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REVIEW

The impact of cognitive challenges in major depression: the role of the primary care physician

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ABSTRACT

Nearly 1 in 5 Americans will struggle with major depression in their lives; some will have recurring bouts. Recent psychiatric research has given new attention to the prevalence of cognitive deficits in major depression and the impact such deficits have on remission and overall life functioning. When depression is partially treated i.e., leaving residual symptoms, patients have higher rates of relapse and lower functional outcomes. Impaired cognitive functioning is a frequent residual symptom, persisting in about 45% of patients even when emotional symptoms have improved, and results in a disproportionate share of the functional impairment, particularly in the workplace. Patients with depression have disrupted circuitry in brain regions responsible for cognition and it is therefore important to screen depressed patients for cognitive as well as emotional symptoms. Cognitive dysfunction should be evaluated in every mood disordered patient with validated self-report scales such as the Patient Health Questionnaire-9 or the Beck Depression Inventory and objective measures of cognitive function are also very very useful. Two easily administered tests are the Trails B Test and the Digit Symbol Substitution Test. Each take less than two minutes and measure working memory, executive function, and processing speed and can track cognitive improvement in depressed patients. Treatment of cognitive dysfunction in major depression is complicated by the 'serotonin conundrum': SSRI's frequently do not treat to full remission, and can cause cognitive blunting—actually adding to cognitive problems. Based on recent data including results from a recently completed meta-analysis by McIntyre and colleagues, an evidence-based algorithm for treating cognitive symptoms in depression is presented. A hierarchy of antidepressants and augmentation strategies based on the best available evidence is discussed. In conclusion, cognitive symptoms in major depressive disorder have been recognized as a target of therapeutic improvement by the FDA and have become a focus of clinical importance.

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Introduction

Have you ever been faced with a patient calling for a work note due to problems with depression? How many times have you been asked to fill out a disability form for a patient who is not doing well both from a physical and from an emotional perspective? These are problems that primary care physicians deal with on a near-daily basis.

With a lifetime prevalence of 15–20%, nearly one in five Americans will struggle with an episode of major depression at some point in their lives [1]. Psychiatric research is giving new attention to the prevalence of cognitive deficits in major depression and understanding the impact such deficits have on global function [2–7]. Both psychotherapeutic intervention with various types of cognitive remediation and medical intervention with various medication options have become an area of increased interest [4–7]. Cognitive dysfunction in major depressive disorder was the topic of the February 2016 meeting of the FDA Advisory Panel for Drug Evaluation and Research. After hearing testimony, the panel voted 8:2 in favor of recommending the development of pharmacologic interventions targeting cognitive symptoms in major depression. This historic decision has created a path for the development of specific pharmacologic treatments for cognitive dysfunction in major depressive disorder.

Remission as a goal of treatment

A number of studies have examined residual symptoms in major depressive disorder and the importance of treating depression to symptomatic remission [8,9]. The data are clear: when major depression is only partially treated, patients have higher rates of relapse, lower functional outcomes, and present a host of physical and psychological symptoms to their primary care doctors [10]. Clinicians have historically been trained to screen for sleep, energy, mood, suicidality, and anxiety, but cognitive symptoms – one of the nine core symptoms defined by DSM-5 – are frequently overlooked [11]. A 3-year depression intervention study conducted in primary care offices found 94% of patients had cognitive deficits during an episode of major depression; not an unexpected outcome. What was unexpected was that following appropriate treatment for an appropriate length of time, 44% of patients

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continued to have cognitive symptoms, despite emotional improvement [10].

Normalizing the brain

Patients with major depression have abnormal neurologic function in a variety of brain circuitry. Functional imaging studies including MRI, PET, and fMRI show that depressive illness disconnects emotional, physical, and cognitive circuitry [12–14]. Limbic regions associated with mood regulation become hyperactive, with increased neural activity, blood flow, and glucose uptake [12]. Limbic pathways reverberate with an excess negative valence of emotions such as worry, sadness, hopelessness, or despair. In depressed brains, limbic circuitry is 'hot.' By contrast, neural pathways in the prefrontal cortex and anterior cingulate are 'cold'; they have decreased neural activity, with deficits in attention, working memory, processing speed, and mental flexibility. Finally, in depressed patients, brain regions which modulate sleep and circadian rhythms become disrupted [12].

Normalization of a depressed brain therefore means returning areas with increased, deceased, or disrupted neural activity back to normal functioning. Limbic regions which were hyperactive must slow in activity. The prefrontal cortex and associated cognitive areas must activate so patients regain mental flexibility, working memory, and processing speed. Regions modulating sleep and circadian rhythms must normalize these associated functions [12].

Recognition of cognitive deficits

Cognitive processes are divided by neuropsychologists into domains such as working memory and attention. 'Cognition' thus refers to multiple processes occurring in multiple, but connected regions of the brain, most occurring in near simultaneity [15].

The neurologic impact of major depression is a constellation of cognitive deficits involving a number of brain structures, including the anterior cingulate and prefrontal cortex [12,13]. These cognitive deficits are quantified with a variety of neuropsychological batteries, including measures of global intelligence such as the Wechsler Adult Intelligence Scale (WAIS) or the Wechsler Intelligence Scale for Children (WISC) [16,17]. A variety of computerized batteries assess processing speed and attention; the Cambridge Neuropsychological Test Automated Battery (CANTAB) and MATRICS Consensus Cognitive Battery are examples [18,19]. Neuropsychologists then ascribe the deficits seen in major depression to particular cognitive domains, including working memory, processing speed, visual and verbal memory, verbal fluency, and executive function [3,15].

The data from cognitive batteries show that individuals with major depression have deficiencies in cognitive processing, not only during episodes of major depression but also between episodes, at times when mood has partially or completely improved [10]. Major depression creates neurologic dysfunction which leads to cognitive and functional impairment in individuals' lives, the result is academic failures, missed work days and a lowered capacity to meet the obligations of daily life. Major depression causes a decrease in both working memory and processing speed, i.e. the ability to remember what you are doing and then use that information in a time-efficient manner [2].

To paint a clinical picture, imagine a secretary, at her desk trying to answer her phone and enter information into her computer at the same time, when her ability to remember what was said on the phone and what is being typed is decreased by 40–50%. Alternatively, imagine an accountant helping a client with a brain 40% less able to remember what was just read and use that information in a time-efficient manner. Now, further imagine both of these individuals visiting their physician, who asks how they are doing with their major depression, and they each say, 'Well my mood is better but I'm still not doing well' – and the physician fails to recognize that each patient has residual cognitive impairment associated with their depression, which interferes with their day-to-day function.

Practical recommendations for detection of cognitive issues in the primary care setting

Major depression is defined as a constellation of nine symptoms which overlap for a minimum of 2 weeks but often last 6–12 months [11,20]. While most clinicians have learned to screen for issues around mood, sleep, energy, and appetite, cognitive impairment is present in 90–95% of patients during a major depressive episode and is one of the most frequent residual symptoms with approximately 45% of patients continuing to struggle with cognitive impairment between major depressive episodes [10]. In an effort to improve functional outcomes, the cognitive symptoms of major depression should be investigated for every patient during and between episodes of major depression.

Ask basic questions such as 'How is your concentration? How is your memory? How is your focus? Are you able to think at your usual speed?' – these are critical questions that should be asked of every depressed patient.

Studies have shown that cognitive impairment often goes overlooked by clinicians and patients alike and that patient's subjective perception of cognitive impairment is heavily influenced by their mood state [6,15]. Effort should be taken to screen for both (1) objective and (2) subjective measures of cognitive impairment in the office and (3) to educate patients so that they can better screen themselves. Both clinician and patient should understand that cognitive impairment is a frequently associated neurologic symptom of major depression. The use of routine screening tools such as the Patient Health Questionaire-9 (PHQ9) and the Beck Depression Inventory (BDI) is a step in the right direction for subjective symptoms and are easily implemented in the primary care setting [21,22]. The PHQ-9 and BDI are validated depression scales self-administered by the patient, and both ask questions about cognitive function.

In addition to asking patients for their own (subjective) reports, easily administered objective measures of cognitive function are also available. Two sensitive tests to measure processing speed and working memory are the Trails B Test and the Digit Symbol Substitution Test (DSST) [23,24]. The trails

test measures the time taken to connect dots on a page in an organized and prespecified manner, thus measuring the ability to retain information and utilize working memory – tasks critical to overall cognitive function. The DSST is another easily used, well-validated measure of processing speed and working memory. Originally developed by the military in the early 1900s to detect cognitive impairment associated with closed head injury, the DSST can be administered in your office in approximately 2 min. It is widely incorporated into larger cognitive batteries including a number of the basic IQ tests [17]. The DSST shows the testee the numerals 0–9; each numeral is paired with a symbol in a coding 'legend.' Individuals are given a sheet with a list of numbers and asked to place the corresponding symbol beneath each number as quickly as possible for 90 s. The score is the number of correct pairings. The DSST requires the ability to retain information and to use it quickly. Individuals with major depression have a decrease in the ability to process information and utilize information on this test, and the DSST has been shown to be a fairly sensitive measure of improvement in cognitive function associated with depression treatment [8]. In addition to Trails B and DSST, a number of other tests are in development to simplify the measurement and understanding of cognitive deficits in patients struggling with mood disorders.

Treatment considerations

The role of the SSRI

The role of the primary care physician in treating major depressive disorder has changed dramatically over the past 20 years with the advent of fluoxetine and other selective serotonin reuptake inhibitors (SSRIs). Unlike earlier tricyclic antidepressants which had narrow therapeutic windows and could be lethal in overdose, the SSRIs ushered in a new generation of relatively safe and reasonably well-tolerated medications that have become widely accepted in primary care. SSRIs have been found to be safe and fairly well tolerated for the constellation of depression and anxiety symptoms which are frequently encountered in primary care. SSRIs increase intrasynaptic concentrations of serotonin by blocking the serotonin transport pump and have no direct effect on norepinephrine, dopamine, acetylcholine, histamine, or other neurotransmitter systems. SSRIs have allowed the use of a single medication to treat both depression and anxiety or both where they coexist. The selectivity of SSRIs has minimized cardiac effects, orthostasis, and has ameliorated cholinergic and histaminergic side effects. The limited overdose potential of SSRIs has led to an increased willingness among primary care physicians to treat mental health challenges that are encountered on a daily basis with their patients.

The serotonin conundrum

Two critical issues with the use of SSRIs have failed to receive adequate attention.

(1) **Low remission rates** – While SSRIs yield some symptom improvement in the majority of patients with depression, only a small minority (between 25% and 35%) will achieve symptomatic remission of major depressive symptoms when treated with an SSRI at an appropriate dose for an appropriate period of time. The NIH-funded STAR*D Study found a 27% symptomatic remission rate after 3 months of citalopram at 'optimal therapeutic doses' averaging around 40 mg/day [8]. The STAR*D study was consistent with similar studies conducted in primary care settings which have repeatedly found SSRI monotherapy remission rates of 25–35%. Further complicating the issue was the finding that even among the 25–35% of patients who achieved symptomatic remission, only a percentage of those patients actually achieved functional remission, i.e. returned to normal function in daily life activities such as work, school, social activities, and at home. As noted earlier, for patients receiving antidepressant treatment, studies have consistently shown that on average 44% of patients and in some studies as many as 95% of patients continue to struggle with ongoing cognitive deficits even when their emotional symptoms have achieved significant improvement [10,25].
(2) **Cognitive blunting** – In addition to often failing to improve cognitive deficits experienced by patients struggling with major depression, globally raising serotonin can have direct detrimental effects on mental flexibility and alertness for a subset of our patients [26,27]. A side effect experienced by a proportion of patients receiving SSRI treatment includes mental fogginess, impaired focus, and cognitive blunting [25]. Stimulation of the serotonin 2A receptor may decrease cortical arousal in the prefrontal cortex and thereby worsen cognitive impairment in some patients receiving SSRI treatment.

The question then becomes if cognitive dysfunction is the primary driver of disability and work impairment among our patients with major depressive disorder and if SSRIs often do little to improve cognitive deficits and may even worsen neurologic function in the prefrontal cortex, how should we approach these cognitive disabilities among our patients with major depressive disorder?

(1) Ask every depressed patient about cognitive function.
(2) Track major depressive symptoms and treat all symptoms aggressively into symptomatic remission.
(3) Monitor for ongoing cognitive deficits in all treatment phases of depression. Verify that not only have emotional symptoms remitted but cognitive difficulties have normalized as well. The goal is no ongoing functional impairment due to any residual symptoms – emotional, physical, or cognitive.

Evidence-based algorithm for medication treatment of cognitive symptoms in major depression

Rosenblat, Kakar, and McIntyre recently completed a thorough meta-analysis of the 'cognitive effects of antidepressants in

major depressive disorder,' published in the International Journal of Neuropsychopharmacology [28]. This meta-analysis published in 2015 found nine placebo-controlled trials with a total of 2550 participants evaluating the cognitive effects of vortioxetine (n = 728), duloxetine (n = 714), citalopram (n = 84), sertraline (n = 49), nortriptyline (n = 32), phenelzine (n = 28), and paroxetine (n = 23). Of the seven antidepressants with placebo-controlled trials, only vortioxetine showed significant improvement in psychomotor processing speed when objectively measured with a test such as the DSST. In comparison, duloxetine, phenelzine, nortriptyline, and three SSRIs – paroxetine, citalopram, and sertraline – failed to significantly improve processing speed in placebo-controlled trials [29–34]. Vortioxetine was also found to have significant improvement on processing speed/executive function/working memory on the Trails B Test, whereas duloxetine and sertraline failed to show such improvement. Both vortioxetine and duloxetine showed improvement of delayed recall as measured by the Rey Auditory Verbal Learning Test (RAV). Two head-to-head trials of buproprion versus SSRIs – paroxetine and citralopram – revealed a trend for bupropion to have a more pronounced improvement of working memory than SSRIs; however, this trend did not reach overall statistical significance in either trial [35,36]. In three head-to-head trials of SSRIs versus tricyclic antidepressants, SSRIs were less detrimental for working memory than tricyclic antidepressants – which carry an anticholinergic burden; however, this trend did not reach statistical significance [37].

Published in 2016 Lancet Psychiatry, Shilyansky et al. recently reported the results of a large international study evaluating the 'Effect of antidepressant treatment on cognitive impairments associated with depression to predict optimized treatment in depression' where they assessed 1008 individuals aged 18–65 years struggling with major depressive disorder [25]. These individuals were randomly assigned in a 1:1:1 fashion for 8 weeks of prospective antidepressant treatment with escitalopram, sertraline, or venlafaxine extended release. They found baseline impairment in five cognitive domains; attention, response inhibition, verbal memory, decision speed, and information processing before antidepressant therapy. After 8 weeks of prospective antidepressant treatment, they found no relative improvement in any of these five cognitive domains irrespective of antidepressant treatment group, even in patients whose depression remitted acutely according to clinical measures. Their study found that 95% of individuals with major depressive disorder continued to have significant cognitive impairment after 8 weeks of prospective antidepressant treatment with either of these three commonly used antidepressants.

Level 1. Vortioxetine

Vortioxetine at doses of 5–20 mg has been shown to be beneficial not only for treatment of major depressive symptoms but also for significant improvement of cognitive symptoms associated with major depression [38–40]. Vortioxetine, which acts as a serotonin 1A agonist, a serotonin 1B partial agonist, a serotonin 1D antagonist, a serotonin 3 antagonist, and a serotonin 7 antagonist in addition to having moderate affinity for the serotonin reuptake pump has been shown in preclinical models to increase prefrontal cortex neural firing rates and increase pyramidal cell arborization [41,42]. Preclinical data implicate vortioxetine's blockade of 5HT3 and 5HT7 for these neurocognitive effects. In clinical trials, patients with major depression on vortioxetine have shown improvement in working memory, processing speed, and verbal memory in three prospective, double-blind, placebo-controlled studies. Katona et al. showed that 5 mg of vortioxetine improved verbal memory in depressed geriatric adults similar to 60 mg of duloxetine, whereas only vortioxetine significantly improved cognitive function as measured by the DSST with duloxetine failing to show significant improvement on the DSST in the same trial [39]. These findings were then replicated in a follow-up study of middle-age adults with major depression where vortioxetine and duloxetine once again showed improvement in verbal memory on the RAV but with only vortioxetine improving working memory and processing speed on the DSST and Trails B [40]. A third placebo-controlled study replicated the cognitive benefits of vortioxetine with doses of both 10 and 20 mg demonstrating significant improvement in cognitive deficits as manifest on the RAV, the DSST, and Trails B [38]. Taken in total, these three studies show that vortioxetine improved both auditory memory and processing speed/working memory in patients struggling with major depression. While no studies have been powered to prospectively measure the 'head-to-head' efficacy of vortioxetine verses other antidepressants, only vortioxetine has shown significant improvement on these cognitive measures compared to placebo. Of significant importance for a subset of our population which struggles with both major depression and gradually increasing cognitive difficulties was the geriatric study where vortioxetine helped improve cognitive deficits in elderly adults struggling with major depression.

2. Duloxetine

Duloxetine, which raises levels of both serotonin and norepinephrine has been hypothesized to potentially improve cognition by its noradrenergic properties. Major depressive disorder clinical trials of duloxetine have shown improvement in verbal memory on the RAV but have failed to show significant improvement on DSST or Trails B test which are a measures of working memory and processing speed [29,30,39,40]. The interest in duloxetine is at least partially fueled by the fact that other noradrenergic agents such as atomoxetine have been shown to be procognitive in patients struggling with associated difficulties such as attention-deficit hyperactivity disorder or attention-deficit hyperactivity disorder with comorbid anxiety [43].

3. Bupropion

Bupropion, which raises levels of both norepinephrine and dopamine, has been shown to have some beneficial cognitive effects in mood disorders but more importantly in this regard has been shown to help adults struggling with attention-deficit disorder [35,36,44]. While no large, placebo-controlled studies of cognition in major depression exist, several smaller studies in adults with cognitive deficits associated with

attention-deficit hyperactivity disorder have shown that bupropion with its combination of dopamine and noradrenergic effects has the potential to be potentially procognitive.

4. Modafanil/armodafanil

Modafinil and its isomer have shown cognitive benefits in both alertness and attentional difficulties for adults struggling with conditions such as narcolepsy, sleep shift disorder, and in some studies of attention-deficit disorder [44]. These agents whose exact therapeutic mechanisms of actions still remain to be 100% elucidated tend to increase overall arousal within the brain which may help with alertness, cognitive processing, and residual cognitive deficits in some patients struggling with major depressive disorder.

5. Psychostimulants

A variety of psychostimulants, i.e. methylphenidates, amphetamines, amphetamine salts, and lisdexamphetamine, have been evaluated with regards to residual depressive symptoms and cognitive symptoms in major depression [7,45]. Whereas the results of these trials have been negative or mixed, individual patients have clearly benefited from augmentation of psychostimulants on top of antidepressant treatment options. The recommendations of the authors are that these are options that should be considered after the above agents have not improved cognitive symptoms and when warranted, longer acting psychostimulants with less risk of rebound and abuse liability should be utilized whenever possible in comparison with their shorter acting counterparts.

6. Atypical antipsychotic augmentation

Atypical antipsychotic augmentation of antidepressants with agents such as aripiprazole, quetiapine, olanzapine, brexpiprazole, or cariprazine have all been shown to significantly improve major depressive symptoms in patients struggling with residual depressive symptoms after standard antidepressant pharmacotherapy [45]. These agents should all be considered in patients struggling with residual depressive symptoms which will also commonly include residual cognitive deficits associated with their major depressive episode. Whereas there is very little, if any, cognitive data about these atypical augmentation options, the initial strategy of treating depression to remission and aggressively pursuing residual symptoms causing any type of functional impairment would apply to these agents. A potential risk/benefit ratio with any of the atypical antipsychotics includes their potential for weight gain, metabolic syndrome, sedation, and akathisia should always be taken into account with regards to the therapeutic decision-making on whether or not to pursue these treatment options as augmentation strategies.

Summary

Day in and day out, primary care physicians see the impact of patients struggling with major depression. Patients may at first present with emotional symptoms due to depression, concomitant symptoms of irritability, anger, anxiety, agitation, or with physical complaints such as chronic pain, palpitations, irritable bowel, fatigue, or insomnia. Only recently has the role that cognitive symptoms play in driving functional disability for our patients with major depression come to light. About 95% of patients with major depression struggle with neurologic impairment which causes difficulties in processing speed, working memory, auditory memory, and executive function. Even when treated to therapeutic remission of emotional symptoms, approximately 45% of major depressive disorder patients continue to have significant cognitive symptoms while in emotional symptom remission. These cognitive symptoms have been shown to be the primary driver of workplace absenteeism and workplace disability along with causing significant functional impairments in activities of daily living with their family, friends, and peers.

Major depression is a neurologic illness which affects emotional modulation and balance in the limbic system, impairs cognitive functioning in the anterior cingulate and prefrontal cortex, along with disrupting basic circadian rhythm in the brain stem and associated areas. For major depression to truly go into functional remission, all three of these areas must achieve normalization of brain activity. Primary care physician by nature of their ongoing therapeutic relationship have become the primary source of treatment for patients struggling with major depressive difficulties. A simple screening for subjective cognitive symptoms such as 'How is your memory', 'How is your thinking', 'Are you thinking as clearly as you used to', 'Are you having any problems remembering things' will easily pick up a large percentage of patients struggling with cognitive deficits. Objective measurement with tests that look at processing speed and working memory along with functional scales which use informant information from friends and family members can also be utilized to gather more objective data about cognitive performance during depressive disorders. Given that 95% of patients with major depression have cognitive problems during a depressive episode and the fact that cognitive problems tend to be the most common residual difficulties despite remission of emotional symptoms, it emphasizes the need for every patient with major depression to be screened for cognitive difficulties both initially and throughout treatment.

For patients struggling with major depression and associated cognitive difficulties, traditional antidepressants such as SSRIs have been shown to have very little impact on cognitive dysfunction associated with major depression. The number one goal would be to treat major depressive symptoms to therapeutic and functional remission with no ongoing residual functional impairment due to either emotional symptoms of depression, circadian rhythm symptoms of depression, or cognitive symptoms of depression [46].

Evidence-based medicine shows that SSRIs may be ineffective for treatment of cognitive symptoms associated with depression with effects similar to or slightly worse than placebo for the cognitive domains of depression. In addition to psychotherapeutic interventions, evidence-based medicine would tend to rank the following medication treatment options with regards to their improvement of cognitive symptoms in depression:

(1) Vortioxetine
(2) Duloxetine

(3) Bupropion
(4) Modafinil/armodafanil
(5) Psychostimulants
(6) Augmentation strategies such as atypical antipsychotics that have been shown to improve patients struggling with residual major depression.

The exciting news both for clinicians and for patients is that cognitive symptoms in major depression have recently been recognized as a target of therapeutic improvement by the FDA and by other governing agencies such as the European Union and are increasingly the focus of clinical research. Thus begins the dawn of a new era where we are learning how to better diagnose and treat individuals struggling with cognitive dysfunction due to a major depressive disorder.

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