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Perspective

Cognitive Dysfunction in Major Depressive Disorder: Effects on Psychosocial Functioning and Implications for Treatment

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Major depressive disorder is a common condition with a high rate of recurrence, chronicity, and staggering economic burden, including disability in the workforce.[1] In 2010, MDD was the second leading medical cause of burden globally, with highest estimates of disability in people of working age.[2] In Canada, the annual prevalence of MDD is 3% to 4% overall, and 79% of people with MDD report some interference with work functioning, either decreased work productivity and (or) absenteeism.[1] In addition to work impairment, the psychosocial impact of MDD often affects a person's level of functioning in family and social relationships. While there is clearly an association between improvement in depressive symptoms and functioning, symptom improvement can also be dissociated from functional improvement and work loss.[3,4] Hence there has been increasing recognition that symptomatic remission is an insufficient goal of treatment for MDD and that return to premorbid psychosocial functioning should be targeted.[5]

Cognitive dysfunction refers to deficits in attention, verbal and nonverbal learning, short-term and working memory, visual and auditory processing, problem solving, processing speed, and motor functioning. Cognitive dysfunction may be a primary mediator of functional impairment in MDD.[6] Cognitive complaints are core symptoms of acute MDEs, and diminished ability to think or concentrate and (or) indecisiveness are criterion items for the diagnosis of MDD. Several other core symptoms of MDD may act as mediators of cognitive dysfunction, including psychomotor retardation, amotivation, fatigue, insomnia, and mood disturbances. Deficits on neuropsychological testing are well demonstrated in people with MDD, compared with healthy subjects, with many studies and meta-analyses showing moderate effect sizes in neurocognitive domains of processing speed, attention, executive function, learning, and memory[7,8] as well as in cognitive affective bias. Cognitive affective bias reflects distorted information processing and (or) focus moving away from positive stimuli and toward negative stimuli,[7] and abnormal responses to negative feedback and decision making.[9]

It is also apparent that, while cognitive dysfunction in MDD may improve with treatment and resolution of depressive symptoms, cognitive deficits can still be detected even in periods of symptom remission. In a 3-year, follow-up study of patients with MDD, the proportion of time with cognitive complaints was reported as 94% during acute depressive episodes; this remained at 44% despite full or partial symptom remission during treatment.[10] Cognitive performance on tests of immediate memory, attention,[11] and processing speed[12] was reported to be inferior in patients with MDD who met criteria for remission, compared with healthy subjects. Meta-analyses show that cognitive deficits in executive function are still present in remitted patients,[13,14] which may explain persistent psychosocial impairment in remission.

While it is beyond the scope of our paper to review the underlying pathophysiology, recent evidence points to neural mechanisms that also support a neurocognitive model of depression.[15] Overall, cognitive dysfunction, work, and psychosocial limitations are

prevalent in patients with current and remitted depression.[10] Therefore, we hypothesize that cognitive dysfunction may be a major mediator of psychosocial limitations in patients with MDD.

We aimed to review recent evidence that cognitive dysfunction is a mediator of functional disability in MDD, and that pharmacotherapy and psychotherapy specifically target the cognitive domain. We conducted a PubMed literature search for the period from January 2000 up to January 2014 to identify relevant studies (search strategy available on request) for this review.

Clinical Implications

- There is some empirical evidence that cognitive dysfunction is a mediator of functional disability in patients with MDD.
- Mechanistically dissimilar ADs appear to benefit measures of cognition independent of their effects on global depression symptom severity.
- Future studies should address screening, assessment, and mitigation of cognitive dysfunction, with the goal of improving patient outcomes in MDD.

Limitations

- This is a narrative, not a systematic, review of the relevant literature.
- Few studies have examined the direct and (or) indirect benefits of ADs on cognitive dysfunction, limiting the strength of conclusions that can be drawn.

Cognitive Dysfunction and Psychosocial Functioning

The relations between cognitive dysfunction and psychosocial functioning in MDD are complicated by the heterogeneity of depressive symptoms and episodes, cognitive skills, and domains of psychosocial functioning. For example, objective assessments of cognitive performance suggest that patients with melancholic depression have significantly greater impairment in memory and executive function, compared with patients with nonmelancholic depression.[16] In addition, severity of symptoms,[17–19] cumulative duration of depressive episodes,[20] and presence of comorbidities[7] were all independently and negatively correlated with cognitive function. The multidimensionality of cognition, coupled with the known heterogeneity of MDD symptoms and the diversity of domains of psychosocial functioning, poses challenges to understanding the nature of the relation linking these 3 concepts.

Online eTable 1 summarizes studies evaluating the association between cognitive dysfunction and functional impairment in patients with MDD. The evidence suggests that cognitive dysfunction is associated with and may mediate functional impairments in MDD. However, systematic reviews[21,22] have highlighted the limited evidence base of studies relating objective cognitive dysfunction with psychosocial functioning. Deficits in cognitive domains, including attention and processing speed, executive function, and verbal knowledge, have been correlated with some measures of psychosocial functioning.[17] However, some studies have evaluated only subjective measures of cognition, which may be susceptible to patients' biases and insights into their illness. Buist-Bouwman et al[23] reported that more than one-quarter of the impact of MDD on work loss was directly attributable to self-reported cognitive complaints (that is, difficulty concentrating, memory, understanding, and ability to think clearly). Indeed, among 6 activity limitations (that is, mobility, self-care, cognition, social interaction, discrimination, and embarrassment or feelings of shame), only cognition and embarrassment (which may reflect stigma) were significant mediators of the association between MDD and work or role dysfunction.[23] Cognitive dysfunction[10,24,25] and functional impairments[5,25] are 2 of the most common residual complaints among patients with MDD who achieve symptomatic remission. In a study[25] of patients with MDD treated with ADs for at least 3 months who were considered to be in partial or complete remission, 30% to 50% reported residual cognitive symptoms that interfered with functioning.

Taken together, these data support an association between cognitive dysfunction and functional impairment in patients with MDD, especially in the work domain, and even when symptomatic remission has been achieved. However, the cross-sectional designs of most studies provide limited capacity to infer causality of this association.

Abbreviations

AD	antidepressant
AP	antipsychotic
BD	bipolar disorder
CBT	cognitive-behavioural therapy
MDD	major depressive disorder
MDE	major depressive episode
RCT	randomized controlled trial
SNRI	serotonin-norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor

Assessment of Cognitive Dysfunction in Major Depressive Disorder

The bias toward negative cognitive schemes found in MDD is likely to contribute, at least in part, to the high percentage of patients reporting subjective cognitive complaints during depressive episodes. The discordance between subjective complaints and objective measures of cognitive dysfunction highlights the importance of clinically based screening for both subjective and objective cognitive functioning. However, one of the key clinical challenges is in the lack of consensus on best tools to accurately and efficiently assess cognition in clinical settings. No single test or test battery

has emerged as the gold standard in MDD. This is in contrast to initiatives, such as the Measurement and Treatment to Improve Cognition in Schizophrenia (commonly referred to as MATRICS) Consensus Cognitive Battery, developed to evaluate the impact of new medications on cognition in schizophrenia,[26] and a similar consensus battery to assess neurocognition in BD.[27]

Regardless of the distinction between subjective and objective findings of cognitive impairment during an MDE,[18] subjective cognitive complaints should trigger additional investigation into sleep quality and (or) other medical comorbidities, as these factors are known to negatively affect cognitive performance.[7] For example, sleep may have pro-cognitive effects[28] and sleep deprivation affects numerous domains of cognition.[29]

Effects of Antidepressants on Cognitive Dysfunction

Interventions targeting cognition may reduce depressive symptoms and improve functional outcomes.[23] If it is determined that cognitive dysfunction is a core component of an MDE and is not secondary to sleep disturbances, fatigue, other medications, or comorbidities, treatment options include pharmacotherapy and (or) psychotherapy directed at specific cognitive domains or augmentation strategies to treat residual cognitive symptoms.

Online eTable 1 summarizes the effects of ADs on cognitive dysfunction in patients with MDD. Most classes of ADs have been associated with some degree of improvement in neuropsychological tests, compared with placebo.[30–37] There are fewer studies comparing the cognitive effects of different ADs. In a study in older adults with depression treated for 12 weeks, sertraline was superior to nortriptyline and placebo in significantly improving verbal learning, but there were no effects on other neuropsychological measures.[38] Some data suggest that SNRIs may have greater effects on neurocognitive dysfunction than SSRIs. An 8-week study[35] comparing duloxetine with placebo in elderly patients with MDD evaluated a composite outcome involving a battery of 4 cognitive tests measuring verbal learning and memory, selective attention, and executive functioning. Duloxetine was associated with a significantly greater improvement in the composite cognitive score than placebo; path analysis showed that this effect was largely driven by verbal learning and recall.[35] In an RCT in adult patients with MDD, duloxetine was more effective than escitalopram at improving episodic and working memory at the end of 24 weeks of acute treatment[24] and 24 weeks later, when patients were unmedicated during a recovery phase.[33]

There is also some support from small and uncontrolled studies that bupropion, a putative noradrenaline and dopamine reuptake inhibitor, can improve some cognitive measures in patients with depression. Treatment with bupropion for 12 weeks improved measures of visual memory and mental processing speed in 20 patients with MDD.[32] A naturalistic study of outpatients with depression responding to at least 4 weeks of AD treatment found that those who received bupropion had similar scores as healthy subjects on a battery of neurocognitive tests, whereas those treated with SSRIs or venlafaxine did not.[37]

Several studies with newer agents have been designed to include cognitive function as a primary or key secondary outcome. For example, a study[39] in older patients with MDD found that vortioxetine, a multimodal AD that acts as a serotonin reuptake inhibitor, 5-HT_{1A} agonist, and $5HT_3$ and $5HT_7$ antagonist, and duloxetine both had significant effects on verbal learning and memory, compared with placebo, but only vortioxetine had significant effects on a test of processing speed and executive function. Results of a large clinical trial evaluating the effects of vortioxetine, compared with placebo, on measures of cognitive dysfunction as a primary end point in younger adults with MDD, support the beneficial effects of this agent on objective and subjective measures of cognitive function.[40]

Taken together, these results support a modest beneficial effect of ADs on some cognitive domains in patients with MDD, with the strongest evidence to date supporting SNRIs for verbal and visual memory, as well as vortioxetine for numerous domains. Despite these promising findings, it should be acknowledged that there is a paucity of large RCTs with objective cognitive measures as primary end points, which limits the strength of the conclusions that can be drawn. Many studies have evaluated cognitive outcomes before and after treatment rather than comparing them with placebo, potentially biasing the results by learning effects. Further, few studies have directly compared the effects of different ADs on cognitive outcomes. Several studies have been conducted in samples of older patients with depression, which may not be generalized to younger adults and working populations. It is also possible that objective and subjective cognitive complaints may not be tapping into a similar substrate, underscoring the need to assess both objective and patient-reported cognitive outcomes. Finally, there has not been systematic investigation of AD effects on both cognitive and psychosocial functioning.

Overall, the effect of ADs on cognitive domains and functioning still remains an emerging area of investigation. The nature of the relation between pharmacotherapy and cognition is likely to be modulated by the type of depression, the specific pharmacologic agent, and specific cognitive and functional domains. Therefore, more controlled studies are required before clinical recommendations can be established with confidence.

Effects of Psychotherapy on Cognitive Dysfunction

Psychotherapeutic strategies may be helpful for cognitive complaints in MDD, but there are surprisingly few studies of psychotherapy and subjective or objective cognitive dysfunction. Studies have shown that CBT not only improves depressive symptoms but also improves psychosocial functioning in patients with recurrent MDD[41];

it is plausible that this improvement may be mediated by improved cognition. Conradi et al[42] randomized adults who were receiving usual care in the primary care setting to psychoeducation or psychoeducation plus CBT. During 2 years of follow-up, the subgroup of patients with highly recurrent depression (≥4 episodes) who received psychoeducation plus CBT reported cognitive symptoms (indecisiveness, unclear and slow thinking, and concentration problems) significantly less of the time (15%, representing 3.6 months of the time), compared with the psychoeducation only intervention (47%, representing 11.3 months of the time). Psychotherapy programs that address cognitive rehabilitation and remediation have been investigated in schizophrenia[43] and bipolar depression,[44] and may also be effective for neurocognitive symptoms in MDD.[45] Modifying the negative memory bias in patients with MDD may also reduce cognitive vulnerability and prevent depressive relapse.[46] These studies suggest that CBT and memory-specific therapies hold promise to alleviate subjective cognitive symptoms and dysfunction in patients with acute or remitted MDD. Another important question for further research is whether specific psychotherapies can address specific cognitive deficits (for example, CBT for negative cognitive bias and interpersonal psychotherapy for social cognition deficits).

Managing Residual Cognitive Symptoms

Managing residual cognitive symptoms in treated patients whose depressive symptoms are improved constitutes another important clinical challenge, given the associations between cognition and daily life functioning. For patients with residual cognitive dysfunction after AD treatment, cognitive side effects should first be ruled out.[25] For example, nortriptyline has been associated with poorer immediate free recall performance, compared with placebo.[47] ADs with anticholinergic and sedative properties may have negative cognitive side effects; these are seen primarily with the older tricyclic ADs, but have also been reported with paroxetine and mirtazapine.[48] Adverse effects on cognition are also associated with benzodiazepines and hypnotics,[49] which are commonly used in the adjunctive treatment of MDD. Cognitive side effects may be especially prevalent and impairing in working patients with depression[50] and in patients with late-life depression who do not respond to AD treatment.[51]

Augmentation strategies may be beneficial to treat residual cognitive symptoms. Numerous pharmacotherapy augmentation strategies have shown efficacy in MDD, including lithium[52] and atypical APs,[53] but cognitive dysfunction has not been specifically examined in these studies. Moreover, there is evidence that lithium is associated with adverse cognitive side effects that may negatively impact psychosocial functioning.[54] Likewise, there is evidence to suggest that, in BD, atypical APs may worsen cognitive performance.[55,56] Psychostimulants may be expected to have positive effects on cognition, but augmentation studies of osmotic-release oral system-methylphenidate[57,58] and lisdexamfetamine[59,60] in MDD have shown inconsistent results on depressive symptoms and subjective neurocognitive measures, although the latter were not always measured. A recent meta-analysis of modafinil augmentation studies in MDD found only a nonsignificant trend to positive effects on depressive symptoms, and cognitive measures were not reported.[61] Hence there is as yet little evidence to support specific medications that can address residual neurocognitive and psychosocial dysfunction in patients with MDD.

Conclusions

The inadequacies in both symptom and functional outcomes in MDD invite the need for a pivot toward other dimensions of MDD (for example, cognitive dysfunction) that are principal mediators of functional impairment. In keeping with this view, a testable hypothesis would be that mitigation of cognitive dysfunction in MDD would improve functional outcomes. While there is evidence that cognitive dysfunction in MDD may mediate impairments in psychosocial and work functioning, both during acute depressive episodes and remission, there is still a need for more rigorous studies of these relations. There is also some evidence that current pharmacologic and psychotherapeutic treatments improve cognitive functioning in MDD, but little information on their impact on psychosocial functioning and on residual symptoms. Newer pharmacologic agents that directly target cognitive dysfunction and cognitive remediation psychotherapies may help address these unmet patient needs. Further, there is a need for better screening and assessment methods to specifically assess subjective and objective cognitive function in MDD, with the goal of improving patient outcomes.

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Table 1. Summary of primary articles evaluating the associations between psychosocial functioning and cognition, and between antidepressant treatment and cognitive outcomes in MDD (listed in chronological order).

Reference	**Subjects**	**Age (yr)**	**Gender (% F)**	**Baseline HAM-D-17 / MADRS**	**Study design**	**Outcomes**
Associations between psychosocial functioning and cognition						
McCall and Dunn, 2003[62]	77 inpatients with severe MDD, prior to ECT	56.7 ± 15.8	64	28.9 ± 5.0	Cross-sectional study	Global cognition score correlated with activities of daily living.
Jaeger et al, 2006**Error! Bookmark not defined.**	48 inpatients with MDD	39.6 ± 12.7	67	16.5 ± 7.1	6-month prospective study	Objective measures of non-verbal, learning, and motor at baseline predicted functional outcomes at 6 months.
Naismith et al, 2007**Error! Bookmark not defined.**	21 patients with MDD and matched controls	53.9 ± 11.8	76	21.7 ± 4.4	Cross-sectional study	Self-rated cognitive deficits and objectively-measured psychomotor function predicted physical disability.

Buist-Bouwman et al, 2008**Error! Bookmark not defined.**	21,425 adults; 847 (4.0%) reported MDD episode in last 12 months	-	-	-	Cross-sectional study	Strong association between MDD and psychosocial function. Concentration, attention, and embarrassment mediated the relationship between MDD and function.
Withall et al, 2009[63]	48 inpatients with MDD	38.0 ± 10.6	67	28.3 ± 5.7 at baseline; 10.7 ± 6.0 at follow up	4 month prospective study	Deficits in several neurocognitive domains predicted functional outcome at 4 months followup.
Baune et al, 2010**Error! Bookmark not defined.**	26 outpatients, current MDD	46.0 ± 12.1	27	18.0 ± 5.9	Cross-sectional study	Current MDD = lower cognition scores in all domains vs. healthy controls, and in visuo-spatial /constructional and attention vs. previous MDD. Previous MDD = lower score in immediate memory and attention vs. healthy controls. Employment status was associated with deficits in cognition scores.
	44 patients with previous MDD	44.2 ± 15.9	73	6.8 ± 4.3		
Godard et al, 2011[64]	16 outpatients with MDD	49.5 ± 12.3	81	31.2 ± 5.1 (29-item)	Cross-sectional study	Significant correlations between neuropsychological deficits and functional impairment.
Associations between antidepressant treatment and cognitive outcomes						

Reference	Subjects	Age (yr)	Gender (% F)	Baseline HAM-D-17 / MADRS	# of episodes	Study design	Cognitive outcomes
Meyers et al, 1991**Error! Bookmark not defined.**	9 patients with MDD treated with nortriptyline	73.4 ± 8	-	Nortriptyline: 5.0 ± 3 Placebo : 6.7 ± 3	-	Cross-over design. 8-26 weeks of nortriptyline followed by 1 week of placebo	Nortriptyline worsened immediate, but not delayed, free recall. No difference between placebo and nortriptyline on measures of immediate and delayed recognition memory.
Constant et al, 2005**Error! Bookmark not defined.**	20 outpatients with MDD treated with sertraline and matched controls	47.7 (range: 21-74)	60	Baseline BDI: 25.6 ± 8.0	1st or 2nd MDE	7-week prospective study	Patients with MDD: disturbances in attention, executive, and psychomotor function vs. controls. Sertraline improved attention, executive, and psychomotor function.
Ferguson et al, 2003**Error! Bookmark not defined.**	25 patients with MDD treated with reboxetine	Range: 18-65, as per design	-	>20, as per design	-	Two 8-week, placebo-controlled, double-blind RCTs	Reboxetine: improved sustained attention and cognitive functioning speed at day 56 vs. baseline. Paroxetine and placebo: no significant effect on
	23 patients with MDD treated with paroxetine		-		-		

	74 patients with MDD treated with placebo		-		-		these cognitive endpoints.
Gualtieri et al, 2007**Error! Bookmark not defined.**	27 outpatients with MDD treated with SSRI	43.8	59	-	-	Cross-sectional study	SSRI patients: scored lower on psychomotor speed, cognitive flexibility, and reaction time vs. matched controls. Venlafaxine patients: scored lower on reaction test during a Stroop test vs. matched controls. Bupropion patients: did not differ from matched controls in any cognitive domain.
	27 outpatients with MDD treated with venlafaxine	46.1	59	-	-		
	27 outpatients with MDD treated with bupropion	44.0	74	-	-		
	27 matched controls	43.8	63	-	-		
Raskin et al, 2007**Error! Bookmark**	207 outpatients with MDD treated with duloxetine	72.6 ± 5.7	60	22.4 ± 3.8	5.0 ± 15.0	8-week placebo-controlled, double-blind RCT	Duloxetine: significant improvement in composite cognitive score vs. placebo (improvement mainly

not defined.	104 outpatients with MDD treated with placebo	73.3 ± 5.7	58	22.0 ± 3.6	6.3 ± 13.6		driven by verbal learning and memory).
Herrera-Guzman et al, 2008**Error! Bookmark not defined.**	20 outpatients with MDD treated with bupropion	24.5 ± 4.7	92	Responders: 26.8 ± 6.1 Non-responders: 21.8 ± 3.3	5.3 ± 5.5	8-week clinical trial	Low pretreatment visual memory and processing speed were predictive of good response to bupropion. Visual memory and processing speed improved during treatment.
Culang et al, 2009**Error! Bookmark not defined.**	84 outpatients with MDD treated with citalopram	79.8 ± 4.0	54	24.4 ± 4.3	-	8-week double-blind, placebo-controlled RCT	Citalopram responders: improved in visuospatial functioning vs. non-responders, but not vs. placebo responders. Citalopram responders: improved in psychomotor speed vs. citalopram non-responders, but not vs. placebo.
	90 outpatients with MDD treated with placebo	79.3 ± 4.7	62	24.3 ± 3.9	-		
Herrera-Guzman et al,	36 patients with MDD treated with escitalopram	32.9 ± 8.7	86.1	25.3 ± 4.0	3.8 ± 4.8	24-week clinical trial	Both treatments improved episodic memory, working memory, mental

2009**Error! Bookmark not defined.**	37 patients with MDD treated with duloxetine	33.2 ± 8.6	75.7	25.1 ± 5.3	3.6 ± 3.5		processing speed and motor performance. Duloxetine was more effective than escitalopram at improving episodic and working memory.
Herrera-Guzman et al, 2010**Error! Bookmark not defined.**	36 patients with MDD previously treated with escitalopram	32.9 ± 8.7	86.1	25.3 ± 4.0	3.8 ± 4.8	24-week follow-up after cessation of medication	Patients with remitted MDD performed worse on verbal and visual memory, attention, and working memory vs. healthy controls. Patients previously treated with a SNRI performed better in episodic visual and verbal memory vs. patients previously treated with a SSRI.
	37 patients with MDD previously treated with duloxetine	33.2 ± 8.6	75.7	25.1 ± 5.3	3.6 ± 3.5		
Culang-Reinlieb et al, 2012**Error! Bookmark not defined.**	33 patients with MDD treated with sertraline	64.9 ± 8.8	61	23.9 ± 4.4	-	12-week clinical trial	Sertraline patients: improved more on verbal learning vs. nortriptyline
	30 patients with MDD treated with nortriptyline	63.5 ± 8.2	60	24.9 ± 5.4	-		

Katona et al, 2012**Error! Bookmark not defined.**	156 elderly patients with MDD treated with vortioxetine	70.5 ± 4.8	69	22.7 ± 3.9	-	8-week double-blind, randomized, placebo- and active-controlled trial	Vortioxetine (LU AA21004), but not duloxetine, improved speed of processing, verbal learning and memory vs. placebo
	151 elderly patients with MDD treated with duloxetine	70.9 ± 5.5	66	22.3 ± 3.9	-		
	145 elderly patients with MDD treated with placebo	70.3 ± 4.4	62	22.7 ± 3.9	-		
McIntyre et al, 2014[Error! Bookmark not defined.]	195 MDD outpatients treated with vortioxetine 10 mg/d	45.4 ± 12.2	69	31.6 ± 3.8	2.3 ± 1.7	8-week multinational, double-blind, randomized, placebo-controlled trial	Vortioxetine 10 and 20 mg/d significantly improved a composite of cognitive measures (DSST and RAVLT) vs. placebo Patient-reported cognition was also significantly improved with vortioxetine vs. placebo.
	207 MDD outpatients treated with vortioxetine 10 mg/d	46.1 ± 11.8	64	31.7 ± 3.5	2.6 ± 2.1		

	196 MDD outpatients treated with placebo	45.6 ± 12.1	66	31.3 ± 3.8	2.4 ± 2.0		

Data are presented as mean ± SD unless otherwise noted. '-' denotes that data were not available. BDI: Beck Depression Index; F: females; HAM-D-17: 17-item Hamilton depression scale; MADRS: Montgomery-Asberg Depression Rating Scale; MDD: major depressive disorder; SD: standard deviation; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; RCT: randomized controlled trial; MDE: major depressive episode; DSST: digit symbol substitution test; RAVLT: Ray auditory verbal learning test.