Cognitive Symptoms in Patients With Major Depressive Disorder and Their Implications for Clinical Practice

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ABSTRACT

Context: The literature regarding cognitive symptoms in major depressive disorder (MDD) is vast and often contradictory. To provide clinicians with a concise understanding of these prevalent and disabling symptoms, this overview describes what is known regarding cognitive symptoms in patients with MDD, the limitations of the current literature, and the implications of these data for current and future clinical practice.

Evidence Acquisition: PubMed searches were conducted to identify studies, meta-analyses, and systematic reviews evaluating cognitive function (not cognitive bias) in patients with MDD. Search terms used in combination with *MDD* were *cognition, cognitive dysfunction, memory, psychomotor processing,* and *executive function.* Searches were limited to articles available in the English language and those published between April 2007 and March 2012. Additional studies and those describing screening tools were identified using reference lists and PubMed "related citations." Ongoing trials were identified by searching for *cognitive dysfunction* and *MDD* at www.ClinicalTrials.gov. Relevant articles were obtained and reviewed by the author.

Results: Small sample size and inconsistent assessment tools were identified as major limitations of studies assessing clinical characteristics and risk factors for cognitive symptoms. Meta-analyses and systematic reviews were used to mitigate this limitation.

Conclusions: Cognitive symptoms of depression are prevalent and associated with earlier illness onset and longer episode duration. They can have an adverse impact on the treatment course of MDD as well as on functional recovery in depression. Further studies are needed to help determine whether certain treatments can be more effective than others at targeting these symptoms.

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Diminished ability to think or concentrate and difficulty in making decisions are cardinal symptoms of a major depressive episode (MDE), as reflected in the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition.[1] These symptoms are likely to reflect deficits in cognitive functions such as memory, attention, executive functioning, and psychomotor speed. Cognitive symptoms of patients with depression contribute substantially to the burden of major depressive disorder (MDD). In one study of 274 subjects with depression, 71% ranked difficulty concentrating among the top 4 most troubling symptoms.[2] Moreover, on average, individuals with persistent cognitive symptoms after antidepressant treatment have poorer functional outcomes[3,4] and are less likely to remit[5] and more likely to relapse.[6]

Despite the adverse impact of cognitive impairment on MDD outcomes, the biological underpinnings of these symptoms are not well understood. However, imaging studies show evidence of aberrant function in brain regions associated with the modulation of emotional, motivational, cognitive, and behavioral manifestations of mood disorders.[7–12] To date, numerous studies have evaluated cognitive function in patients with MDD, but most are small and involved patient populations with heterogeneous diagnoses, depression severity, treatment status, and testing methods. As a result, findings across studies are inconsistent.[13,14] Meta-analyses have attempted to address some of the heterogeneity, and emerging data indicate that the research focus is shifting to treatment options for patients with MDD with cognitive dysfunction. The objectives of this overview are to summarize the current literature on cognitive symptoms in patients with MDD and to discuss the implications of any insights for current and future clinical practice.

EVIDENCE ACQUISITION

PubMed searches were conducted to identify studies, meta-analyses, and systematic reviews evaluating cognitive function (not cognitive bias) in patients with MDD. Search terms used in combination with *MDD* were *cognition, cognitive dysfunction, memory, psychomotor processing,* and *executive function*. Searches were limited to articles available in the English language and those published between April 2007 and March 2012. Earlier studies and those describing screening tools were identified using reference lists and PubMed "related citations." Ongoing trials were identified by searching for *cognitive dysfunction* and *MDD* at www.ClinicalTrials.gov.

Publications that included data from patients with psychiatric disorders other than unipolar depression were included only if the unipolar depression sample was analyzed separately.

RESULTS

Defining Cognitive Symptoms

Definitions of specific cognitive domains vary considerably across studies, in part because cognitive functioning in itself is a complex process requiring the simultaneous integration of multiple domains. For the present analysis, the focus is on examining cognitive function in depression as the sum of 5 domains: psychomotor speed, declarative memory, working memory, executive function, and attention (Table 1; for details, see review by Mendelsohn et al[15]). Each domain is further categorized into several sub-elements of functioning.

Table 1. Cognitive Function Domains and Subcategories[a]

Cognitive Function	Description
Psychomotor processing	Cognitive operations that enable sensation, perception, and motor actions
Perceptual functioning	Searching and detecting perceived target
Motor functioning	Activities such as finger tapping or manipulation of pegs in a grooved pegboard
Both	Digit-symbol substitution or response time tasks
Declarative memory	Acquisition and retention of information demanding conscious or explicit learning
Episodic memory	Encoding, consolidation, and retrieval
Semantic memory	Learning of factual knowledge—also demand executive function
Working memory	Brief online storage and manipulation of stored information that requires executive functioning
Executive functions	Planning, decision making, anticipation, and reasoning
Planning	Identification and organization of steps required to reach an end
Decision making	Probabilistic choice and delays related to reward
Response inhibition	Use of higher-level executive control to suppress an unwanted prepotent response
Attention	Dependent on reception, selection, and filtering of information
Sustained	Capacity to maintain attentional activity or responding over an extended period of time
Selective or focused	Ability to attend preferentially to 1 or 2 relevant stimuli while suppressing distractions
Divided	Ability to respond to multiple tasks simultaneously—maintain and shift attention as needed
Concept shifting (set-shifting); cognitive flexibility	Allows alternating between types of responding depending on the task conditions and context

[a]As explained by Mendelsohn et al.[15]

Cognitive Impairment in MDD Versus Nondepressed Controls

Difficulty with concentration or decision making is one of the defining symptoms of MDD.[1] Of 1,426 patients with MDD examined in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study,[16] 89.6% reported difficulty with concentration at baseline; of the 30 items on the Inventory of Depressive Symptomatology, only depressed mood (96.8%) and fatigue (91.1%) were more common. Psychomotor slowing was reported to affect as many as 63.7% of patients enrolled in the STAR*D study. Interestingly enough, the percentage of those with psychomotor slowing was similar in patients considered to have a first episode (60.1%) and those with recurrent MDD (64.9%).

Several meta-analyses and systematic reviews were also reviewed (Table 2). Wagner et al[17] conducted a meta-analysis of executive function measured in 15 studies involving 375 subjects with unipolar, nonpsychotic depression and 481 healthy controls. Compared with nondepressed controls matched for age and IQ or years of education, subjects showed significant impairment in response inhibition, cognitive flexibility, and semantic verbal fluency, with effect sizes of 1.18, 1.11, and 0.92, respectively. Strategic planning and organization were moderately impaired.

Another recent meta-analysis[18] of data from 15 samples (N = 644; mean age, 39.4 ± 10.2 years) involving subjects with a first episode of MDD also found that subjects had significantly worse performance on executive function components (attentional switching, verbal fluency, and cognitive flexibility) compared with healthy, age-matched controls. Deficits in psychomotor speed and attention were also noted in this subject population. Working memory and verbal learning and verbal memory scores were not significantly different from scores for healthy controls.

In apparent contrast, a study[19] of 68 young adults (aged 21–35 years) with MDD and no comorbid psychiatric illness, most of whom were experiencing a first episode, found no significant difference in processing speed, attention, and executive functioning compared with healthy, age-matched controls. However, subjects did have mild deficits in verbal learning compared with healthy controls. Moreover, in a similar study,[20] results showed that the presence of psychiatric comorbidities was not associated with worse cognitive function.

Clinical Points

- Cognitive dysfunction is prevalent in major depressive disorder.
- Cognitive symptoms of depression often respond insufficiently to antidepressant therapy.
- Clinicians should screen for and measure the severity of cognitive symptoms in patients with major depressive disorder.

Correlates of Cognitive Dysfunction in MDD

A number of sociodemographic and clinical factors have been linked to cognitive dysfunction in MDD. In the aforementioned meta-analysis by Lee et al,[18] for instance, age, education, and symptom severity were risk factors for worse cognitive performance in first-episode MDD. Specifically, in that report, older age was associated with worse scores on psychomotor speed tests ($\beta = 0.68$; $P < .01$), visual learning and memory ($\beta = 0.78$; $P < .005$), attentional switching ($\beta = 0.62$; $P = .09$), verbal fluency ($\beta = 0.74$; $P < .05$), and cognitive flexibility ($\beta = 0.88$; $P < .005$) compared with controls. Lower educational achievement among patients was also found to correlate with worse verbal learning and memory ($\beta = -0.78$; $P < .01$), visual learning and memory ($\beta = -0.63$; $P = .09$), and attentional switching ($\beta = -0.98$; $P < .05$). Finally, inpatient status, which may indirectly reflect symptom severity, was found to be associated with slower psychomotor speed ($\beta = 0.74$; $P < .005$), poorer working memory ($\beta = 0.55$; $P = .09$), poorer verbal learning and memory ($\beta = 0.46$; $P = .10$), and poorer visual learning and memory ($\beta = 0.76$; $P < .005$).

In a separate study, McDermott and Ebmeier[21] examined the relationship between depressive symptom severity and patterns of cognitive deficits in MDD. In order to do so, results from 14 studies were analyzed. Greater symptom severity positively correlated with poorer executive function (weighted

Table 2. Meta-Analyses and Systematic Reviews Summary

Meta-Analysis or Systematic Review	Patient Population (age range)	No. of Studies (N)	Findings
Lee et al, 2011[18]	First-episode MDD (≥ 18 y; mean age, 39 y)	13 studies; 15 samples (N = 644)	Cognitive deficits vs healthy controls in psychomotor speed, attention, visual learning, memory, and executive functioning (attentional switching, verbal fluency, and cognitive flexibility)
Wagner et al, 2012[17]	Unipolar, nonpsychotic depression (30–53 y)	15 studies (N = 375 patients; N = 481 healthy controls)	Significant impairment in response inhibition, cognitive flexibility, and semantic verbal fluency Significant improvement in performance after treatment compared with performance prior to treatment
Hasselbalch et al, 2011[13]	In remission from MDD (21–74 y)	11 studies (N = 500 with MDD; N = 471 healthy controls)	Nine studies showed significant decrements in sustained and selective attention, memory, and executive function
McLennan and Mathias, 2010[22]	Treated for depression (33–77 y)	17 studies (N = 1,269)	Effect sizes for scores on 1 test of executive function (Dementia Rating Scale initiation and perseveration subtest), 2 tests of psychomotor speed (Stroop Color and Stroop Word, number completed), 1 test of construction (Wechsler Adult Intelligence Scale Block Design), and 1 test of memory (Wechsler Memory Scale) prior to drug treatment discriminated between treatment responders and nonresponders
McDermott and Ebmeier, 2009[21]	Major or minor depression (32–58 y)	14 studies (N not specified)	Severity of depression correlated with decrements in episodic memory, executive function, and processing speed

Abbreviation: MDD = major depressive disorder.

mean effect size, –0.32), processing speed (weighted mean effect size, –0.16), and episodic memory (weighted mean effect size, –0.31), but not with poorer semantic memory (weighted mean effect size, –0.11) or visuospatial memory (weighted mean effect size, –0.17). Finally, in a third report, Castaneda et al[20] found that earlier age of MDD onset in young adults was associated with a greater likelihood of having impaired executive functioning.

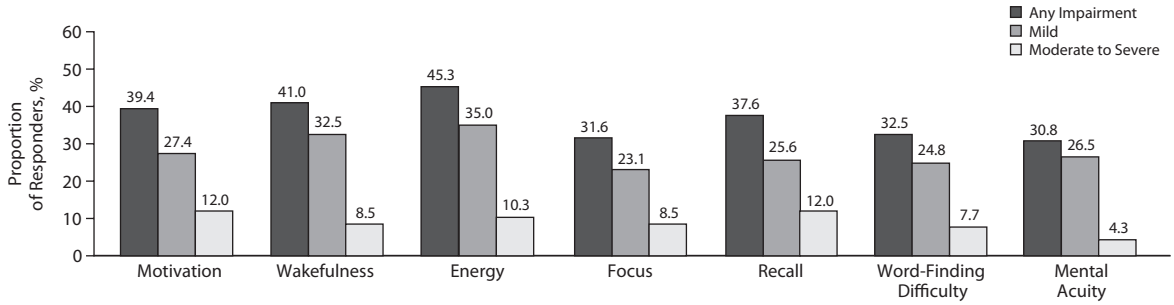
Cognitive Dysfunction as a Predictor of Outcome in the Treatment of MDD

Preliminary evidence, largely accrued from studies involving the treatment of older (aged ≥ 65 years) patients with MDD, suggests that the presence of cognitive symptoms renders clinical response or syndromal remission more difficult to achieve or even maintain.[22] A meta-analysis by McLennan and Mathias[22] was designed to test the hypothesis that cognitive impairment, particularly executive dysfunction, is associated with poor response to antidepressant medication. Seventeen studies were pooled, involving a total of 1,269 patients and employing a total of as many as 90 different tests and subtests (60 of which were only used in 1 study). Approximately half of the 17 studies included were focused on elderly patients. Five cognitive tests provided good discrimination (Cohen's effect size > 0.5) between patients who responded to antidepressant medication versus those who did not, one of which was a test of executive function. Results at baseline in the Stroop Color and Word test (information processing speed), the Block Design test of the Wechsler Adult Intelligence Scale (visual construction skills and information processing speed), and the delayed recall item of the Wechsler Memory Scale–Revised Logical Memory subtest were also strong response predictors to antidepressant therapy. However, the authors pointed out that findings failed to replicate across all tests designed to measure a specific cognitive domain (ie, executive functioning). Given the multitude of tests employed, the results of this study were suggestive of predictive potential but were not conclusive.

In a separate study to determine the correlation of executive function with the remission probability during selective serotonin reuptake inhibitor (SSRI) treatment, Morimoto et al[5] evaluated 70 older patients (aged ≥ 60 years) who received 12 weeks of escitalopram 10-mg therapy. Abnormal performance on the complex verbal initiation/perseveration item of the Mattis Dementia Rating Scale, a measure of verbal strategy utilization on a semantic fluency test, was predictive of remission failure (hazard ratio = 1.48; 95% confidence interval [CI], 1.01–2.2; $P = .043$). No significant relationship was measured between remission rate and information processing speed, simple verbal initiation/perseveration involving rapid naming of clothing items, consonant or vowel perseveration, double-alternating movements, alternate tapping, or graphomotor design. These findings further suggest that dysfunction in brain regions involved in executive function may be related to SSRI response, a finding which, if substantiated in other studies, may provide a useful tool for individualizing patient care.

Vascular depression is used to describe depression, usually occurring later in life, that is characterized by underlying cerebrovascular disease. Sheline et al[23] investigated cognitive functioning and white matter hyperintensities, considered hallmarks of vascular depression, on magnetic resonance imaging. Treatment response to flexible-dose sertraline was evaluated in 217 subjects with MDD and aged ≥ 60 years. Subjects with a history of dementia, stroke, neurodegenerative disease, or other severe and unstable conditions were excluded. Among subjects who completed 8 weeks of treatment, the 33% who remitted (achieved ≤ 7 on the Montgomery-Asberg Depression Rating Scale) had significantly better performance on baseline episodic memory measures, language processing, processing speed, and executive functioning than nonremitters.

Figure 1. Proportion of Responders With Cognitive and Physical Impairment (Cognitive and Physical Functioning Questionnaire) (N = 117)[a]



[a]Reprinted with permission from Fava et al.[24]

A separate study by Alexopoulos et al[6] of 58 subjects (aged ≥ 65 years) with MDD evaluated relapse over 16 weeks of continued nortriptyline treatment. Abnormal initiation and perseveration scores, considered executive function measures, contributed to an increased relapse risk (odds ratio = 0.80; 95% CI, 0.66–0.98; $z = -2.2$; $P < .03$). However, relapse rates were not correlated with memory impairment. During a 2-year, placebo-controlled maintenance phase involving subjects from this same study, overall, 35% (15/43) of subjects (11 in the placebo group and 4 in the active-treatment group) had a recurrent episode. Deficits in initiation and perseveration were associated with a 17% greater relative risk of recurrence. Memory scores did not correlate with recurrence. The number of previous episodes, medical comorbidities, disability, and poor social support were not predictive of recurrence.

Cognitive Dysfunction as a Residual Symptom

Among treatment responders or remitters, cognitive difficulties may often persist. In one large, cross-sectional study by Fava et al[24] of 117 patients with MDD, treatment response was defined as a score of < 9 on the Harvard Department of Psychiatry/National Screening day Depression Score (HANDS) scale. More than 30% of subjects meeting this criterion reported residual inattentiveness, forgetfulness, word-finding difficulty, apathy, and mental slowing. Within the group with residual cognitive problems, 53% reported forgetfulness, 35% had word-finding difficulties, and 32% complained of mental slowness (Figure 1).

Consistent with these results, a subsequent systematic review[13] of studies evaluating cognitive functioning in remitted MDD subjects found that 9 of the 11 studies reported significantly worse functioning in MDD patients in the areas of sustained and selective attention, memory, and executive function compared with healthy, age-matched controls. Unfortunately, however, according to the authors the heterogeneity of study designs precluded a quantitative pooling of the data. Subsequent to publication of the review, the same group undertook a study of cognitive functioning in 88 MDD patients who were in either remission or recovery (mean duration of remission, 6.4 years; range, 0.3–13.8 years) compared with 50 healthy controls.[25,26] Despite the lengthy duration of remission/recovery of most individuals (only 5 patients had been symptomatic within the year prior to entering the study), the patient group showed significantly worse scores on tests of attention and visuomotor speed.[25] The severity of cognitive impairment correlated positively with the cumulative duration of prior episodes and, in particular, episodes with psychotic features.[26]

However, not all studies support the finding that the cumulative duration of the prior episode predicts residual cognitive impairment in remitted/recovered MDD patients. In a separate study, for instance, Bora et al[27] found that, among euthymic individuals with a history of MDD, deficits in processing speed and verbal memory were significantly more severe among those with late-onset (aged ≥ 60 years) depression compared with adults whose first MDE occurred at a younger age. Both groups of patients showed cognitive deficits relative to healthy controls. These findings suggest that, unlike in younger patients where the impact of depressive symptoms over time on learning and cognition appears to play a more prominent role, cerebrovascular disease may greatly contribute to both depressive and cognitive symptoms in individuals who develop depression later in life.

As with depressive symptoms, cognitive symptoms do not appear to be equally responsive or unresponsive to treatment, both within and across various populations stratified by age. A systematic review of 30 studies,[28] for instance, assessed which cognitive domains were most likely to improve with treatment in patients with major depression. In general, the authors concluded that verbal learning and memory, and, to a lesser degree, psychomotor speed were most sensitive to improvement alongside mood symptoms regardless of age. Psychomotor speed was more likely to improve with mood symptoms in older subjects, while attention and executive function measures were less sensitive to improvement in both groups.

As with any residual symptom in MDD, it is also important to determine the "trait versus state" nature of cognitive dysfunction vis-à-vis the depressive episode itself. At least 3 studies[18–20,29] argue in favor of a strong "state" component. First, in 1 study, although cognitive symptoms were present in a population with early or first-episode MDD,[18] cognitive dysfunction appeared to increase with age rather than stay constant. In a separate study, Castaneda et al[19,20] did not find significant cognitive impairment in depressed young

adults (aged 21–35 years). However, in this young adult population, earlier age at MDD onset was associated with a greater likelihood of having impaired executive functioning. Finally, in a third study[29] that involved adolescents (mean age, ~ 15.3 years; mean age at MDD onset, 12.5 years), deficits in executive functioning were exhibited in 20 subjects with acute MDD compared with 17 healthy individuals matched for age, sex, pubertal development, and estimated IQ, but not in 20 previously depressed subjects who had achieved remission. Taken together, these studies suggest residual cognitive impairment is related to age and duration of MDD in younger patients. Large, prospective longitudinal studies are needed to truly answer the state or trait question.

IMPLICATIONS FOR CLINICAL PRACTICE

Assessment

Cognitive symptoms are among the most distressing for patients with MDD[2,20] and limit functional recovery.[3,4] Thus, as with overall depressive symptoms, patient assessment is important to determine the severity of baseline cognitive symptoms as well as to monitor treatment response and functional disability. The Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ)[30] is a 7-item assessment that specifically asks patients about difficulty with concentration and memory. The CPFQ shows good internal consistency, stability over time, and sensitivity to treatment response and is short enough to be administered routinely in clinical practice.

Treatment Selection

There is a paucity of studies suggesting treatment advantages with one antidepressant over another with respect to cognitive outcome measures. One trial[31] evaluated duloxetine 60 mg in elderly patients (N = 311; mean age, 72 years) with recurrent depression. Approximately 10% of the patients enrolled had mild dementia. Compared with placebo, duloxetine treatment significantly improved the primary efficacy outcome—change from baseline in the composite cognitive score. The improvement in the composite cognitive score was driven largely by a significant improvement in the verbal learning and recall test. There were no significant improvements in tests of attention or executive function (digit-symbol substitution, 2-digit cancellation, or letter-number sequencing tests) over the 8-week study duration. Subsequently, a longitudinal, nonrandomized study (N = 73; mean age, 33 years) involving treatment with escitalopram or duloxetine assessed cognitive functions at 3 time points: before treatment, at the end of treatment,[32] and after 24 weeks of unmedicated recovery.[33] Most subjects remitted at 24 weeks of treatment (14% had partial remission). At the end of treatment, the duloxetine group achieved greater improvement in baseline episodic memory and working memory compared with the escitalopram group.[32] Cognitive deficits had further improved 24 weeks after treatment withdrawal; however, the neuropsychological deficit pattern was the same as at the end of treatment. In addition, the SSRI group was still more impaired in episodic visual and verbal memory than the selective norepinephrine reuptake inhibitor (SNRI) group.[33] However, a study of more rigorous design (ie, randomization to one treatment vs another, blinding) would be required in order to begin substantiating the claim of superiority of SNRIs over SSRIs, or vice versa, in terms of cognitive functioning in MDD.

More recently, in an 8-week, double-blind, randomized clinical trial comparing 5 mg of vortioxetine, a novel, multimodal antidepressant, with 60 mg of duloxetine and placebo in elderly patients with MDD, cognitive assessments (the Rey Auditory Verbal Learning Test [RAVLT] and the Digit Symbol Substitution Test [DSST]) were included as exploratory endpoints.[34] Interestingly, patients receiving vortioxetine 5 mg showed significant improvement in the DSST and tests of acquisition and delayed recall versus placebo, whereas duloxetine was superior to placebo only on the RAVLT with path analysis (aimed at determining to what degree improvement in cognitive functioning is independent to the overall improvement in depressive symptoms), demonstrating that Lu AA21004 had an 83% direct effect on the DSST (duloxetine, 26%). On RAVLT acquisition, Lu AA21004 had a 71% direct effect (duloxetine, 65%). On RAVLT delayed recall, vortioxetine had a 72% direct effect (duloxetine, 66%). This trial has yet to be replicated.

With respect to other agents, in a small study (N = 20), Herrera-Guzmán et al[35] made the observation that subjects who had low scores on verbal memory and processing speed tests at baseline were more likely to respond to the antidepressant effects of the norepinephrine-dopamine reuptake inhibitor bupropion 150 mg than those with higher scores. Among the 12 responders, bupropion treatment was associated with improvement in these cognitive dimensions as well.[35] Since cognitive dysfunction is, in some studies, associated with poorer outcome during treatment with agents other than bupropion, the results of this pilot study[35] may suggest a preferential role for bupropion versus SSRIs or SNRIs in such patients, although this hypothesis remains speculative until tested under randomized, double-blind study conditions.

There are also emerging, albeit very preliminary, data suggesting the use of adjunctive treatment strategies in resolving residual cognitive dysfunction in MDD. A 6-week, double-blind, randomized trial evaluated *S*-adenosylmethionine (SAMe) added to a current antidepressant regimen (SSRI or SNRI) in 46 subjects with treatment-resistant depression.[36] SAMe is a major methyl donor essential for neurotransmitter synthesis, which has previously been shown to improve response and remission rates when used as adjunctive therapy in this population.[37] Subjects receiving adjunctive SAMe therapy showed significant improvement in recall and word-finding scores on the CPFQ compared with those receiving placebo.[36] In another trial, adjunctive therapy with modafinil, a dopamine reuptake inhibitor, improved Stroop interference test scores in subjects.[38] Psychostimulants and other catecholaminergic agents are currently being investigated in clinical trials (ClinicalTrials.gov identifiers: NCT01148979, NCT01435759, NCT01436149, NCT01497548,

NCT01185340, NCT00840034, and NCT01173601) alone or in combination with antidepressants to determine their efficacy in improving cognitive symptoms of depression.

Nonpharmacologic interventions may be useful in older individuals with major depression and poor executive function who can be difficult to treat. Problem-solving therapy teaches patients to set goals, identify ways to reach the goals, and assess results. In a 12-week trial, elderly patients given problem-solving therapy had more improvement in disability in depressed, executive-impaired function than those given supportive therapy, which did not teach problem-solving strategies.[39] Moreover, the benefits of problem-solving therapy were proportionately greater in individuals with greater disability. Unfortunately, disability increased in both treatment groups after therapy, and the initial difference between treatments was not sustained.

DISCUSSION

Cognitive symptoms, such as difficulty concentrating and psychomotor slowing, are prevalent in patients with MDD and contribute substantially to the disease burden. Their potential adverse impact on functional recovery is particularly troubling because residual cognitive symptoms are not uncommon in remission and recovery phases. Various study results designed to refine our understanding of the cognitive profile of patients with MDD have been inconsistent, with a large proportion of the data being derived from older subjects. The factors contributing to the inconsistent findings are complex and have been analyzed by Douglas and Porter,[28] among others. Primarily, the inconsistency reflects heterogeneity within the MDD patient population (eg, in terms of age, degree of medical comorbidity) and diversity in study designs and cognitive assessment tools. Nonetheless, several general conclusions may be drawn from available data. Cognitive symptoms occur early in the course of the disorder. Although symptoms do improve with antidepressant treatment, they do so at an unsatisfactory degree and often persist well into remission and even through posttreatment recovery, potentially impeding restoration of premorbid psychosocial functioning. Finally, although there is preliminary evidence to suggest that some pharmacologic strategies may be more successful in resolving cognitive dysfunction in MDD, such evidence is far from being conclusive. Developing treatment strategies specifically targeting cognitive dysfunction in MDD could help advance the standard of care for depression, leading to individualized treatment approaches for such patients.

Given the multitude of symptoms that can constitute a major depressive episode, it would be essential for future research to try to parcel out to what degree cognitive symptoms (in relation to overall episode severity) (1) improve with any given treatment (especially those which are thought to target cognitive symptoms specifically), (2) adversely impact MDD treatment outcome, and (3) adversely impact functional recovery (since cognition is essential to functional recovery). Path analyses, such as those employed by Katona et al,[34] can serve as valuable tools in answering such questions. Specifically, as mentioned in the relevant section of this review, a number of medications (as either monotherapies or adjunctive treatments) are currently being studied for their potential to target depressive symptoms overall as well as cognitive symptoms in particular. It would, therefore, be important to see to what degree the resolution of cognitive symptoms with such treatments can be attributed to the overall reduction in depressive symptoms and to what degree it is independent. Comparisons among agents would be particularly useful. Similarly, path analyses could also help determine to what degree the adverse impact of cognitive functioning on probability of remission and recovery is due to these symptoms independently, as opposed to overall episode severity or other potential confounding factors (ie, cerebrovascular illness, Axis III comorbidity, chronic inflammation, early age at onset). The potential for such confounding can also be tested with respect to the presence of residual cognitive symptoms in patients who are treatment responders or remitters. Most importantly, path analyses can help us understand to what degree functional improvement during the treatment of MDD with various antidepressant agents can be attributed to the reduction in overall episode severity versus cognitive symptom severity. Ultimately, such analyses, particularly if validated with the collection and analysis of surrogate biomarkers (which can also serve as endpoints in path analyses), can lead the way to treatment strategies specifically tailored for MDD patients with moderate-to-severe cognitive dysfunction.

Two main limitations of this work should be noted. As with any review article, important contributions to the literature may have been inadvertently omitted from inclusion in the present review. This may, particularly, be the case with new and unpublished works. Similarly, other experts in the field may have reviewed the same articles and synthesized the review in a different way and with different conclusions. Clinicians and researchers interested in furthering their knowledge in this topic should seek additional sources of information, whether in the literature or educational events.

In conclusion, cognitive symptoms of depression are prevalent and associated with earlier illness onset and greater episode duration. They can have an adverse impact on the treatment course of MDD as well as on functional recovery in depression. Further studies are needed to help determine whether certain treatments can be more effective at targeting these symptoms than others.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), modafinil (Provigil), nortriptyline (Pamelor, Aventyl, and others), sertraline (Zoloft and others), vortioxetine (Brintellix).

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