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Procognitive Effects of Antidepressants and Other Therapeutic Agents in Major Depressive Disorder:
A Systematic Review

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ABSTRACT

Objective: To review the efficacy of antidepressants and other therapeutic agents for the treatment of cognitive impairment in adults with major depressive disorder (MDD).

Data Sources: We conducted a database search of MEDLINE, PsycINFO, and Embase through Ovid on May 7, 2019. The year of publication was not restricted. The search terms "Major Depressive Disorder," "depress*," "cognit*," and "therapeutics" were used.

Study Selection: The studies included in this review were clinical trials of antidepressants and other therapeutic agents in MDD populations. Participants were aged between 18 and 65 years and had a *DSM-III, -IV,* or *-5* diagnosis of MDD. In total, 2,045 research papers were screened, 53 full-text articles were assessed, and 26 articles were eligible to be included in this systematic review.

Data Extraction: The data and quality of research papers were assessed and screened by 2 independent reviewers. Discrepancies were resolved through a third reviewer.

Results: Overall, studies demonstrated that tricyclic antidepressants do not have procognitive effects, while vortioxetine and bupropion have demonstrated procognitive effects in MDD populations relative to selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors. Several non-antidepressant agents, such as modafinil, amphetamines, and erythropoietin, have also demonstrated significant positive effects on cognition in depression.

Conclusions: Present-day antidepressants and other agents have demonstrated procognitive effects in MDD, but the findings between various agents are mixed. Further research looking at objective measures of cognitive performance would be helpful to obtain more definitive results regarding the efficacy of therapeutics for cognitive impairment in MDD.

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Clinical Points

- Despite the common persistence of cognitive impairment in populations with major depressive disorder (MDD), treatment options are understudied and limited.
- A review of all potential therapeutic agents is necessary to inform future research investigating the benefits of pharmaceutical agents for cognitive impairment in MDD.
- So far, vortioxetine seems to be a viable treatment option for MDD patients with cognitive impairment.

Major depressive disorder (MDD) affects over 300 million people and is currently the leading cause of disability worldwide.[1] According to the *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition (*DSM-5*),[2] MDD is characterized by a marked change in mood and/or anhedonia and the presence of several other psychophysiological changes, such as disturbed sleep, changes in appetite, fatigue, and a diminished ability to think or concentrate.[2] Cognitive impairment is estimated to affect approximately two-thirds of individuals with MDD.[3] The *DSM-5* characterizes cognitive impairment as difficulty with thinking, concentrating, or making decisions.[2] However, impairments on neuropsychological tests in MDD populations have also been demonstrated in the domains of processing speed, attention, executive function, learning, and memory with moderate effect sizes.[4,5] Moreover, these deficits remain present despite full or partial remission of MDD symptoms.[6] In particular, executive dysfunction tends to persist, which may contribute to the psychosocial impairment[7–9] commonly experienced by those with remitted MDD.[10] Psychosocial functioning is understood as the degree to which individuals adequately interact with their environment across daily, occupational, and social domains.[11] It is well established that cognitive deficits in MDD are associated with impaired psychosocial functioning.[12] Additionally, studies show a positive relationship between self-reported cognitive impairment and loss of occupational productivity, impaired social functioning, and reduced daily functioning.[7,13,14] Thus, there is strong evidence suggesting that MDD is associated with impairments in multiple cognitive domains and that these impairments are notably associated with difficulties in psychosocial functioning.

Pharmacologic Treatments in Major Depressive Disorder

While extensive research has been conducted on the effects of antidepressants on depressed mood, the procognitive effects of antidepressants and other therapeutic agents have not been thoroughly investigated. A systematic review and meta-analysis[15] concluded that antidepressants, such as tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and norepinephrine-dopamine reuptake inhibitors (NDRIs), have a significant positive effect on psychomotor speed and delayed recall in adults with MDD, though no significant difference between the classes of antidepressants was found. Yet, that review included only studies of antidepressants with the primary mechanism of action being monoamine modulation in 1 or more of the following categories: SSRIs, SNRIs, serotonin antagonist and reuptake inhibitors, noradrenergic and specific serotonergic antidepressants, TCAs, and multimodal antidepressants. This led to the exclusion of certain antidepressants, such as bupropion, as well as non-antidepressant agents. Additionally, the paper did not investigate the relationship between cognition and functional outcomes. Finally, new clinical trials have been conducted since the publication of this previous review, which we will explore in the current review.

Vortioxetine, a multimodal serotonergic antidepressant, is the first antidepressant recognized by the US Food and Drug Administration for its procognitive effects.[16] Moreover, there is evidence that bupropion improves cognitive functioning in patients with depression.[17] More recently, adjunctive agents, such as amphetamines,[18] erythropoietin, and modafinil,[19] have been investigated for their cognitive effects in MDD. To date, clinical trials looking at the procognitive effects of therapeutic agents in MDD populations have obtained positive findings; however, these studies are limited by their small sample sizes, heterogeneous cognitive measures, and lack of objective measures of cognitive functioning.

The Current Review

Cognitive impairment is an important yet understudied phenomenon in MDD and should be considered a treatment priority as it is strongly related to psychosocial impairment. Therefore, the primary objective of the current systematic review is to examine the overall efficacy of antidepressants and other therapeutic agents in MDD, with a focus on objective measures of cognition. Previous studies reporting cognitive improvements based on participant self-reports lend themselves to low validity, considering the weak relationship between reported and actual cognitive impairment[20] and the strong relationship between cognitive complaints and depressive symptomatology.[21] Consequently, the use of objective measures only is a key strength of this study and will give a more realistic assessment of the procognitive effects of the discussed pharmacologic agents. As a secondary outcome measure, we will examine functional outcomes and their relation to cognitive improvements. Thus, this review aims to offer a detailed overview of the procognitive efficacy of antidepressant and non-antidepressant agents. Accordingly, this article will provide practical information regarding the need for future studies assessing the efficacy of the most successful agents for treating cognitive impairment in MDD.

METHODS

Search Methods

A comprehensive database search of MEDLINE, PsycINFO, and Embase through Ovid was conducted on May 7, 2019, using the following search terms: "Major Depressive Disorder" OR "depress*" AND "cognit*" AND "therapeutics," "antidepressant agent," "antidepressant," "procognitive

treatment," "clinical trial," "psychostimulant," OR "procognitive." Duplicates were removed automatically by Ovid using the "deduplicate" function. Results were then screened manually for any remaining duplicates by author M.J.B. In addition, ClinicalTrials.gov was searched, using the terms "cognition" and "depression." Additional papers were identified from the reference section of the included articles. Authors M.J.B. and S.R.V. independently assessed the search results for eligibility. The authors resolved all discrepancies through discussion with coauthor S.J.M.

Inclusion Criteria

1. Randomized controlled and open-label trials assessing the effects of pharmacologic interventions (antidepressant and non-antidepressant agents) on cognition.
2. Studies measuring objective cognitive functioning.
3. Studies of human participants between 18 and 65 years of age who met *DSM-III*, *-IV*, or *–5* or *International Classification of Disease* (*ICD*)*-10* or *-11* criteria for MDD.
4. Articles written in English.
5. There was no restriction on year of publication.

Exclusion Criteria

1. Single-dose trials.
2. Naturalistic studies.
3. Studies in which psychotherapy was the primary intervention being investigated.
4. Studies that included only subjective cognitive outcome measures.
5. Studies including participants with concurrent suicide risk.
6. Studies in which participants met criteria for other psychiatric disorders, such as bipolar disorder, attention-deficit/hyperactivity disorder (ADHD), psychotic disorders, substance use disorder, or posttraumatic stress disorder; comorbid anxiety was not excluded, as it is a common comorbidity of MDD.

Quality of Assessment

The quality of papers was assessed using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) checklist.[22,23] All placebo-controlled and active-comparator studies had a low potential for selection bias and performance biases because they used double-blind, treatment randomization procedures. In the open-label studies, participants received the same treatment, which minimized selection bias; however, performance bias could not be excluded. Additionally, because details regarding the blinding of outcome assessments were not given, detection bias could not be considered. A minimum of 70% of participants enrolled in the studies completed the trial. Although the GRADE criteria deem 80% apt, we considered 70% an acceptable rate based on the study population. All studies reported significant and nonsignificant results, demonstrating a low selective reporting bias. None of the studies ended prematurely. Table 1 summarizes the GRADE criteria for the included studies.

Table 1. GRADE Criteria Checklist[a]

GRADE Item	Results
Selection bias *Was random sequence generation used?*	RCT and active comparator studies: yes Open-label: NA
Performance bias *Was there blinding of participants?*	RCT and active comparator studies: yes Open-label: no
Detection bias *Was there blinding of outcome assessment?*	RCT and active comparator studies: unclear Open-label: unclear
Reporting bias *Were more than 80% of participants enrolled in trials included in the analysis?*	Did not meet criteria: Peselow et al 1991 (NR)[24] Spring et al 1992 (NR)[25] Bastos et al 2013 (74%)[26] Greer et al 2014 (70%)[27] Herrera-Guzmán et al 2009 (72%)[28] Wesnes et al 2017 (NR)[29] Herrera-Guzmán et al 2008 (77%)[30]
Selective reporting *Were data reported consistently for the outcome of interest?*	RCT and active comparator studies: yes Open-label: yes
Did the trials end as scheduled?	All trials ended as scheduled

[a]Based on references 22 and 23.
Abbreviations: NA = not applicable, NR = not reported, RCT = randomized controlled trial.

RESULTS

Of 2,045 articles identified through the database search and additional search methods, 53 full-text articles were assessed for eligibility, and 26 were included in the systematic review (Figure 1). Studies were excluded for reasons such as lack of objective measures of cognition, nondepressed study populations, and inappropriate age of study population.

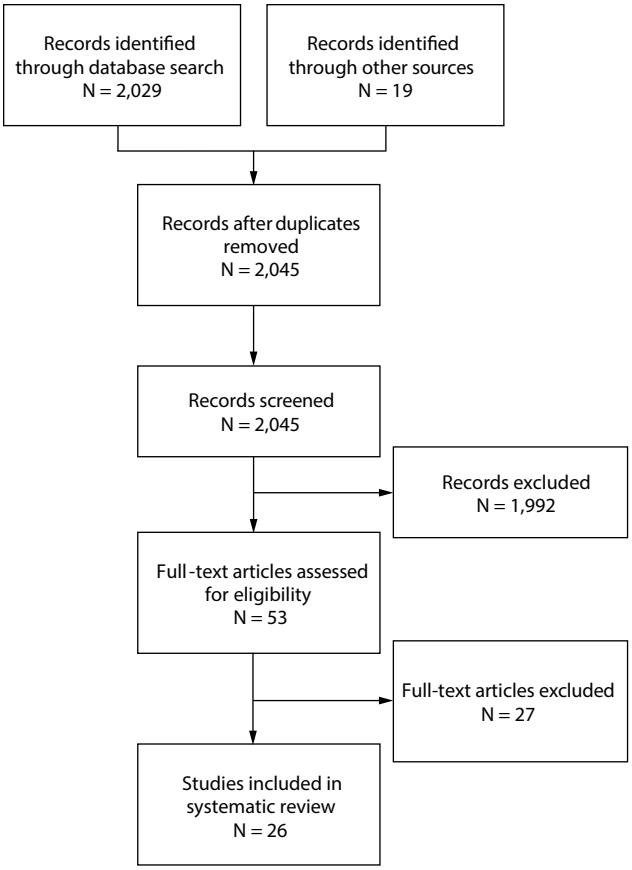
Description of the Studies

The included articles were published between 1982 and 2018. Of these 26 articles, 13 were randomized controlled trials (RCTs), 7 were open-label trials, and 6 were active comparator studies. Sample sizes varied from 17 to 598 MDD participants: 13 studies included a sample size of less than 50 people, 9 included a sample size between 50 and 200, and 4 had a sample size greater than 200 (Figure 2). Study duration ranged from 1 week to 24 months. The mean age of subjects ranged from 24 to 56 years, with an average age of 42. The average proportion of females was 65% across the included studies. It is important to note that one study[31] included a female-only sample and another study[32] included a male-only sample. We classified study medications as TCAs, SSRIs and other serotonergic agents, SNRIs, NDRIs, and non-antidepressant agents.

Tricyclic Antidepressants

Cognition. In general, the studies included in this review were unable to conclude that TCAs are efficacious at

Figure 1. Flow Diagram of the Numbers of Studies Included and Excluded in the Review



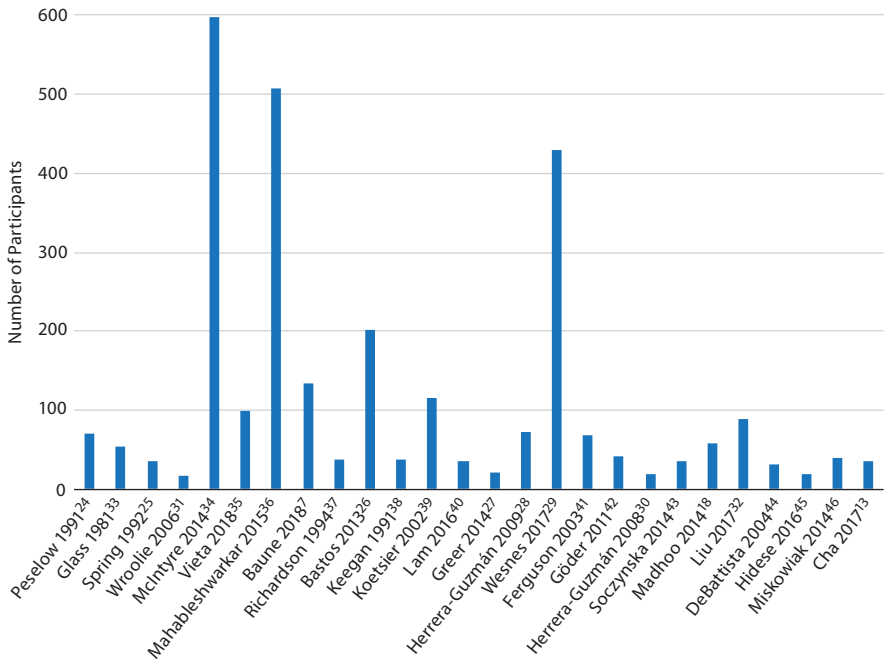
improving cognition in MDD. One study[33] (N = 54) found that 12 weeks of imipramine significantly improved short-term memory functioning, but not performance speed, compared to placebo in participants with moderate levels of depression (mean Hamilton Depression Rating Scale [HDRS] score = 20.0) at baseline. An open-label study[24] (N = 71) found that 4 weeks of imipramine was significantly associated with improvements on memory tasks, but this was dependent on depression severity. The participants in this study had higher levels of depression (mean HDRS = 24.7; mean Montgomery-Asberg Depression Rating Scale [MADRS] score = 30.5) at baseline.

Conversely, amitriptyline was not found to be associated with improvements in cognitive functioning. An RCT[25] (N = 35) found that following 4 weeks of amitriptyline, no significant improvements were found in psychomotor performance in individuals with severe depression (mean HDRS = 24.7) at baseline. In addition, 2 studies[37,38] (both with N = 37) found that amitriptyline was associated with significantly worse performance on tests of verbal learning compared to fluoxetine. These 2 studies did not include information regarding baseline severities of depression. This makes it difficult to infer whether changes in cognition were related to changes in depressive severity.

Selective Serotonin Reuptake Inhibitors and Serotonergic Agents

Cognition. Two active comparator studies (both with N = 37)[37,38] found that fluoxetine was associated with significant improvements on verbal learning scores compared to amitriptyline after 6 weeks of treatment. Conversely, a

Figure 2. Number of Participants That Completed Each Study



larger RCT[26] (N = 202) found that 24 months of fluoxetine was not associated with a significant improvement in cognitive performance over time in a sample of moderately depressed individuals (mean Beck Depression Inventory [BDI] score = 26.7). These results hold more weight than the former studies as this study was placebo-controlled, included a large sample, and lasted 24 months. Therefore, these results suggest that fluoxetine does not have significant effects on cognition.

An RCT[39] (N = 116) found that 4 weeks of fluvoxamine treatment significantly improved attention and reaction time (RT) in individuals with severe depression (mean HDRS = 27.3) at baseline. However, this improvement was mediated by depression severity ($r = 0.44$, $P < .05$).[39]

An open-label study[31] (N = 17) found that 12 weeks of escitalopram treatment in individuals with moderate depression (mean HDRS = 21.2) was correlated with significant improvements in measures of attention and processing speed, verbal memory, nonverbal memory, and executive functioning. However, this study also found that escitalopram was associated with significant worsening of verbal fluency.[31] These results should be interpreted with caution because this study included a small female-only sample and had no placebo-controlled group.

Finally, vortioxetine treatment was associated with significant improvements in multiple domains of cognitive functioning.[7,34–36] Specifically, 1 study[34] (N = 598) found that following 8 weeks of treatment in participants with moderate depression (mean MADRS = 31.5), 2 doses of vortioxetine (10 mg/d and 20 mg/d) were significantly superior to placebo in improving global cognition. The largest effect sizes (Cohen effect size, $d = 0.51$ for 10 mg and $d = 0.52$ for 20 mg) were obtained on the Digit Symbol Substitution Test (DSST), a measure of executive functioning, speed of processing, and attention.[34] Additionally, half to two-thirds of the effect of vortioxetine was a direct effect on cognition, rather than a consequence of depressive symptom improvement.[34] Other, more recent studies[7,35,36] have supported these findings, demonstrating that vortioxetine is associated with improvements in cognitive functioning in individuals experiencing moderate levels of depression.

Functional outcomes. Paroxetine and escitalopram were not associated with functional improvement.[7,35] After 8 weeks (N = 508), vortioxetine led to significant improvements in functional capacity ($P < .001$).[36] However, another RCT (N = 134)[7] and active comparator study (N = 99)[35] did not obtain significant results for the effect of vortioxetine on functional capacity.

Despite contradicting results regarding the direct effect of vortioxetine on functional outcomes, it was found that change in cognitive performance was positively correlated with change in performance-based functional capacity for those taking vortioxetine ($r = 0.21$, $P = .02$).[7] Further, after 8 weeks of vortioxetine or escitalopram treatment, a partial correlation was obtained ($r = 0.31$, $P = .006$) between the DSST and functioning, reflecting a moderate relationship between cognitive performance and functional capacity.[35]

Serotonin and Norepinephrine Reuptake Inhibitors and Norepinephrine Reuptake Inhibitors

Cognition. Conflicting results were found for the efficacy of reboxetine. After 1 week of reboxetine treatment (N = 41), no significant improvements in cognitive flexibility, declarative memory, or visual and motor skills were found in individuals with moderate depression (mean HDRS = 20.7).[42] This could be due to the short study duration. Conversely, another study (N = 68) found that after 8 weeks, reboxetine was significantly associated with improvements on measures of attention and RT.[41] Information regarding sample severity of depression was not provided.

Significant improvements in attention and RT measures were found in severely depressed individuals (mean MADRS = 35.2) treated with 8 weeks of levomilnacipran versus placebo (N = 429).[29] These improvements were greater for individuals who were more cognitively impaired at baseline compared to those with less impairment.

Furthermore, 8 weeks of open-label treatment (N = 36) with desvenlafaxine was associated with significant improvements in cognitive flexibility, processing speed, and global cognition ($d = 0.43$, $P = .003$) in outpatients with moderate depression (mean MADRS = 28.5).[40]

Finally, duloxetine was associated with significant improvements in the domains of psychomotor speed, visual memory, decision making, and verbal learning and memory after 12 weeks of open-label treatment (N = 21) in individuals with moderate depression (mean HDRS = 19.1).[27] However, improvements in verbal learning and memory were moderated by change in depressive severity ($r = 0.54$, $P < .004$).[27] Duloxetine was also associated with significant improvements in episodic memory, compared to escitalopram, after 24 weeks (N = 73) of treatment in individuals with severe depression (mean HDRS = 25.2).[28] Moreover, duloxetine was associated with significant increases in mental processing speed variables and working memory (WM); however, duloxetine did not significantly separate from escitalopram on these measures.[28] Conversely, duloxetine did not separate from placebo on tests of executive functioning, processing speed, and attention in an 8-week RCT (N = 508) comparing its efficacy to vortioxetine and placebo.[36] The results of the latter study should be taken into consideration as it is the only placebo-controlled study and included a large sample of participants with moderate depression (mean MADRS = 31.7).

Functional outcomes. Eight weeks (N = 36) of desvenlafaxine treatment resulted in significant improvements in functional outcomes (measured using the Lam Employment Absence and Productivity Scale [$d = 1.35$, $P < .001$]; Sheehan Disability Scale [$d = 1.45$, $P < .001$]; and Health and Work Performance Questionnaire [$d = 0.89$, $P < .001$]).[40]

Norepinephrine-Dopamine Reuptake Inhibitors

Cognition. Following 8 weeks of open-label bupropion treatment, participants (N = 20) with severe depression (mean HDRS = 24.8) significantly improved on measures

of memory and some measures of mental processing speed; improvement was greater in responders versus nonresponders.[30] A study (N = 36) comparing the effects of bupropion to escitalopram found that 8 weeks of bupropion in individuals with moderate depression (mean HDRS = 23.4) was associated with significant improvements on measures of verbal memory and nonverbal memory, but not WM or composite memory.[43]

Functional outcomes. Following 8 weeks of bupropion, significant improvements were observed on functional measures; however, this improvement was not significantly greater than that found with escitalopram.[43] The same study found that change in immediate verbal memory directly influenced psychosocial functioning.[43]

The details of all studies assessing the efficacy of antidepressant agents are outlined in Table 2.

Non-Antidepressant Agents: Psychostimulants

Cognition. Following 9 weeks of lisdexamfetamine dimesylate augmentation to SSRI therapy in remitted MDD patients (N = 59), significant improvements in executive functioning were found compared to placebo; however, there was no difference between lisdexamfetamine dimesylate and placebo on composite cognition.[18] The lack of positive findings on composite cognition could be due to the inclusion of a study population with mild levels of depression (mean MADRS = 12.3).

An open-label study (N = 90) found that 60 mg of caffeine, but not 120 mg, was associated with improved cognition.[32] However, this study included a male-only sample, making it difficult to generalize these findings to females with MDD. Moreover, these participants experienced mild levels of depression (mean HDRS = 14.1; mean MADRS = 18.3).

Other Non-Antidepressant Agents

Cognition. An open-label study (N = 31) of modafinil augmentation therapy in moderately depressed participants (mean HDRS = 21.4; mean BDI = 20.6) found that 4 weeks of modafinil was associated with significant improvements on a test of executive functioning,[44] though no other neurocognitive tests showed such improvements.[44] The lack of positive findings could be attributed to the short study duration and small sample size.

Eight weeks of erythropoietin administration enhanced recall memory and recognition memory more than placebo in individuals with treatment-resistant depression (mean HDRS = 20); these effects were maintained over the entire 14 weeks of the study (N = 39).[46]

L-Theanine, an amino acid, was associated with significant improvements in executive functioning and verbal memory after 8 weeks of open-label administration (N = 20) in a sample with mild depression (mean HDRS = 12.5).[45] Finally, following 12 weeks of intranasal insulin treatment in participants (N = 35) with treatment-resistant depression (mean MADRS = 25.9), no effects on cognition were found.[13]

The details of studies assessing the efficacy of non-antidepressant agents are outlined in Table 3.

DISCUSSION

The aim of this systematic review was to assess the efficacy of various antidepressants and other therapeutic agents for relieving cognitive impairment in MDD. Specifically, studies assessing the effects of pharmaceutical agents on objective measures of cognition in adults with MDD were assessed.

Tricyclic Antidepressants

Overall, studies assessing the efficacy of tricyclic antidepressants demonstrated that TCAs are not procognitive. While individuals taking imipramine experienced significantly improved memory, significant correlations were also obtained between memory tasks and depressive symptom measures, suggesting that imipramine did not directly improve memory.[24] Furthermore, amitriptyline may have significant adverse effects on memory.[25] Eligible studies that examined TCAs were limited by their relatively small sample size and short study duration, and none of the studies assessing the efficacy of TCAs investigated their effect on functional capacity. Moreover, these studies included differing objective measures of cognition which may explain different results across studies. Nevertheless, further research on the efficacy of TCAs for cognitive impairment is not warranted as studies have consistently demonstrated that TCAs, such as amitriptyline and clomipramine, have lower acceptability rates than other efficacious antidepressants.[47]

Selective Serotonin Reuptake Inhibitors and Serotonergic Agents

In general, the studies included in this review suggest that older SSRIs, such as fluoxetine and fluvoxamine, are not procognitive, but that newer serotonergic agents may exert positive effects on cognitive functioning. Escitalopram, a newer antidepressant, was correlated with improved executive functioning, attention, processing speed, verbal memory, and nonverbal memory, but worsened verbal fluency.[31] However, recent studies have found that escitalopram is inferior to other new antidepressants, such as vortioxetine and duloxetine, at improving cognitive impairments in adults with MDD.[28,35]

The results obtained in the included studies extended the evidence of vortioxetine's procognitive efficacy previously demonstrated in elderly patients with MDD.[48] Vortioxetine's effect on cognition appears to be largely direct and independent, rather than an epiphenomenon of depressive symptom improvement,[34] suggesting that vortioxetine could be used to target cognitive impairment specifically. Vortioxetine's procognitive efficacy is likely due to its ability to modulate a wide range of neurotransmitters (ie, dopamine [DA], norepinephrine [NE], γ-aminobutyric acid [GABA]),[49] in addition to its multimodal serotonergic actions. Improvements in cognitive functioning with vortioxetine were positively correlated with improvements in functional capacity.[7] This finding is important, as MDD is consistently associated with impaired global functioning.[50] Thus, among serotonergic agents, vortioxetine

Table 2. Summary of Studies Investigating the Effects of Antidepressant Agents on Cognitive Measures

Study (by Main Drug Type Investigated)	Study Medication (Dosage)	N (end)	Mean Age (y)	Proportion Female	Duration	Design	Diagnosis	Outcome Measures	Results	Limitations
Tricyclic Antidepressants (TCAs)										
Peselow et al 1991[24]	Imipramine (IMI; 150–300 mg/d)	71	49	50%	4 wk	Open-label	MDD (HDRS ≥ 16)	Cognition: digit span; superspan digits; Buschke; fragmented pictures	After 4 weeks, IMI significantly associated with improvements in implicit memory ($P < .002$), short- and long-term memory ($P = .05$), and retrieval efficiency from remote memory ($P < .05$) Significant correlations between HDRS, MADRS, and memory tasks ($P < .05$)	Short study duration No placebo
Glass et al 1981[33]	Imipramine (150 mg/d)	54	43	65%	12 wk	RCT	MDD or minor depressive disorder or intermittent depressive disorder (HDRS ≥ 16)	Cognition: tapping speed, lift-off RT, item recognition procedure	IMI led to a significant decrease in number of short-term memory errors ($P < .001$) after 12 weeks No significant drug effects on performance speed and reaction time in the memory task	Differences may be due to task complexity
Spring et al 1992[25]	Amitriptyline (AMI; 50–350 mg/d), clovoxamine (50–350 mg/d)	35	34	63%	4 wk	RCT	Major affective disorder, depressive episode, 5 criteria for primary depression (HDRS ≥ 16)	Cognition: verbal recognition memory, Benton visual retention, DSST, tapping test, auditory RT	AMI had adverse effects on recognition memory ($P < .05$) and on visual perception and memory ($P < .01$) No difference in psychomotor performance between groups receiving AMI and clovoxamine	Short study duration
Selective Serotonin Reuptake Inhibitors (SSRIs)										
Wroolie et al 2006[31]	Escitalopram (10–20 mg/d)	17	56	100%	12 wk	Open-label	MDD (*DSM-IV* diagnosis)	Cognition: CVLT, CVLT-II, WMS-III, Stroop test, TMT-A/B, COWAT	After 12 weeks, escitalopram significantly associated with improvements in attention and processing speed ($P = .014$), verbal memory (LM I, $P = .049$; LM II, $P = .005$), nonverbal memory ($P = .041$), and EF ($P = .004$) Escitalopram associated with significant worsening in verbal fluency ($P = .003$)	Small sample size Open-label design Female-only sample
McIntyre et al 2014[34]	Vortioxetine (10 mg/d or 20 mg/d)	598	45	66%	8 wk	RCT	MDD (MADRS ≥ 26), current MDE ≥ 3 months	Cognition: DSST, RAVLT, TMT-A/B, Stroop test, SRT, CRT	After 8 weeks, both doses significantly superior to placebo on composite cognition ($P < .001$) Processing speed, working memory, and visuospatial processing had the largest effect size ($d = 0.51$ for 10 mg/d; $d = 0.52$ for 20 mg)	Exclusion of individuals with milder baseline severity
Vieta et al 2018[35]	Vortioxetine (10–20 mg/d), escitalopram (10–20 mg/d)	99	48	75%	8 wk	RCT (active comparator)	MDD (MADRS ≥ 22), inadequate response to ≥ 6 weeks of SSRI or SNRI	Cognition: DSST, TMT-A/B, Stroop, SRT, CRT, RAVLT Functioning: FAST, UPSA-B	After 8 weeks, cognitive test scores improved in both treatment groups; no significant differences between groups Vortioxetine did not significantly improve functional capacity Correlation between functional capacity and executive functioning, processing speed, and attention (DSST, $P = .006$)	No placebo

(continued)

Table 2 (continued).

Study (by Main Drug Type Investigated)	Study Medication (Dosage)	N (end)	Mean Age (y)	Proportion Female	Duration	Design	Diagnosis	Outcome Measures	Results	Limitations
Mahableshwarkar et al 2015[36]	Vortioxetine (10 or 20 mg/d), duloxetine (60 mg/d)	508	45	65%	8 wk	RCT	MDD (MADRS ≥ 26), subjective reports of cognitive dysfunction, acute MDE ≥ 3 months	Cognition: DSST, TMT-A/B, Stroop test, Groton Maze Learning Test, Detection Task, Identification Task, One-Back Functioning: UPSA, WLQ	After 8 weeks, vortioxetine led to significant improvements in tests of EF, processing speed, and attention ($P < .001$); duloxetine did not separate from placebo Vortioxetine led to improvements in functional capacity ($P < .001$)	Lack of formalized inclusion criteria for cognitive dysfunction
Baune et al 2018[7]	Vortioxetine (10 mg/d), paroxetine (20 mg/d)	134	46	66%	8 wk	RCT	MDD (MADRS ≥ 26), current MDE ≥ 3 months	Cognition: DSST, TMT-A/B, Stroop test, SRT, CRT Functioning: FAST, UPSA-B	After 8 weeks, neither treatment separated from placebo on executive functioning, processing speed, or attention Vortioxetine separated from placebo on composite cognition ($P = .024$) No significant improvement on functional capacity, but cognition positively correlated with functional capacity ($r = 0.213$, $P = .024$)	
Richardson et al 1994[37]	Fluoxetine, amitriptyline (doses not specified)	37	NR	68%	6 wk	RCT (active comparator)	MDD (HDRS > 20 and BDI > 20)	RAVLT	After 6 weeks, significant differences obtained in verbal learning scores between the drug groups, favoring fluoxetine ($P = .0002$)	No placebo
Bastos et al 2013[26]	Fluoxetine (FLU; 20–60 mg/d)	202	30	62%	24 mo	RCT	MDD or depressive disorder NOS (BDI 20–35)	Cognition: similarities, digit span, letter-number sequencing, digit-symbol coding, matrix reasoning, picture arrangement	After 24 months, FLU did not lead to significant improvements in cognitive performance over time	Homogeneity of participant sample
Keegan et al 1991[38]	Fluoxetine (20–80 mg/d), amitriptyline (100–250 mg/d)	37	44	66%	6 wk	RCT (active comparator)	MDD (HDRS-21 ≥ 20 and BDI ≥ 20)	Cognition: RAVLT	After 6 weeks, FLU led to significant improvements on a test of verbal memory ($P = .001$); AMI did not	No placebo
Koetsier et al 2002[39]	Imipramine (200–300 µg/L), fluvoxamine (150–200 µg/L)	116	52	55%	4 wk	RCT	MDD (HDRS > 13)	Cognition: CPT	After 4 weeks, both treatments led to significant improvements in attention ($P < .01$) and RT ($P < .01$) Fluvoxamine led to a significant decrease in omission errors ($P < .01$); IMI did not Attention positively correlated with depression in the fluvoxamine group ($r = 0.44$, $P < .05$)	Short study duration No placebo

(continued)

Table 2 (continued).

Study (by Main Drug Type Investigated)	Study Medication (Dosage)	N (end)	Mean Age (y)	Proportion Female	Duration	Design	Diagnosis	Outcome Measures	Results	Limitations
Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs), Norepinephrine Reuptake Inhibitors										
Lam et al 2016[40]	Desvenlafaxine (flexible, 50–100 mg/d)	36	39	55%	8 wk	Open-label	Outpatients, MDD (MADRS ≥ 23), subjective cognitive complaints (BC-CCI ≥ 6)	Cognition: CNSVS, NCI Functioning: LEAPS, HPQ, SDS	After 8 weeks, desvenlafaxine associated with significant improvements in cognitive flexibility ($d = 0.60$, $P < .001$), processing speed ($d = 0.57$, $P < .001$), and global cognition ($d = 0.43$, $P = .003$) After 8 weeks, functional outcomes improved ($P < .001$) Cognitive-improvement group (measured by NCI) had significantly better outcomes on depressive and functional outcomes than those who did not experience cognitive improvement	Functional capacity based on self-report Open-label design
Greer et al 2014[27]	Duloxetine (30–120 mg/d)	21	31.3	67%	12 wk	Open-label	MDD (HDRS-17 ≥ 16; CGI-S ≥ 4), reported difficulties with concentration and/or cognition (IDS-C ≥ 2)	Cognition: IDS item 15, CANTAB	After 12 weeks, duloxetine associated with improvements in RT, VRM ($P < .05$), and subjective cognition Significant relationship between HDRS and change in verbal learning and memory ($r = 0.54$, $P < .004$)	Small sample size Open-label design
Herrera-Guzmán et al 2009[28]	Duloxetine (60 mg/d), escitalopram (10 mg/d)	73	33	81%	24 wk	RCT (active comparator)	MDD (HDRS-17 ≥ 18)	Cognition: WAIS-III, RAVLT, PRM, PAL, DMS, SRM, RT	After 24 weeks, duloxetine and escitalopram led to significant improvements in episodic memory ($P < .000$), mental processing speed ($P < .01$), and working memory ($P = .014$) Duloxetine showed superior improvements in episodic memory compared to escitalopram	No placebo Mainly female sample
Wesnes et al 2017[29]	Levomilnacipran extended-release (40–120 mg/d)	429	45	65%	8 wk	RCT	MDD (MADRS ≥ 30), current MDE ≥ 4 weeks	Cognition: digit vigilance, SRT, CRT, POA, COA, cognitive RT, RT variability	After 8 weeks, significantly greater improvements in attention and RT found with levomilnacipran in the intent to treat (ITT) population and in the higher cognitive impairment groups ($P < .01$)	Baseline MDD characteristics not consistent across cognitive impairment subgroups Not designed to provide sufficient statistical power in all subgroups
Ferguson et al 2003[41]	Reboxetine (8–10 mg/d), paroxetine (20–40 mg/d)	68	NR	NR	8 wk	RCT	MDD (HDRS-17 > 20)	Cognition: CDR test battery, COA factor score, Combined Speed factors	After 8 weeks, reboxetine led to significant improvements in attention and performance speed ($P < .05$) Paroxetine did not lead to significant improvements on any cognitive measure	Mean age and proportion female NR
Göder et al 2011[42]	Citalopram (9–27 mg/d), reboxetine (4–8 mg/d)	41	31	76%	1 wk	Active comparator study	MDD (HDRS-17 ≥ 15)	Cognition: TMT-A/B, shift of attention, fluency test, final acquisition, recall, retention, mirror tracing	Neither treatment led to significant improvements on cognitive tests	Short study duration No placebo

(continued)

Table 2 (continued).

Study (by Main Drug Type Investigated)	Study Medication (Dosage)	N (end)	Mean Age (y)	Proportion Female	Duration	Design	Diagnosis	Outcome Measures	Results	Limitations
Norepinephrine Dopamine Reuptake Inhibitors										
Herrera-Guzmán et al 2008[30]	Bupropion sustained-release (150 mg/d)	20	24	92%	8 wk	Open-label	MDD (HDRS-17 ≥ 18)	Cognition: CANTAB, WAIS-III digit span, DMS, SSP, RAVLT, PRM, PAL, SRM, processing speed, MTS, RT, RVP, Stroop test, COWAT, set shift, SWM, SOC	After 8 weeks, bupropion associated with significant improvement on tests of episodic memory ($P < .04$), visual learning, and memory ($P = .028$, $P = .029$) Memory improvement was greater in responders than nonresponders ($P < .05$)	Small sample size Open-label design
Soczynska et al 2014[43]	Bupropion extended-release (150–300 mg/d), escitalopram (10–20 mg/d)	36	38	53%	8 wk	RCT (active comparator)	MDD (HDRS-17 ≥ 16), current MDE	Cognition: CVLT-II, measures from the WMS-III, BVMT-R Functioning: SDS, EWPS	After 8 weeks, bupropion led to significant improvements in verbal ($P = .001$) and nonverbal memory ($P < .001$) but not in working or composite memory Both treatments led to significant improvements in global functioning ($P < .001$) and work productivity ($P = .045$) Improvements in immediate verbal memory exerted a direct influence on improvements in global functioning ($P = .006$)	No placebo

Abbreviations: BC-CCI = British Columbia Cognitive Complaints Inventory; BDI = Beck Depression Inventory; BVMT-R = Brief Visuospatial Memory Test—Revised; CANTAB = Cambridge Neuropsychological Test Automated Battery; CDR = Cognitive Drug Research (cognitive battery); CGI-S = Clinical Global Impression scale—Severity of Illness; CNSVS = CNS Vital Signs; COA = Continuity Of Attention; COWAT = Controlled Oral Word Association Test; CPT = Continuous Performance Test; CRT = Choice RT Task; CVLT = California Verbal Learning Test; DMS = Delayed Matching to Sample; DSST = Digit Symbol Substitution Test; EF = executive function; EWPS = Endicott Work Productivity Scale; FAST = Functional Analysis Screening Tool; HDRS = Hamilton Depression Rating Scale; HPQ = Health and Work Performance Questionnaire; IDS = Inventory for Depressive Symptomatology; LEAPS = Lam Employment Absence and Productivity Scale; LM I, LM II = Logical Memory I, Logical Memory II; MADRS = Montgomery-Asberg Depression Scale; MDD = major depressive disorder; MDE = major depressive episode; MTS = Match to Sample Visual Search; NCI = Neurocognitive Index; NOS = not otherwise specified; NR = not reported; PAL = Paired Associates Learning; POA = Power Of Attention; PRM = Pattern Recognition Memory; RAVLT = Rey Auditory Verbal Learning Test; RCT = randomized controlled trial; RT = reaction time; RVP = rapid visual information processing; SDS = Sheehan Disability Scale; SOC = Stockings of Cambridge; SRM = Spatial Recognition Memory; SRT = Simple RT Test; SSP = Spatial Span; SWM = Spatial Working Memory; TMT = Trail Making Test; UPSA-B = University of California, San Diego Performance-Based Skills Assessment (Brief); VRM = verbal recognition memory; WAIS-III = Wechsler Adult Intelligence Scale; WLQ = Work Limitations Questionnaire; WMS = Wechsler Memory Scale.

Table 3. Summary of Studies Investigating the Effects of Non-Antidepressant Agents on Cognitive Measures

Study (by Main Drug Type Investigated)	Study Medication (Dosage)	N (end)	Mean Age (y)	Proportion Female	Duration	Design	Diagnosis	Outcome Measures	Results	Limitations
Psychostimulants										
Madhoo et al 2014[18]	Lisdexamfetamine dimesylate (LDX; 20–70 mg/d)	59	40	69%	9 wk	RCT	MADRS ≥ 18, self-reported executive dysfunction	Cognition: BRIEF-A informant-report, NCI derived from CNSVS	After 9 weeks, no significant differences in cognition between LDX and placebo LDX significantly improved participant-reported EF ($P = .0006$)	
Liu et al 2017[32]	Caffeine (60 or 120 mg/d)	90	41	0%	4 wk	RCT	Current MDE (HDRS = 10–18; MADRS = 14–24)	Cognition: MoCA	Cognition significantly increased after 60 mg caffeine but not 120 mg ($P < .05$)	Male-only sample
Other Non-Antidepressant Agents										
DeBattista et al 2004[44]	Modafinil (100–400 mg/d)	31	48	58%	4 wk	Open-label	MDD (HDRS-17 > 16), complaints of hypersomnia, fatigue, daytime somnolence, impaired daytime alertness	Cognition: Stroop test, WAIS-III, TMT-A/B	After 4 weeks, modafinil associated with significant improvements in EF ($P < .04$); no other neurocognitive test showed significant change	Short study duration Open-label design Carryover effects
Hidese et al 2016[45]	L-theanine (250 mg/d)	20	43	80%	8 wk	Open-label	MDD (*DSM-5* diagnosis)—included remitted and unremitted patients at baseline	Cognition: Stroop test, BACS	After 8 weeks, theanine associated with significant improvements in response latency ($P = .001$) and error rate ($P = .036$) in a test of EF Theanine associated with significant improvements in verbal memory ($P = .005$) and EF ($P = .016$)	Small sample size Open-label design Mean HDRS-21 score at baseline was 12.5—mild MDD
Miskowiak et al 2014[46]	Erythropoietin (40,000 IU)	39	43	69%	14 wk	RCT	MDD (HDRS-17 > 17), treatment resistance based on the TRAQ	Cognition: RAVLT Functioning: GAF, QOL	After 14 weeks, erythropoietin led to significant improvements in recall ($P = .02$) Erythropoietin significantly improved recognition memory vs placebo ($P = .03$)	Did not screen or exclude comorbid Axis II disorder
Cha et al 2017[13]	Intranasal insulin (1.6 mL/d)	35	47	63%	12 wk	RCT	MDD (HDRS-17 ≥ 20), TRD (nonresponse to ≥ 2 treatments)	Cognition: CVLT-II, D-KEFS (verbal fluency, TMT-A/B, DSST, CFQ), CANTAB	No significant improvements on overall mood, neurocognitive function, or self-reported quality of life	Included patients with TRD; many other studies did not

Abbreviations: BACS = Brief Assessment of Cognition in Schizophrenia, BRIEF-A = Behavior Rating Inventory of Executive Function for Adults, CANTAB = Cambridge Neuropsychological Test Automated Battery, CFQ = Cognitive Failures Questionnaire, CNSVS = CNS Vital Signs, CVLT = California Verbal Learning Test, D-KEFS = Delis-Kaplan Executive Function System, DSST = Digit Symbol Substitution Test, EF = executive function, GAF = Global Assessment of Functioning, HDRS = Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder, MDE = major depressive episode, MoCA = Montreal Cognitive Assessment, NCI = Neurocognitive Index, QOL = quality of life, RAVLT = Rey Auditory Verbal Learning Test, RCT = randomized controlled trial, TMT = Trail Making Test, TRAQ = Treatment Response to Antidepressants Questionnaire, TRD = treatment-resistant depression, WAIS-III = Wechsler Adult Intelligence Scale, WMS = Wechsler Memory Scale.

has consistently demonstrated its superiority at improving cognitive and functional impairment in MDD.

Serotonin and Norepinephrine Reuptake Inhibitors and Norepinephrine Reuptake Inhibitors

Newer SNRIs are also superior to older SNRIs (eg, reboxetine) at improving cognition in MDD. For instance, both levomilnacipran and desvenlafaxine, newer antidepressants, resulted in significant improvements in measures of cognitive functioning. For levomilnacipran, greater improvements were found in those with higher baseline cognitive impairments,[29] suggesting the utility of the drug for individuals with poor baseline cognitive functioning. Moreover, levomilnacipran and desvenlafaxine have shown efficacy in improving functional outcomes in individuals with MDD.[29,51,52] Finally, 2 studies[27,28] demonstrated that duloxetine improves multiple domains of cognitive functioning. However, in a study comparing its efficacy to vortioxetine and placebo, no significant improvements were found on measures of cognition.[36] Discrepancies between studies could be due to the heterogeneity of the cognitive measures used and the fact that the first 2 studies[27,28] did not include control groups. Nevertheless, another study (which did not meet inclusion criteria for this review due to improper age range) supports duloxetine's procognitive effects: a double-blind, placebo-controlled trial, conducted in an elderly population with recurrent MDD, found that duloxetine resulted in a significant improvement in global cognition.[53]

Norepinephrine-Dopamine Reuptake Inhibitors

It has been hypothesized that antidepressants with potent noradrenergic effects enhance cognition.[17] Among included studies, bupropion was shown to have positive effects on cognition, specifically on memory and processing speed. Other studies support these findings. One study, which did not meet criteria for this review, found that 8 weeks of bupropion improved neurocognitive performance in patients with MDD and concurrent suicide risk.[54] This study was excluded due to the inclusion of individuals with suicide risk. Additionally, bupropion has been shown to have superior effects to SSRIs on memory in a naturalistic study.[17]

Multiple studies, including those in this review, have suggested that improvement in verbal memory following bupropion treatment is associated with greater improvement in global functioning.[55,56] The mechanism of action of bupropion has been scarcely studied in human populations. Commonly suggested mechanisms are the reuptake inhibition of DA and NE by bupropion and its primary metabolite hydroxybupropion.[57,58] One microdialysis study that used the Porsolt animal model of depression measured neurotransmitter levels in the nucleus accumbens of mice and found increased extracellular concentrations of DA and NE in response to bupropion administration.[57] Another study found elevated levels of these neurotransmitters in the rat prefrontal cortex (PFC) in response to bupropion.[57] Noradrenergic reuptake inhibition in the PFC is shown to improve executive deficits in MDD[4]; this was not found in either of the 2 included studies investigating bupropion. However, the first study[43] included a small sample (N = 20) of younger individuals (mean age = 24). Younger individuals may not experience the same level of impairment as older individuals with MDD since cognitive impairments have been shown to be related to the cumulative duration of depressive episodes.[5] Moreover, the second study[30] did not include cognitive measures that assess executive functioning.

Non-Antidepressant Agents: Psychostimulants

Stimulant agents have also been investigated for their effectiveness at improving cognitive impairments in MDD. Executive function deficits are of particular interest in MDD[59] as they result in significant problems in coping with stressful life events.[18,60] NE and DA are important neurotransmitters involved in maintaining executive functions mediated by the PFC[61]; consequently, agents that modulate these neurotransmitters may improve executive functioning in MDD.[18]

There is evidence that lisdexamfetamine, a stimulant typically used to treat ADHD, is able to regulate these neurotransmitters. Specifically, lisdexamfetamine is converted to the active metabolite D-amphetamine, which blocks the reuptake of catecholamines, subsequently increasing their release.[61,62] Consequently, lisdexamfetamine may be able to enhance cognitive functioning in the PFC. For instance, lisdexamfetamine has been shown to ameliorate subjective executive dysfunction in patients with residual depressive symptoms.[63] However, among eligible studies, lisdexamfetamine did not significantly improve objective cognition. The absence of positive results on objective measures could be due to the use of self-reported executive dysfunction as an inclusion criterion.

Another stimulant, caffeine, is frequently used for its psychoactive properties.[32] Caffeine was found to enhance the activity of 6 typical antidepressants in mice.[64] Of eligible studies, one study found that low doses of caffeine enhanced cognition in adults with MDD.[32] Specifically, improvements were seen in subtests of the Montreal Cognitive Assessment, which measures higher cognitive functions, such as executive functioning and WM, and lower cognitive abilities, such as attention. These findings are supported by the general consensus that low doses of caffeine improve lower cognitive functions, such as RT and attention.[65] There is less research on the effects of caffeine on higher cognitive abilities.[65] Future studies should further investigate the impact of stimulants on objective cognitive impairments and their relationship with improvements in work and life functioning.

Other Non-Antidepressant Agents

Finally, other therapeutic agents were investigated for their procognitive efficacy. Modafinil is an effective wake-promoting agent that has stimulant-like properties.[44] One study (which did not meet inclusion criteria due to its use of a single dose of modafinil) found that modafinil significantly improved episodic memory and WM in individuals with remitted depression.[66] Modafinil was also

found to counteract cognitive impairments associated with sleep deprivation.[67] DeBattista and colleagues[44] found that modafinil was associated with significant improvements in executive functioning, but not in other cognitive domains. However, this study was limited by its small sample size (N = 31) and short study duration (4 weeks).

Erythropoietin has also been explored for its procognitive effects. Systemically administered erythropoietin is able to cross the blood-brain barrier[68] and exert neuroprotective and neurotrophic effects in neuropsychiatric disorders.[69] In one study, erythropoietin was found to enhance recall memory and recognition memory in MDD.[46] Finally, L-theanine is an amino acid that is contained in green tea and has been suggested to have psychotropic effects.[45] L-Theanine was correlated with improved cognition; however, the study was limited by its small sample (N = 20) and open-label design.[45] It is difficult to make definitive conclusions regarding the procognitive efficacy of non-antidepressant agents as there are few clinical trials focusing on these. Future studies should continue to assess the effectiveness of these agents using larger samples, controlled trials, and objective cognitive measures as primary outcome measures.

Limitations

There were several limitations to the studies included in our review. Seven of the 26 studies were open-label. A lack of blinding to study medication can lead to patient and experimenter bias, which can subsequently influence the results. There was a substantial difference between sample sizes across studies. Moreover, many of the studies were short-term (ie, 4 weeks), which restricts the ability to make any conclusions regarding long-term treatment effects on cognition.

A key limitation to the review was the large diversity of objective measures used in the included studies. This heterogeneity makes it difficult to compare study results and to make definitive conclusions regarding treatment outcomes. In addition, the majority of studies did not include objective cognitive functioning as a primary outcome measure, resulting in the use of brief cognitive batteries. These batteries may not encompass the broad range of cognitive domains that may be impaired in MDD. A strict focus on studies that include objective cognitive functioning as a primary outcome measure would be ideal. However, very few of these studies currently exist.

Newer drugs, such as vortioxetine, are more likely to be studied for their procognitive efficacy because older drugs have low acceptability rates.[47] Nevertheless, this may introduce bias favoring newer drugs over older ones. Specifically, newer drugs are more likely to be investigated, increasing the likelihood that positive results are obtained for these agents.

It is also important to note that patients' symptom profiles may bias drug choice and response. For instance, those with psychomotor slowing are more likely to be prescribed and respond to bupropion.[70] Consequently, sample populations in bupropion studies may have psychomotor slowing due to recruitment bias and may show greater efficacy compared to studies in which symptom profiles are not considered.

In addition, the included studies include heterogenous samples that may include participants without objective cognitive impairment. If unimpaired patients are included in trials for cognition, they are likely to weaken the treatment effect observed in participants who are impaired and who do show positive improvements. This introduces an important limitation to studies that did not limit their sample to participants with objective cognitive impairments.

In this systematic review, we excluded studies that included participants with bipolar disorder. This was done to ensure a homogenous study population and because bipolar patients are more cognitively impacted by their illness than unipolar depressed patients.[71] However, this represents a limitation since information regarding the procognitive effects of certain drugs may be missing. For instance, ketamine has been studied for its procognitive efficacy in samples that include bipolar patients.[72]

Finally, while the current review is comprehensive, a meta-analysis would be ideal. However, the purpose of this systematic review was to synthesize the best available evidence regarding the procognitive efficacy of therapeutic agents. A meta-analysis with the use of statistical methods was not conducted as it was not within the expertise of our research team. Future studies should consider conducting a meta-analysis on the summarized studies.

In conclusion, the aim of this review was to investigate the effects of antidepressants and other agents on cognitive impairments in adults with MDD, with a strict focus on objective measures of cognitive functioning. Although some positive effects have been found for multiple cognitive domains, the results of different studies are contradictory and inconclusive. Overall, vortioxetine has the greatest support for its procognitive effects; SNRIs, NRIs, and bupropion also show promise, but more research is needed. Although some agents show promising results, the rates of cognitive impairment remain high despite remission.[6] Nevertheless, the cause of cognitive impairment in MDD is complex: severity of symptoms,[73] cumulative duration of depressive episodes,[5] and presence of comorbidities[4] all contribute to impaired cognition in MDD. Additionally, individuals differ in terms of experienced impairments, and therapeutic agents may also differ in regard to which cognitive impairments they target. Consequently, targeting cognitive deficits in current and residual MDD is difficult. Future studies should continue to investigate the effect of antidepressants and non-antidepressant agents using standardized and objective cognitive testing as a primary outcome measure. Furthermore, it would be beneficial to explore the impact of these therapies on functional outcomes and how these relate to improvements in cognitive functioning and depressive symptomatology. The current review offers a thorough summary of present-day pharmacologic treatments for cognitive impairment in MDD. The findings of this review will help inform clinicians for prescribing effective medications for patients with MDD and cognitive impairments.

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For the CME Posttest, see next page.

POSTTEST

To obtain credit, go to PSYCHIATRIST.COM **(Keyword: August CME) to take this Posttest and complete the Evaluation.** A $10 processing fee is required.

1. **Adriana is a 55-year-old woman previously diagnosed with major depressive disorder (MDD). She has been treated with amitriptyline for the last decade and has not experienced a major depressive episode in many years. Adriana comes to you complaining of cognitive symptoms, specifically forgetfulness and trouble finding the right words. She asks for your help in improving these symptoms, as they are affecting her quality of life and daily functioning. No other signs of dementia are found. What action should you take, according to current evidence?**
   a. Add escitalopram to her treatment regimen
   b. Taper off amitriptyline and monitor Adriana for improvements in cognitive symptoms and recurrence of depression
   c. Switch Adriana to another tricylic antidepressant agent, such as imipramine
   d. Refer Adriana to a cognitive training program

2. **Which antidepressant currently has the greatest support for improving cognitive deficits in patients with MDD?**
   a. Escitalopram
   b. Bupropion extended release
   c. Bupropion sustained release
   d. Vortioxetine

3. **Zahir is a 25-year-old male university student with MDD. He has been treated successfully for his mood symptoms with bupropion extended release 300 mg/d, but he has complained of having trouble concentrating and remembering course content for several months. Zahir's previous physician added vortioxetine to his treatment regimen but quickly stopped due to serious side effects. What course of action would you take to improve Zahir's cognitive symptoms, on the basis of current evidence?**
   a. Stop bupropion and try vortioxetine only
   b. Add escitalopram
   c. Add modafinil
   d. Add lisdexamfetamine