTHER NONTRADITIONAL APPROACHES

Despite fairly strong evidence of the efficacy of pharmacologic and specialized psychotherapy approaches, clinicians may find it easier to persuade older patients to use holistic and other nontraditional approaches (such as physical activity, music or art therapy, or meditation), particularly if these patients have not previously received mental health treatment. There are at least three reasons for this. First, holistic and other nontraditional interventions, which often have not been designed for any specific disease and are used by many persons without mood or cognitive symptoms, may be viewed by patients as more acceptable. For older adults who resist the idea of taking medications or participating in a manualized therapy, and for providers who recognize the advantages of nontraditional interventions, a number of these approaches can represent further possible therapeutic tools that can be implemented with relatively little harm. Then, as the therapeutic alliance develops, the clinician can work with the patient to determine whether there is need for more traditional, evidence-based approaches. Alternatively, these types of interventions may also be used as adjunctive treatments with patients whose symptoms have not fully remitted in response to traditional treatments.

Second, older adults often have comorbid physical diseases that they may initially find easier to discuss with their clinicians than depression and cognitive problems. Since many holistic and nontraditional approaches have been shown to have value for a wide range of physical diseases, these approaches may be potentially effective tools to address both mental and physical health issues in older patients, as long as their medical providers are in agreement. Third, the mental health community is acquiring a growing appreciation of technologically diverse (as reflected by the development of apps for behavioral approaches in other mental health diseases) and culturally diverse (as reflected by the newly available board certification in Integrative and Holistic Medicine) approaches and of alternative and complementary medicine. Many of the approaches we discuss, such as meditation, art therapy, or spiritual exercises or practices, are challenging to study because some of their intrinsically subjective qualities cannot be rigorously and precisely defined. Although this may be seen as a difficulty, it is also inherently part of the beauty of these treatments, and it brings back the "art" as we realize the limits of our own understanding of the science of late-life depression.

We discuss a wide range of holistic and other nontraditional interventions—including physical activity and cognitive activity, lifestyle interventions, technological interventions, religion

and spirituality, and music, art, and dance therapy—for which there is an emerging body of evidence with regard to depression and comorbid cognitive impairment and/or which have shown promising results in research; however, due to space limitations, we do not cover all nontraditional approaches, such as psychoeducation for lifestyle interventions (Norrie et al. 2011), social support, volunteering, and light therapy.

Physical Activity

The evidence suggests that physical activity has modest benefits for late-life depression and cognitive impairment. Proposed mechanisms for the benefits of physical activity, based on animal models and human studies, include: biochemical effects on neurotrophic factors, neurotransmitters such as the serotonin transporter system, and the hypothalamus-pituitary-adrenal axis; neuroprotective effects on various areas, including the hippocampus frontal lobes; and modulation of the default network as visualized on functional MRI studies. A number of clinical trials have also shown beneficial effects of physical activity for cognition as well as depression, and these are detailed elsewhere (Erickson et al. 2013). However, large-scale clinical trials demonstrating that physical activity has therapeutic benefit for mood and/or cognition symptoms in late-life depression with comorbid cognitive impairment remain to be reported, and at this time, the hypothesis that physical activity may affect the interaction between late-life depression and cognitive impairment requires further exploration.

Cognitive Training

Cognitive training is a structured intervention in which patients practice cognitively demanding tasks, such as computer exercises, to either protect or enhance their current levels of cognitive abilities. Some evidence suggests that cognitive training may have cognitive benefits in depressed older adults. For example, Naismith et al. (2011) found that after receiving a cognitive training and psychoeducation intervention, older adults with a history of well-controlled MDD had benefits in memory performance. Mowszowski et al. (2014) also demonstrated that cognitive training in a small group of individuals with MCI or late-life depression resulted in improvements in verbal fluency and subjective memory difficulties. Exergaming (video gaming that combines entertainment and physical activity) is another modality that may provide cognitive benefits (Anderson-Hanley et al. 2012). One small study suggested that exergaming in late-life subsyndromal depression may have both physical and cognitive benefits, and further studies are merited (Rosenberg et al. 2010).

Technological Interventions

Various types of technological interventions are being studied in the field of mental health. The first type combines technological approaches with traditional approaches, such as Internet-based psychotherapies (traditional psychotherapies modified to increase accessibility and/or overcome barriers to successful participation) (Donker et al. 2013a) or exergaming (physical activity and cognitive stimulation through a technological interface) (Rosenberg et al. 2010). These technological interventions may also function independently, for example through mobile apps that can be developed not to require any provider intervention and that may be useful in the treatment of depressive symptoms (at least in the general population) as well as other mental health conditions (Donker et al. 2013b). These interventions, particularly mobile apps developed for other medical conditions that are frequently comorbid with depression and cognitive impairment, may also have behavioral and cognitive benefits. However, existing evidence is not yet persuasive. For example,

computer- and mobile-based devices for diabetes did not demonstrate improved cognitive or behavioral outcomes (Pal et al. 2013).

Another technological intervention may directly assist patients with performing duties, for example by using robots to serve as companions or assist with daily activities. Odetti et al. (2007) performed a preliminary study examining the acceptability of animaloid companion robots (animal-shaped robots that serve as substitute pets and can also be programmed to remind patients of daily activities such as taking pills or checking email) in patients with MCI and early dementia. Future studies are needed to determine whether these may also be beneficial for patients with late-life depression with comorbid cognitive impairment.

Religion and Spirituality

As cultural competency has gained importance in the field of psychiatry, the role of religion and spirituality in the treatment of depression in older adults continues to receive growing recognition in the medical establishment. One example of this growing recognition is the adaptation of manualized psychotherapy to incorporate spirituality and faith-based components. Ceramidas (2012) examined the feasibility of faith-based cognitive behavioral therapy in adults with late-life depression and comorbid cognitive impairment. Although the study was not sufficiently powered to demonstrate significantly different results on psychometric testing, and participation was limited due to some subjects' physical limitations, the subjects and the observing staff reported various positive interactions, which suggests that larger, more rigorous studies of faith-based cognitive behavioral therapy are merited.

Yoga is an ancient practice that is focused on spiritual development and helps to maintain a calm state of mind. Various schools have developed around different ways to achieve this state of mind and spiritual growth. One major theme that reverberates throughout many of these schools is the importance of regulated breathing through various postures to achieve the desired mental state. Despite some studies suggesting the value of yoga for spiritual, physical, and mental benefits, one major challenge in the interpretation of studies involving yoga as a potential therapeutic intervention is the differences between schools (Telles & Singh 2013). Despite significant methodological limitations such as small sample sizes and inadequate controls, a few studies suggest that yoga may reduce depressive symptoms in older adults, although cognitive effects have not been demonstrated (Patel et al. 2012). In a study examining the feasibility of yoga in older adults with cognitive impairment, Hariprasad et al. (2013) found that although participants had trouble remembering and completing the sequences of postures independently, most of them were able to perform the postures. Given this limitation, however, older participants may need modified yoga approaches and additional supervision to ensure successful participation.

Meditation, like yoga, is difficult to define with scientific rigor, because various schools were started within the traditional Eastern culture and were then adopted in Western culture. Authorities do not agree about the universal elements of meditation. Currently, the scientific literature defines meditation in two somewhat opposing fashions: the "method definition," in which meditation is viewed as a rigorous regimen of mental exercises, and the "state definition," in which meditation is viewed as the achievement of an alteration of consciousness or enhanced awareness after the practice of such mental exercises (Nash & Newberg 2013). Meditation alone has been proposed to positively affect a number of cognitive functions in older adults (such as executive functioning, attention, memory, and processing speed), but these studies (like those focusing on yoga) also have significant methodological limitations such as need for replication, sample size, and selective bias (Gard et al. 2014). Further rigorous studies will be needed to see how cognitive and physical limitations may affect the ability of older adults to participate.

Compared to meditation, yoga and tai chi contain an additional physical element that may be theoretically affecting mood and cognitive performance. Tai chi is a form of traditional Chinese martial arts that, like yoga, combines mindfulness and a sequence of graceful physical exercises to maintain ongoing movement in order to achieve stress reduction. A recent review strongly supports the use of tai chi in older adults with depression (Rogers et al. 2009). In a very promising study, 112 nondemented adults 60 and older with depression were treated with escitalopram for 4 weeks and then randomized to either health education or a modified, briefer version of tai chi (tai chi chih) as an adjunct treatment for 10 weeks. The subjects randomized to tai chi chih not only demonstrated greater improvement in physical functioning and decline in the inflammatory C-reactive protein, but they also showed some potential cognitive improvements in memory (Lavretsky et al. 2011). This suggests that modified tai chi (a both cognitively and physically demanding activity) has beneficial cognitive, psychological, and physical effects.

Music, Art, and Dance Therapy

Music therapy may improve depressive and cognitive symptoms in older adults (Cross et al. 2012, Hars et al. 2014). One promising randomized controlled trial showed that weekly multitask exercises with a rhythmic component improved cognitive performance and decreased anxiety (Hars et al. 2014). One study suggested that dance therapy and art therapy may also improve mood in older adults, but their utility in improving cognition has not been as well studied as for depression (McCaffrey et al. 2011, Murrock & Graor 2014).

In summary, most well-designed and implemented larger studies of holistic and nontraditional interventions for older adults have focused on interventions related to physical activity. Very few studies have examined the efficacy of nontraditional interventions in adults diagnosed with late-life depression with comorbid cognitive impairment. More rigorous, larger-scale studies will need to be performed for nontraditional interventions that appear promising. Another potential avenue for further exploration includes the use of nontraditional interventions as an adjunct to well-established traditional interventions.

PHARMACOLOGIC APPROACHES

Antidepressants

Investigators have found that antidepressants, which are the most widely used medications to treat depression in the midst of cognitive impairment, have differing effects on cognition in depressed older adults with comorbid cognitive impairment. Most of the recent literature on depression and cognition has focused on antidepressants that modulate the serotonin system, including selective serotonin reuptake inhibitors and selective serotonin-norepinephrine reuptake inhibitors. Studies have found mixed cognitive effects secondary to selective serotonin reuptake inhibitors, suggesting different cognitive profiles for each type of selective serotonin reuptake inhibitor. Barch et al. (2012) found that sertraline resulted in improvement in episodic memory and executive functioning, but there was no placebo group for comparison. On the other hand, citalopram was associated with difficulty with deficient response inhibition (one measure of executive functioning), verbal learning, and psychomotor speed (Pimontel et al. 2012, Sneed et al. 2010). Use of selective serotonin-norepinephrine reuptake inhibitors, which inhibit both serotonin and norepinephrine reuptake, may be associated with cognitive benefits. In one study, duloxetine was associated with improvement in a composite cognitive measure that included verbal learning and memory, attention, executive functioning, and working memory (Raskin et al. 2007); another study found

that levomilnacipran may have cognitive benefits (mainly attention and reaction time) in late-life depression, but this finding needs further confirmation (Wesnes et al. 2013). Paroxetine is usually avoided in geriatric patients with cognitive impairment because of its anticholinergic effects. We are not aware of any studies examining the cognitive effects of venlafaxine or milnaciprin in late-life depression.

Multimodal antidepressants that indirectly modulate glutamatergic neurotransmission by targeting the serotonergic system have been proposed to target both depression and cognitive systems, but this mechanism awaits further confirmation (Pehrson & Sanchez 2014). Vilazodone was approved by the FDA in 2011 for the treatment of MDD; it functions as both an SSRI and a 5HT1A receptor partial agonist. A clinical trial to determine a therapeutic range in nondemented patients with late-life depression is currently in progress (NCT01608295). Vortioxetine, which was approved in 2013 for the treatment of MDD, acts both by blocking serotonin activity and by modulating serotonin receptor activity. It works as a 5-HT3A and 5-HT7 receptor antagonist, 5-HT1B receptor partial agonist, 5-HT1A receptor agonist, and inhibitor of the serotonin transporter. In one trial in patients 65 and over, vortioxetine showed improvement not only in depressive symptoms compared to placebo, but also in processing speed, learning, and memory (Katona et al. 2012).

No recent studies have examined the cognitive effects of mirtazapine in late-life depression. Bupropion was associated with poorer cognitive performance in cognitively normal elders (Obermann et al. 2013). Although the use of tricyclic antidepressants is not as common as in the 1980s, tricyclic antidepressants are still useful in patients who have failed the more selective antidepressants and are still used for irritable bowel syndrome and chronic pain (such as migraine prophylaxis and neuropathic pain). As part of their side effect profile, tricyclic antidepressants can cause significant cognitive impairment due to anticholinergic effects. Nortriptyline and desipramine are the least anticholinergic among the tricyclic antidepressants and therefore are more commonly used, whereas amitriptyline, imipramine, and doxepin are the most anticholinergic among the tricyclic antidepressants (Khawam et al. 2006). Low-dose doxepin, however, is sometimes used as a sedative in older people.

In summary, none of two FDA quality studies that have independently replicated the same findings has shown that antidepressants can improve cognition in MDD (including late-life depression). Results of recent studies examining cognitive benefits for SSRIs and SNRIs in late-life depression are variable, and although there have been studies of bupropion, mirtazapine, and venlafaxine in late-life depression, they are now old. Antidepressants with anticholinergic effects may even have detrimental cognitive effects. Future studies are needed to confirm whether certain classes of antidepressants may have cognitive benefits in late-life depression with cognitive impairment (Keefe et al. 2014).

Nearly all of the studies conducted so far have focused on patients with acute depressive episodes. Very few studies have shown whether antidepressants improve cognition independent of effects on mood, so improvement of cognition from antidepressants may be potentially attributed to the remission of the depressive episode. Because cognitive deficits in remitted patients are different from cognitive deficits in acute depression, in order to demonstrate a drug-specific effect one would need to demonstrate that the drug improves cognition in fully remitted patients and that its effects are different from another active comparator drug. No drug has met this benchmark. Finally, there is no consensus on what degree of cognitive improvement is clinically meaningful, given that most studies have used statistical significance rather than clinical significance or ADL improvements.

Another caveat is that antidepressants may have a different effect in AD than in MCI; although antidepressants (including sertraline and citalopram) may have some potential use in agitation

in AD, their persistent use has also been associated with cognitive decline (Munro et al. 2012, Porsteinsson et al. 2014, Rosenberg et al. 2012). Potentially promising directions to treat both depressive and cognitive symptoms in older people include the investigation of new multimodal serotonergic antidepressants as well as vitamins and herbal supplements. Stimulants are another understudied area. Methylphenidate has also been used off-label for depression, and it may have benefits for apathy in AD in the absence of depressive features (Rosenberg et al. 2013); however, stimulants have not been shown to improve cognition in randomized controlled trials of MCI or AD. Additional studies will need to examine whether methylphenidate may have positive effects for older depressed adults with comorbid cognitive impairment.

Cholinesterase Inhibitors and N-Methyl-D-Aspartate Antagonists

Data on the use of cholinesterase inhibitors in older adults with MDD and comorbid MCI to either ameliorate cognitive deficits or prevent cognitive decline are limited, and the few available studies report conflicting findings in terms of cognitive and mood outcomes. Pelton et al. (2008) and Reynolds et al. (2011) found that donepezil may have some cognitive benefits in depressed patients with MCI, but Holtzheimer et al. (2008) did not. Furthermore, in a posthoc subgroup analyses, Reynolds et al. (2011) found that although donepezil might have potential cognitive benefits, it could also result in more depressive symptoms. Interestingly, Lu et al. (2009) also found that the addition of donepezil delayed progression of patients with MCI and depressive symptoms to AD, but not of patients with MCI without depressive symptoms. DOTCODE is an ongoing multisite, double-blind, randomized controlled trial to test whether the addition of donepezil to an open-label antidepressant treatment will decrease the conversion rate from MCI to dementia; the trial will also investigate secondary outcomes for various measures of cognition, mood, and functioning (Pelton et al. 2013).

Ketamine, an intravenous anesthetic, has been shown to have rapid antidepressant efficacy in younger adults with refractory MDD, and this has led to a recent interest in the examination of glutamatergic neurotransmission in depression (Pehrson & Sanchez 2014). However, one initial trial examining the efficacy of ketamine in late-life depression did not demonstrate any efficacy (Szymkowicz et al. 2014). Likewise, memantine, another N-methyl-D-aspartate antagonist that is FDA-approved for the treatment of moderate to severe dementia, has also not been shown to have any efficacy as an adjunctive treatment for MDD in the geriatric population (Lenze et al. 2012, Smith et al. 2013, Zarate et al. 2006).

Vitamins and Herbal Supplements

Despite various studies focused upon the efficacy of vitamins and herbal supplements in populations with MCI or early AD and late-life depression, few investigators have examined the efficacy of these vitamins and supplements in populations with late-life depression and comorbid cognitive impairment. Sinn et al. (2012) found that in older patients with MCI, those who received an omega-3 supplement enriched with docosahexaenoic acid had improvements in both depressive symptoms and verbal fluency, whereas an omega-3 supplement enriched with eicosapentaenoic acid only improved depressive symptoms, which suggests differential effects for the various types of omega-3. Vitamin B12 and folic acid given together may also have positive effects in older adults with depressive symptoms and cognitive impairment (Walker et al. 2012). Despite some promising findings in studies examining the use of St. John's wort, ginkgo biloba, vitamin E, and S-adenosylmethionine in populations with either MCI and dementia or late-life depression,

there is little to no evidence concerning the use of these supplements in late-life depression with comorbid cognitive impairment.

BRAIN STIMULATION THERAPIES

Brain stimulation therapies are another modality used in the treatment of depression that utilizes electrical or magnetic energy to stimulate nerve cells. One major challenge in this field is the cognitive side effects of these therapies, especially ECT. Concern about these cognitive side effects has significantly limited the use of ECT and has led to the development of new brain stimulation therapies such as repetitive transcranial magnetic stimulation and magnetic seizure therapy. The history of brain stimulation therapies began with the development of ECT in the 1930s (NIMH website). Since its introduction, ECT has been used to treat a wide range of neuropsychiatric disorders, including depression, schizophrenia, bipolar disorder, and catatonia. Whereas psychopharmacologic and specialized psychotherapies are employed as first-line treatments for depression, ECT is generally reserved for treatment-resistant depression or life-threatening depression (e.g., catatonia, severe lethality). Despite strong evidence of the rapid efficacy of ECT (especially in geriatric patients or patients with psychotic features), concerns that have limited widespread use of ECT as a first-line treatment include negative stigma in the lay media and post-ECT cognitive adverse effects.

Post-ECT cognitive adverse effects are time limited and include disorientation after each ECT session and anterograde and retrograde amnesia, which onset at the first session and can persist for up to 1 or 6 months after the last session (Lisanby 2007, McClintock et al. 2014). A recent meta-analysis showed that most cognitive side effects from ECT are time limited and may include decreases in processing speed, working memory, learning and memory, and executive functions (Semkovska & McLoughlin 2010). Interestingly, some preexisting cognitive difficulties associated with the neuropsychiatric disease may show improvement after ECT due in part to the resolution of the neuropsychiatric symptoms. Nevertheless, given the concerns about post-ECT cognitive impairment, modifications in electrode placement, pulse waveform, and dosage have been implemented over the years to minimize cognitive side effects while maintaining clinical benefit.

Repetitive transcranial magnetic stimulation uses an electromagnet rather than electrical current to stimulate brain regions. Two studies have demonstrated the feasibility and safety of using repetitive transcranial magnetic stimulation for cognitive deficits in AD (Ahmed et al. 2012, Devi et al. 2014). In one of these studies, patients who received high-frequency repetitive transcranial magnetic stimulation compared to sham showed improvement on the Geriatric Depression Scale, MMSE, and independent activities of daily living (Ahmed et al. 2012). To the best of our knowledge, no studies have examined the therapeutic efficacy of repetitive transcranial magnetic stimulation in a cohort of late-life depressed elderly with comorbid cognitive impairment, although this could be a promising area.

Magnetic seizure therapy is another novel brain stimulation therapy that utilizes the transcranial magnetic stimulation device to deliver a series of targetable magnetic pulses to select brain regions to generate seizures. The main advantage of magnetic seizure therapy is that by targeting select brain regions, the seizure is directed towards desirable areas while avoiding undesirable areas that could result in side effects. Like ECT, the patient requires general anesthesia, and various technical parameters (including magnetic coil configuration and placement, magnetic pulse parameters, and magnetic dosage) can be adjusted to maximize efficacy and minimize side effects. Optimization of the magnetic seizure therapy parameters is important to ensure optimal seizure induction and therefore efficacy of treatment. The mean age of participants in the studies that examined the utility

of magnetic seizure therapy was between mid-40s and mid-50s. The exception was a case report of a 66-year-old female patient with severe major depressive disorder and comorbid obsessive-compulsive disorder and anorexia nervosa. In this case, magnetic seizure therapy was shown to be effective with little to no cognitive side effects (Kosel et al. 2003).

In summary, there is evidence of short-term post-ECT cognitive adverse effects. Longer-term studies are needed to characterize the cognitive course post-ECT and identify which groups may be at higher risk for persistent cognitive difficulties. Although other brain stimulation therapies such as repetitive transcranial magnetic stimulation and magnetic seizure therapy have been found to be cognitively benign, larger longitudinal studies are needed in older adults to confirm these initial findings. Due to the focus on post-ECT cognitive effects, the literature on brain stimulation therapies has been slanted towards the examination of neurocognitive effects after the stimulation therapy. To the best of our knowledge, no studies have examined the efficacy of any of these brain stimulation therapies in a dedicated cohort with a diagnosis of new-onset late-life depression with well-characterized comorbid cognitive impairment.

CONCLUSION

Whereas clinicians have long appreciated the syndrome of late-life depression and comorbid cognitive impairment, researchers continue to uncover the complex interplay of biological and environmental risk factors that result in the development of this syndrome in vulnerable individuals. And although late-life depression with comorbid cognitive impairment is one of the most common psychiatric syndromes in older adults, our knowledge about effective treatments is sparse. The current standard of care for late-life depression and comorbid cognitive impairment usually consists of a bedside examination, and whenever appropriate and available, of additional consultations with neuropsychologists and occupational therapists to address more complex questions of cognitive deficits and functional impairment. After the assessment, the clinician and the other members of the treatment team (which may include a psychologist, social worker, nurse, and/or depression care manager) create a treatment plan in collaboration with the patient and the family. The depressed individual usually receives an initial trial of an antidepressant and/or psychotherapies, and in severe or refractory cases, a trial of ECT or possibly another novel brain stimulation therapy. Clinicians select treatments based on their experience and the treatments' availability, which sometimes can result in prolonged suffering for both patients and families in severe or refractory cases.

There have been many promising developments recently, especially with respect to the characterization of late-life depression in terms of biomarkers, neuroimaging, and the growing number of late-life psychotherapies and holistic and nontraditional interventions for individuals with comorbid cognitive impairment. However, much work remains to be done to validate these findings in larger-scale clinical trials and community-based populations, especially among minorities and lower socioeconomic status groups who have traditionally underutilized mental health care due to limited access and stigma. Ongoing multisite clinical research in the field of early detection in AD and other dementias will also be the source of invaluable publicly available data to better understand the evolution of MCI in relation to neuropsychiatric symptoms, particularly depression.

Ideally, validated findings regarding treatment will be translated into clinical practice (despite funding limitations), given the frequency of the syndrome and the disability resulting from it. The future of evaluation and treatment design for late-life depression and comorbid cognitive impairment could incorporate other modalities, such as calculation of risk factor burden, genotyping, serum biomarkers, and neuroimaging, in order to better characterize the patient's prognosis (particularly with regards to suicidality) and improve selection of treatments and determination of

treatment response. Other important areas for development of future treatments are health services studies examining the incorporation of technology, such as telehealth or Internet-based versions of highly effective specialized psychotherapies, to ensure wider distribution of depression treatments, and the use of multimodal treatments combining pharmacologic treatments, psychotherapies, and holistic and nontraditional interventions to reduce the rate of treatment-resistant depression in older adults and to treat more effectively both cognitive and mood symptoms.

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