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Cognitive Impairment in Depressed Older Adults: Implications for Prognosis and Treatment

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Late-life depression is often accompanied by cognitive impairment. Although estimates vary, studies have shown that combined depression and cognitive dysfunction is present in roughly 25% of older adults (1). The number of community residents with both depressive symptoms and impaired cognition doubles every five years after the age of 70. In some cases, the syndromes of depression and cognitive impairment may be related to the same underlying disorder (e.g. vascular dementia, hypothyroidism), whereas in other cases depression and cognitive impairment may be relatively independent, and simply coexist. Differential diagnosis and treatment decisions can be complicated by various factors. Cognitive changes, which are part of the depressive syndrome, can be severe, incipient dementing disorders may have physical and cognitive symptoms that mimic depression, or cognitive impairment may be part of a subclinical dementing disorder unmasked by the pathophysiological changes of depression.

Cognitive Impairments in Geriatric Depressed Patients without Dementia

Neuropsychological impairments spanning many cognitive domains including episodic memory, visuospatial skills, verbal fluency, and psychomotor speed have been reported consistently in late-life depression. These impairments, particularly memory impairment, were attributed to dysfunction in subcortical structures related to mood regulation such as the hippocampus (2). Deficits in executive function are also common in geriatric depression occurring in nearly 40% of elderly depressed patients (3). Replicated studies have indicated that among cognitive impairments, deficits in executive functions are of particular importance given their demonstrable, negative effect on clinical outcomes (3-6). The specifics of this topic are discussed below.

Depression in Patients with Dementing Disorders

Estimates of the rates of depression in dementing disorders range from 30 to 50% (7). Major depression or clinically significant depressive symptoms can be found in between 17 and

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40% of Alzheimer's disease (AD) patients (8). Depression in AD is notable for prominent disturbances in initiation or motivation, fatigue, psychomotor slowing and apathy. Patients with subcortical dementias, including vascular dementia and Parkinson's disease (PD), are more likely to experience depression than patients with AD, with rates in PD reaching 50% (9). Symptoms of depression often overlap with the motor features of PD, which may make differential diagnosis particularly challenging (9).

A first episode of depression presenting in late life is, in some cases, a prodrome of a dementing disorder. Depressed mood has been associated with an increased risk of incident dementia (10). For example, depressive symptoms predicted cognitive decline of elderly women during a four-year follow-up study (11). In addition, in patients with subthreshold cognitive symptoms, those suffering concurrent depressive symptoms are more likely to progress to dementia (12). However, more recent data suggest that there is a significant decline in functioning that precedes late-onset depressive symptoms in AD, and that cognition declines subsequently (8).

The prevalence of depressive symptoms decreases as AD progresses. Patients exhibit fewer mood-related symptoms, but increased agitation and psychomotor slowing. The rates of depression in AD patients remain stable for roughly the first three years of follow-up. Rates of depression decline in the fifth year of follow-up by as much as 30% (8).

Depression as a Risk Factor for Dementia

Studies attempting to link geriatric depression with subsequent dementia have shown conflicting results. Although one recent meta-analysis showed an almost two-fold risk for the development of AD in patients with history of depression (13), another found this association only when depressive symptoms had appeared within 10 years prior to onset of dementia (14). Other individual studies have failed to find this association (15).

The increased risk for dementia may be conferred by factors such as severity, age of onset, or number or length of episodes of depression. Depressive episodes with onset more than 10 years prior to dementia are associated with AD at any age, suggesting that depression may be a risk factor for dementia (14). Some studies suggest that only the most severe cases of depression increase risk for later development of dementia (16). Multiple depressive episodes may promote the clinical expression of dementia in patients with AD.

“Depression with Reversible Dementia” Syndrome

Some older adults with late-life depression may exhibit a reversible dementia syndrome (previously termed “pseudo dementia”), i.e. a cognitive impairment that mimics dementia but diminishes upon remission of depression. These patients usually have a severe, late-onset depression but a mild dementia syndrome. When compared to AD patients with concomitant depression, ‘reversible dementia’ patients have more psychic and somatic anxiety, early morning awakening and loss of libido (17). It is important to note that large percentage of these patients progress into irreversible dementia within 2-3 years (18).

Cognitive Impairment and the Course of Depressive Symptoms and Signs

Abnormal performance on select tests of executive functioning predicts adverse clinical outcomes in geriatric depression including poor and slow antidepressant response, relapse and higher levels of functional disability. The term ‘executive functions’ encompasses a variety of cognitive abilities, such as planning, organizing, self-monitoring, inhibiting pre-potent responses and strategy generation (19). Furthermore, performance on measures of executive function can affect and be affected by performance in non-executive cognitive domains, such as processing speed and memory (20). For example, decrements in performance on the Initiation/Perseveration (I/P) subscale of the Dementia Rating Scale (DRS) and the Stroop Color Word tests predicted poor response to SSRI (21). Though not a classic measure of executive function, the I/P domain of the DRS tests multiple coordinated cognitive skills that require executive functioning.

In order to clarify the specific executive functions associated with remission, we completed an analysis that examined the contribution of each function individually. Among the functions tested by the I/P, only semantic fluency (the Complex Verbal portion; CV/IP) predicted remission during treatment with escitalopram (5). Performance on speeded verbal tasks such as the CV/IP can be improved by the use of strategies, such as the organization of responses into superordinate verbal categories (semantic organization) (e.g. replying with words belonging to the same category (fruit; e.g. grapes, bananas, oranges, etc.), rather than separate categories (e.g. bread, bananas, milk, etc.). Completing strategic semantic tasks such as the CV/IP also requires selection of words from multiple activated responses, and suppression of semantically or phonemically related but inapplicable words. In the above study, the use of semantic strategy, an executive function, explained performance differences between remitters and non-remitters (5).

We followed up these findings with a second study that demonstrated that the use of the same executive function, semantic strategy, explained both verbal memory performance and remission rates of geriatric depression (4). These studies are the first to define a single executive function that is predictive of remission with antidepressant drug treatment, regardless of the task by which it is elicited. Testing semantic strategy could be a useful tool added to the clinical assessment of depressive symptoms to improve clinician's ability to identify patients at risk for poor antidepressant drug response (4).

Prognosis of Cognitive Impairment

Mild cognitive impairment during depressive episodes in late life does not progress to dementia in most cases. Instead, it is a stable disturbance that improves only moderately when depressive symptoms are ameliorated (22). However, follow-up studies suggest that geriatric patients with depression and more severe cognitive symptoms, such as ‘reversible dementia’, are at an increased risk for developing irreversible dementia (18). Taken together, these studies suggest that 9–25% of elderly patients with depression and an initially reversible dementia develop irreversible dementia each year. In addition, some patients presenting with both cognitive dysfunction and late onset depression, may already be

experiencing the beginning stages of a dementia. This view is supported by recent studies suggesting that depression may be a prodrome of some dementing disorders (23).

Treatment of Depression with Cognitive Impairment in the Elderly

Evaluation

Evaluation of depressive syndromes in cognitively impaired patients is complicated by the symptom overlap with dementia, the instability of depressive symptoms over time, and the poor ability of elderly patients to report their symptoms. If criteria for one of the depressive syndromes are met, an antidepressant treatment trial should be offered. Beyond the benefits of alleviating the suffering and complications of depression, remission of the depressive syndrome can increase the clinician's ability to evaluate the severity of the remaining cognitive impairment and plan for further treatment and follow up. If frank cognitive impairment is suspected, the clinician should refer the patient for consultation with a neurologist and/or neuropsychologist. Variability in the course of elders with depression and cognitive impairment suggests the need for careful follow up, particularly in cases where executive dysfunction is suspected.

Pharmacologic Treatment

The Expert Consensus Guideline recommends antidepressant drug therapy combined with a psychosocial intervention as the treatment of choice for geriatric depression (24). Tricyclic antidepressants have not been found to improve cognitive function in depressed older adults. In fact, there is some data to suggest they may worsen cognitive functions. Nortriptyline was shown to compromise verbal learning performance of depressed older adults more than placebo (25). Conversely, some SSRIs may improve cognitive function mainly in patients whose depressive symptoms subside after treatment. Specifically, sertraline has been shown to improve performance on tests of attention, episodic memory, and executive function, but only in treatment responders (26). Similarly, depressed older patients with an antidepressant response to citalopram showed improvement in psychomotor speed, and visuospatial functioning. However, citalopram treatment appeared to worsen verbal learning and processing speed in patients who remained depressed despite treatment (27). Further discussion on pharmacotherapy of late-life depression can be found in Avari et al in this volume.

Psychotherapies

Non-pharmacological interventions should be considered, particularly in patients who do not respond fully to pharmacotherapy. Psychotherapies have been developed to remedy the behavioral deficits of depressed older adults with cognitive impairments associated with poor response to antidepressants. As an example, problem solving therapy (PST) was modified to directly treat behavioral abnormalities of patients with late-life depression and executive dysfunction. PST is based on the premise that helping patients become better managers of their lives reduces stress and thus ameliorates depression. PST trains patients to identify problems central to their well-being and provides a method for selecting and implementing problem-solving plans. PST aimed at remedying behavioral deficits has been effective in treating elderly depressed patients with executive dysfunction (28). The article

by McGovern et al in this volume offers a detailed discussion on psychotherapies for depressed older adults with and without cognitive impairment.

Computerized Cognitive Remediation

Certain types of computerized cognitive remediation can improve brain functioning by inducing neuroplasticity (i.e. nCCR). We have proposed that computerized cognitive remediation that relies on the induction of neuroplasticity and targets brain networks associated with clinical outcomes in late life depression has the potential to improve treatment response. Recently, we proposed a novel treatment model using nCCR to improve the functioning of cerebral networks responsible for executive functioning and associated with poor response to antidepressants (29). Our nCCR treatment model is based on the assumption that neuroplastic changes that improve the function of cerebral network abnormalities contributing to antidepressant resistance would improve symptoms and signs of late-life depression. Preliminary evidence suggests that nCCR treatment induces a clinically meaningful improvement of both cognitive and affective symptoms (30).

Conclusions

Impairment in episodic memory, visuospatial skills, verbal fluency, and psychomotor speed are common in late-life depression. Despite these cognitive abnormalities, most depressed older adults do not develop dementia syndromes. However, some cases of late-onset depression represent the first behavioral abnormalities (prodrome) of dementing disorders. A large number of older adults suffering from “depression with reversible dementia” proceed to develop Alzheimer's disease or mixed Alzheimer's and vascular dementia. This syndrome was previously termed “pseudo dementia” because it was incorrectly thought to have a benign long-term outcome. Finally, early-onset, recurrent, severe depression is a risk factor for development of dementia in late life.

Replicated findings suggest that executive dysfunction predicts treatment response to antidepressant drugs. Psychotherapies have been developed to address the behavioral deficits of depression with executive dysfunction and found effective. Neuroplasticity based computerized cognitive remediation targeting brain networks responsible for executive functioning has been developed, and preliminary studies are encouraging.

Appendix

Cognitive Function	Bedside Examination	Neuropsychological tests	
		Test:	Measures:
General Cognitive Function	MMSE	Dementia Rating Scale – 2 (DRS-2)	
	MOCA	Repeatable Battery for Assessment of Neuropsychological Status (RBANS)	

Cognitive Function	Bedside Examination	Neuropsychological tests	
Attention	Cannot hold a telephone number in mind	Test: Digit Span (WAIS-IV)	Measures: Auditory Attention/Working Memory
	Easily distracted	Brief Test of Attention (BTA)	Auditory Attention
	Tasks take too long	Digit Symbol & Coding	Divided Attention/Working Memory
	Poor concentration	Letter- Number Sequencing	Working Memory
Memory	Poor recall of recent events	Benton Visuospatial Memory Test- Revised (BVM-T-R)	Non-Verbal Learning & Memory
	Need of reminders	California Verbal Learning Test-II (CVLT-II)	Verbal List Learning & Memory
		Hopkin's Verbal Learning Test – Revised (HVL-T-R)	Verbal List Learning & Memory
	Repeats self	Logical Memory Subtest (WMS-IV)	Verbal Contextual Learning & Memory
Language	Word-finding difficulty	Boston Naming Test -2 (BNT-2)	Confrontation Naming
	Use of vague generic terms	Token Test	Comprehension
	Syntactic errors	Boston Diagnostic Aphasia Examination – 3 rd Edition (BDAE-3)	Comprehensive Language Assessment
	Comprehension difficulty	Animal Naming Test	Semantic Fluency
	Difficulty keeping up with conversation.	Controlled Oral Word Association Test (COWAT)	Letter Fluency
Praxis, Somatosensory & Motor Functions	Difficulty with use of familiar tools (e.g., pen, toothbrush)	Apraxia Exam	Praxis
	Difficulty with sequencing of actions (e.g., show me how you would pour water into a glass?)	Right-Left Orientation	Somatosensory
		Finger Localization	Somatosensory
		Finger Tapping Test	Fine Motor
		Grooved Pegboard	Fine Motor
Visuospatial Functions	Difficulty navigating familiar environment	Clock Drawing Test	Planning, construction
		Judgment of Line Orientation	Visuospatial Perception
		Hooper Visual Organization Test	Visuospatial Integration
		Facial Recognition Test	
Executive Functions	Multi-stage projects are effortful or avoided	Trail Making Test	Set-Shifting
	Poor task persistence	Stroop Test	Cognitive Inhibition/Processing Speed
	Double alternating hand movements.	Controlled Oral Word Association Test (COWAT)	Strategy
		Wisconsin Card Sorting Test (WCST)	Perseveration, Flexibility

Cognitive Function	Bedside Examination	Neuropsychological tests	
		Test: Iowa Gambling Task (IGT)	Measures: Reward-based Decision Making
Social Awareness	Impaired recognition of social cues Takes unusual liberties Apathetic Insistent, overbearing	Apathy Evaluation Scale (AES)	

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Educational Objectives

- 1.** Understand the prevalence, clinical relevance and prognosis of cognitive dysfunction in depressed older adults.
- 2.** Understand the prevalence, clinical significance and prognosis of depression in dementia syndromes.
- 3.** Identify the specific cognitive dysfunctions that are associated with poor treatment response in depressed older adults.
- 4.** Understand how to develop a treatment plan likely to address both cognitive dysfunction and depression in older adults.