CE

Cognitive Deficits in Patients With Depression

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ABSTRACT

Cognitive impairment in patients with depression is often overlooked because cognitive deficits and symptoms of depression often overlap. Understanding the neurobiological aspects of cognitive deficits is important, because cognition evolves as a therapeutic target in treating depression. Cognitive symptoms can precede or linger after symptoms of depression, such as sleep, appetite, and affective symptoms, improve. Emerging literature on medications targeting cognition in patients with depression should be considered when clinical decisions are made. Residual cognitive symptoms have been identified as a predictor of poor outcomes when treating depression. Referral to psychiatry should be considered in patients with residual symptoms where diagnosis is unclear.

Keywords: cognition and depression, screening for cognitive deficits, cognitive domains of depression, treatment of cognitive deficits in patients with depression, neurobiology of cognitive deficits in patient with depression

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CASE

Hilda is a 55-year-old married woman with 2 children in college. She is employed as an administrative assistant at a high school. She has been treated with sertraline for depression for the past year. She notes that her overall mood has improved, that she no longer feels hopeless, and that she is eating and sleeping fairly well. Hilda denies symptoms of anxiety and never experienced symptoms of mania. She drinks alcohol socially, "but never more than 2 drinks," and denies other substance use. Results of routine laboratory evaluations and a complete yearly examination 3 months ago were normal. However, she indicates that she has trouble making decisions and that she has "brain fog," which manifests as having trouble prioritizing and processing tasks at work. These symptoms were not present before her initial symptoms of depression began, and she has no prior psychiatric history. She thinks that her memory is "not as it used to be" and describes word-finding difficulty. She admits to missing her medications about once or twice a week. She worries that she will

This CE learning activity is designed to augment the knowledge, skills, and attitudes of nurse practitioners and assist in their understanding of the evaluation and treatment of cognitive deficits in patients with depression.
At the conclusion of this activity, the participant will be able to:
A. Describe signs/symptoms/neurobiology of patients with depression and cognitive deficits
B. List assessment tools used to identify cognitive deficits in patients with depression
C. Compare treatment options for patients with depression and lingering cognitive symptoms
The authors, reviewers, editors, and nurse planners all report no financial relationships that would pose a conflict of interest.
The authors do not present any off-label or non-FDA-approved recommendations for treatment.

This activity has been awarded 1.0 Contact Hours of which 0.25 credits are in the area of Pharmacology. The activity is valid for CE credit until July 1, 2020.

not be able to handle work responsibilities and that she has dementia.

Typical symptoms of major depressive disorder (MDD) include feelings of sadness, helplessness or hopelessness, inappropriate guilt, loss of interest in previously enjoyable activities, sleep disturbances, decreased energy, appetite changes, psychomotor retardation or agitation, preoccupation with death or thoughts of suicide, and difficulty concentrating or making decisions. Any symptoms causing significant distress should be further addressed clinically.[1] Other diagnoses, such as a medical condition (thyroid disorder or anemia) or bipolar spectrum, should be considered before diagnosing and treating depression conditions because treatment differs. Patients should be referred to psychiatry if symptoms warrant referral, such as patients who are resistant to treatment, or those experiencing psychotic symptoms, substance use, suicidality, or simply when the diagnosis is not clear. This report addresses the patient with MDD experiencing residual cognitive symptoms.

COGNITION AND DEPRESSION

Cognitive deficits have gained interest as a target symptom in relation to other psychiatric conditions, including schizophrenia, bipolar disorder, and attention deficit disorder.[2] It is only in the past decade, however, that interest has heightened in cognitive function relating to depression. Traditionally, the physical and emotional domains of depression have been emphasized. *The Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition, diagnostic criteria lists "diminished ability to concentrate and/or indecisiveness" as criteria for a major depressive episode.[1] These symptoms often overlap with other symptoms of depression[3] (see Table 1).

Studies have shown that most patients with depression report significant cognitive deficits, including deficits in executive function (problem solving, decision making, and judgment), memory, and attention to their daily activities.[6,7] In addition, more than 30% of depressed patients who have responded to therapeutic management for depression have reported residual problems, including inattentiveness, apathy, forgetfulness, word-finding difficulty, and mental slowness.[7] Cognitive deficits can occur before, during, or after a depressive episode and may serve in older adults as a precipitating factor to subsequent depression.[5] Repeated episodes of depression may increase vulnerability to further cognitive deficits, leading to a "kindling" effect, secondary only to that of repeated insults.[6]

Cognitive impairment has also been divided into "hot" and "cold" categories. Hot cognition is related to emotion, whereas cold relates to the cognitive domains. In general, concerns with hot cognition relate to negative bias. For example, patients with depression have a tendency to distort information negatively or to gravitate toward recalling negative information and experiences (negative recall bias), leading to a negative perspective, frustration, and low self-esteem.[3,8] Conversely, healthy people often have the ability to "self-distance" from negative experiences.[9] They are able to look at a situation as from the view of a distant observer and are thus less likely to ruminate on negative aspects of experiences.[10]

Table 1. Components of Cognition[1,3,12]

Component	Related Tasks
Executive function	Ability to make decisions, prioritize tasks, problem solve, or plan despite competing interfering stimuli
Immediate delayed memory	Ability to remember short-term and things from the past. Deficits include word-finding difficulty, forgetting; difficulty inhibiting irrelevant information
Learning	Ability to acquire/assimilate new information
Attention/concentration	Ability to focus despite distracting irrelevant background; capacity to engage in effortful cognitive tasks
Processing-Psychomotor speed	Time in which mental-motor tasks and processes occur and ability to respond

Functional impairment that patients with depression experience is thought to be triggered by cognitive dysfunction, and cognitive deficits have been shown to be a better predictor of daily function than depression severity.[8] Cognitive deficits in patients with depression have been linked to work impairment,[6] with more than 75% of patients with depression reporting a loss in work productivity.[11] Impaired work performance is also the cause of 30% to 60% of costs attributable to depression.[8]

In Hilda's case, her residual symptoms resemble cognitive deficits that linger after initial improvement in physical and emotional symptoms. Cognitive deficits may also contribute to her concerns at work and missing her medications.

NEUROBIOLOGY

Anatomy

Cognitive symptoms of depression result from dysregulation of interacting neural networks involving the prefrontal cortex, amygdala, hippocampus, anterior cingulate cortex, and basal ganglia[4] (see Supplementary Table 2 available online at http://www.npjournal.org). Abnormalities involve both gray matter volume reduction and disruption in white matter connectivity.[3] Interactions between the hippocampus and the prefrontal cortex have been linked to interactions between cognition and emotion. In addition, decreased hippocampal activity is thought to relate to increased negative bias and to the inability of the amygdala to inhibit information.[3]

Neurotransmitters

Overlapping monoamine networks involving serotonergic, noradrenergic, and dopaminergic neural projections contribute to an array of cognitive functions. Evidence indicates that decreased serotonin (5-hydroxytryptamine [5-HT]) neurotransmission has a negative effect on cognitive function and that balancing 5-HT activity is beneficial. Various subtypes of serotonin receptors are expressed throughout many areas of the brain. Procognitive serotonergic effects are thought to be attributed to specific subtype activity at 5-HT_{1A} receptor sites, and 5-HT_3 and 5-HT_7 receptor antagonism.[12]

Serotonergic subtype receptors and glutamate are both current targets identified for treating cognitive impairment in patients with depression, because depletion of glutamate may contribute to depression. Procognitive effects that include learning and memory may stem from interactions between serotonergic system interactions with glutamate, acetylcholine, dopamine, and γ-aminobutyric acid (GABA[12] see Supplementary Table 3, available online at http://www.npjournal.org). Depression is also thought to be associated with decreased neurogenesis, reduced glial cell production, dysregulation in brain-derived neurotropic factor (BDNF), and inflammatory or epigenetic changes.[4] Decreasing GABA activation has been shown to increase BDNF in the hippocampus, increasing neural activity and subsequent cognitive effects,[13] perhaps providing a reason to limit GABAinergic agents, including alcohol and benzodiazepines.

MEASUREMENT

Cognition should be assessed in all patients presenting with depression, given that cognitive improvement has been shown to improve overall functional capacity.[5] Patient history, a brief mental status examination, and the Patient Health Questionaire-9 screener are often used in clinical practice to screen for depression. Even then, further assessment of cognition may be warranted. Cognitive impairment relating to depression is heterogeneous, and deficits are both subjective and objective, making routine screening difficult. At a minimum, cognition should be assessed and documented in the same manner at each visit to assess for improvement.[7]

Measurement-based care has been shown to increase consistency of care and to improve outcomes.[2] However, tools evaluating cognitive impairment in patients suspected of dementia, such as the Mini-Mental State Examination or the Montreal Cognitive Assessment, are not always sensitive enough to detect the subtle changes in cognition that may be seen in patients with depression. The Mini-Cog, another tool to assess cognition when screening for dementia, takes approximately 2 to 3 minutes to complete and is often used in primary care. The tool is in the public domain and is available at https://mini-cog.com/. Other tools evaluating neurocognition are lengthy and not practical for daily clinical use, whereas tools used in primary care settings must be accessible and easily administered.

Regular follow-up allows for the monitoring of serial changes that have taken place since the baseline evaluation. There is currently no standard tool used to screen for cognitive impairment in patients with MDD.[2] Supplementary Table 4 (available online at http://www.npjournal.org) details a few select tools currently available for assessing cognition.

The THINC-Integrated tool (THINC-it) is a recently validated screening tool and is sensitive for detecting cognitive dysfunction in patients with depression. This emerging tool is free, practical, and able to be rapidly administered and interpreted in daily clinical practice.[21] It is computer based and patients complete cognitive assessments that consist of brief game-like tasks. The patient-rated scales listed in the table are sensitive to change and validated and are easily administered and scored. The Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire, a self-report subjective tool, can easily be used in primary care settings. Potvin et al[22] suggest that cognitive functions should ideally include objective and subjective measures because they are not interchangeable.

Hilda's case provides an ideal scenario for screening for cognitive impairment related to depression. First, her cognitive function was assessed using the Mini-Cog. Her score was 4 *of* 5*, indicating a low likelihood of having dementia. Hilda's Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire score was* 28*, indicating cognitive impairment. She again denies any new physical symptoms, anxiety, symptoms of mania, change in alcohol use, or suicidality.*

PHARMACOLOGIC THERAPY

Although the United States Food and Drug Administration has recognized cognitive dysfunction as a valid target for drug development, no medication is currently approved for treating cognitive impairment in patients with MDD.[6] There is a paucity of randomized control trials (RCTs) that have evaluated cognitive function as a primary outcome in patients with depression. Although a few antidepressants from all classes have shown limited improvement in cognition in some patients with depression,[7] no selective serotonin reuptake inhibitor has revealed robust effects, and some may actually worsen cognition.[23]

Newer research suggests that cognitive dysfunction, especially executive function, may be difficult to treat using first-line antidepressants.[6] For example, 1 RCT that evaluated the effects of sertraline, escitalopram, or venlafaxine found no significant effect on cognition in patients treated for depression,[24] suggesting that cognitive deficits may not fully be addressed with first-line treatments for depression. In other small studies, escitalopram, duloxetine, and bupropion were shown to have limited procognitive effects (see Table 5).[25]

Multimodal agents may have a more robust procognitive effect in patients with depression by having a direct effect on 5-HT receptors and targeting serotonergic receptor subtypes (see Supplementary Table 3, available online at http://www.npjournal.org). Vortioxetine,[25] vilazadone, levomilnacipran,[27] and brexpiprazole[26] have all been shown to improve multiple domains of cognition in patients with depression.

The procognitive effects of vortioxetine are thought to be attributable to select 5-HT activity related to 5-HT_{1A} agonism and 5-HT_3 and 5-HT_7 antagonism, all of which may enhance glutamatergic neurotransmission, long-term potentiation, and neuroplasticity.[6] A multitude of 5-HT_7 receptors are located in the hippocampus, hypothalamus, and thalamus, with fewer in the cortex. Blocking 5-HT_3 has been shown to increase levels of serotonin, norepinephrine, dopamine, acetylcholine, and histamine in brain regions associated with depression, such as the prefrontal cortex and hippocampus.[12] Vilazodone, a serotonin partial agonist-reuptake inhibitor, combines 5-HT_{1A} agonism with serotonin-reuptake inhibition. Both actions increase serotonergic bioavailability. Many patients with depression have decreased 5-HT_{1A} density; thus, activating these receptors may optimize 5-HT neurotransmission.[12]

The profile of brexpiprazole, an antipsychotic agent with multimodal activity, is also thought to enhance cognitive function in patients with depression.[26] Levomilnacipran, a norepinephrine serotonergic reuptake inhibitor, is approved by the Food and Drug Administration to treat functional impairment in depression. It is thought to improve concentration and motivation owing to its action on norepinephrine.[27]

Table 5. Drugs in Randomized Controlled Trials to Assess Cognition in Patients With Depression

Drug Name	Type	Finding
Escitalopram	SSRI	Found to improve working memory, attention, and executive function[7]
Duloxetine	SNRI	Found to improve working memory, processing speed, and executive function[7]
Bupropion	Norepinephrine, dopamine reuptake inhibitor	Shown to improve immediate as well as delayed verbal and non-verbal memory, global function, and measures of work productivity[25]
Vortioxetine	Multimodal agent: 5-HT transport inhibitor; 5-HT_{1A} agonist, and 5-HT_3, 5-HT_7, 5-HT_{1D} antagonist, and 5-HT_{1B} partial agonist	Shown to improve overall performance on cognitive testing that included testing the domains including memory, learning, executive function, attention and processing speed (3 large trials)[6,8]
Brexpiprazole	Atypical antipsychotic: 5-HT_{1A} and D2 partial agonist; $5HT_{2A}$, and $5HT_7$ antagonist (combined together may increase extracellular dopamine and acetylcholine)	Used in augmentation with an antidepressant; shown to improve cognition[26]

5-HT = 5-hydroxytryptamine; D2 = dopamine receptor 2; SSRI = selective serotonin reuptake inhibitors; SNRI = serotonin-norepinephrine reuptake inhibitors.

Modafinil, used as an adjunctive treatment for depression, has been shown to improve cognition but needs further study.[6] Procognitive effects are thought to be owing to enhanced glutamatergic transmission, especially to the hippocampus.[6] Interestingly, adjunctive anticholinesterase inhibitors have not been proven effective in improving cognition in MDD.[28] Thus, evidence has evolved that some agents more than others may exert procognitive effects in some patients with depression. From a clinical perspective, a change in medication should be considered for patients with depression who are experiencing residual cognitive deficits.

Limitations to findings related to cognition in patients with depression include (1) no current gold standard to measure cognitive function in patients with depression, (2) a paucity of RCTs having cognition as a primary outcome, (3) heterogeneity of samples used in clinical trials, and (4) difficulty separating improvement in cognitive function from improvement in overall depression.[7]

NONPHARMACOLOGIC PREVENTION AND TREATMENT

Cognitive behavioral approaches have been used to improve cognitive bias in patients with depression, helping individuals gravitate toward optimistic perspectives rather than ruminating on negativity.[29] Thus, if we can help patients change faulty thought patterns to a more positive perspective, subsequent emotions and behaviors are more likely to overall improve. Studies have shown that patients are more likely to remain in treatment when therapy is used as opposed to medication alone, perhaps due to the complexity of depression, the benefits of talking things through, or not understanding how medications work.[30]

Cognitive remediation is an intervention intended to improve cognitive and executive function as well as interpersonal skills by engaging the individual in specific learning activities. Examples include computerized or written exercises to improve problem-solving skills and memory. Cognitive remediation using behavioral strategies[31] and exercise[32] are both promising treatments found to improve cognitive function in patients with depression. By stimulating BDNF, exercise may promote neurogenesis.[33] A study by Kim[34] found that combining physical activity, recreation, and arts and crafts improved cognition and depression in 28 elderly patients. Studies have also shown yoga reduces depression and cognitive decline.[35] Research

on sleep, cytokine regulation, insulin regulation, and use of probiotics shows promise in reference to improving cognition.[25] Further study is needed on using cognitive behavioral training to reduce cognitive bias and incorporating mindfulness and yoga.

Many patients do not recognize cognitive deficits, they just know they feel "bad." Kross et al[10] recommend using the self-distancing cognitive strategy when undergoing a negative experience to mitigate harmful consequences. The ability to solve problems, make decisions, and think quickly are all necessary for optimal functioning at work.

Hilda was interested in further discussing her symptoms. Helping her understand that lack of adherence to prescribed treatment, indecisiveness, slowed thinking, and difficulty with recall likely constitute residual symptoms of depression can give her greater insight into her situation and treatment options. Medications listed in Table 5 were discussed as well as nonpharmacologic options, taking into account the lingering cognitive effects she was experiencing.

The Mental Health Parity and Addiction Equity Act extended availability of mental health care to Americans by requiring that health plans provide similar benefits for mental and medical health conditions. Hence, optimizing the care of patients with depression should be similar to our quest in seeking optimal care for patients with diabetes, heart disease, or cancer. Lastly, we need to keep in mind that state-of-the- art innovative care is often a step ahead of evidence-based care because it takes time for evidence to build.

CONCLUSIONS

Cognitive impairment research, as it relates to depression, is still emerging. Future studies and standards should move toward standardized assessment and evaluation of cognitive outcomes in patients with depression. Multiple serotonin receptors will likely have a role in treating depression, and multiple neurotransmitter interactions involving glutamate and dopamine probably contribute to improving cognitive symptoms of depression. Antidepressant properties that target cognition are an emerging topic that needs further study. Nonpharmacologic strategies should also be entertained. Psychotherapy, the mainstay in treatment for depression, should always be considered in the holistic care of patients suffering from depression.

Discussing cognitive deficits and treatment options, including medication, therapy, and referral, with patients such as Hilda is important, considering current evolving evidence. As with all cases of depression, it is important to rule out other causes of depression and cognitive deficits and consider psychiatric referral. A case like hers shows that shared decision making is an ideal strategy for communicating "best practices."

SUPPLEMENTARY DATA

The Supplementary Tables associated with this article can be found in the online version at https://doi.org/10.1016/j.nurpra.2018.03.006. JNP

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https://doi.org/10.1016/j.nurpra.2018.03.006

Supplementary Table 2. Brain Areas Relating to Cognitive Functions[3,4]

Brain Area	Cognitive Function
Prefrontal cortex	Executive functioning, short-term memory processing
Hippocampus	Memory recall; integration of learning
Amygdala	Decision making, cognitive regulation in emotion
Anterior cingulate cortex	Integration of limbic and prefrontal cortex processing; integrates emotion, memory, and awareness
Basal ganglia	Working memory performance

Supplementary Table 3. Neurotransmission and Cognition[3,12]

Neurotransmitter	Network	Action
Serotonin	Cell bodies originate in the raphe nuclei. Serotonergic neurons widespread—networks to hippocampus, limbic area, prefrontal cortex, basal ganglia	Serotonin regulates physiological processes (temperature, sleep, appetite, pain) and cognitive behavior, including working memory, attention, and emotional behavior. Multiple subtypes have various yet specific functions
Norepinephrine	Cell bodies of norepinephrine neurons originate in locus coeruleus and medullary reticular formation and project to virtually all areas of brain	Noradrenergic system has a role in alertness, working memory and consolidation, attention and executive function. Hypo- and hyper-noradrenergic activation can both impair cognition
Glutamate	An excitatory neurotransmitter is widely distributed in the brain	Contributes to the formation and storage of memories, learning, and regulating neuroplasticity
Acetylcholine	Neurons (central nervous system) arise from cell bodies in the brain stem and forebrain, and project to the cortex, hippocampus	Involved in the formation of memories, learning, reasoning, attention/concentration
Dopamine	Cell bodies originating in the midbrain project to prefrontal cortex	Involved in cognition, motivation/reward, concentration, executive function

Supplementary Table 4. Tools to Assess Cognition

Validated Tool	Items or Tasks, No.	Time Required	Self-Administered	Public Domain	Use inClinical Practice, Research, or Both	Domains Assessed	Objective vs Subjective
MMSE[14,a]	11 items	10 min	No	No	Both	Orientation, registration, learning and memory, attention, construction ability, calculation, recall, language, visuospatial	Objective
MoCA[15,a]	16 items	10 min	No	Yes	Both	Executive function,[b] naming, memory, attention, language, abstraction, orientation, visuospatial, verbal fluency	Objective
SLUMS[16,a]	11 items	7 min	No	Yes	Both	Orientation, recall, calculation, naming, attention, executive function, working memory, language	Objective
Mini-Cog[17,a]	3 items; includes clock drawing task	3 min	No	Yes	Clinical practice	Recall, executive function, visuospatial	Objective
DSST[18]	Matches symbols with numbers based on 9-digit coding table	20 min	No	No	Both	Attention, processing speed, executive function, recall	Objective
RaVLT[19]	List of 15 words read to patient and patient repeats as many words as possible after hearing them within a timed period.	5-15 min	No	Yes	Both	Short term memory, working memory, attention, verbal learning	Objective
MCH-CPFQ[20]	7 items (4 address cognition) scale reporting patient responses on cognitive symptoms experienced; validated for use in patients with depression	3-5 min	Yes	No	Both	Motivation, focus, recall, work finding ability, memory, organization skills	Subjective: compares current function with previous best

continued

Supplementary Table 4. (*continued*)

Validated Tool	Items or Tasks, No.	Time Required	Self-Administered	Public Domain	Use inClinical Practice, Research, or Both	Domains Assessed	Objective vs Subjective
PDQ-D[11]	20-item scale: validated for use in patients with depression; abbreviated version has 5 items	5-10 min	Yes	No	Both	Attention, concentration, prospective/retrospective memory, executive function	Subjective
THINC-it[21]	Battery of objective tests downloaded electronically to assess cognition in patients with depression	15 min	Yes (online)	Yes, but under copyright	Both	Executive function, processing speed, memory, attention, subjective measures	Objective and subjective combined

DSST = Digit Symbol Substitution Test; MGH-CPFQ = Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; PDQ-D = Perceived Deficits Questionnaire; RAVLT = Rey Auditory Verbal Learning Test; SLUMS = Saint Louis University Mental Status Examination; THINC-it = THINC-Integrated Tool.

[a] Tools used to assess cognition for dementia; often lack sensitivity to detect subtle cognitive changes seen in patients with depression.

[b] Reasoning and problem solving.