Cognitive Effects of Pharmacotherapy for Major Depressive Disorder: A Systematic Review

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ABSTRACT

Objective: Cognitive impairment frequently accompanies major depressive disorder (MDD) and can persist during remission. This review examined pharmacotherapy effects on cognitive function in MDD.

Data Sources: PubMed and EMBASE searches were conducted on July 30, 2013, for English language reports of cognitive assessments following pharmacologic monotherapy or augmentation therapy in MDD.

Study Selection: A total of 43 research reports were identified (31 monotherapy [8 placebo-controlled, 11 active-comparator, 12 open-label], 12 augmentation therapy [7 placebo-controlled, 5 open-label]).

Data Extraction: Results reported in each publication were examined for open-label and placebo- or active comparator–controlled studies.

Results: Studies varied widely in terms of size (median, 50 participants; interquartile range, 21–143 participants), populations examined, duration (median, 8 weeks; interquartile range, 6–12 weeks), and neurocognitive assessments used. Most individual studies reported some benefit to cognition with pharmacotherapy, but there was no pattern of response in specific domains and only 12% of individually analyzed changes favored active treatment over placebo or untreated healthy controls. Sample weighted mean effect sizes revealed that verbal memory improved with monotherapy, while the largest treatment effect with augmentation therapy was for visual memory.

Conclusions: Pharmacotherapy may have benefit in reducing cognitive impairment in MDD, with augmentation therapy being a potential approach for addressing cognitive deficits that persist after monotherapy has brought about clinical response or remission. However, given the wide variability in study design and treatment duration across studies, these findings should be interpreted cautiously. More definitive research is required before firm conclusions can be reached.

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It is now recognized that individuals with major depressive disorder (MDD) may exhibit deficits in cognition, including cognitive inefficiency.[1,2] However, of the 9 diagnostic criteria for MDD in the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (*DSM-5*),[3] "diminished ability to think or concentrate, or indecisiveness," is the only disturbance that is clearly cognitive in nature. Other symptoms, such as diminished energy and sleep disturbances, can also adversely affect cognitive function.

Cognition may be impaired in several domains, including processing speed, psychomotor skills, attention, memory, and executive functions. The domains of memory and executive function tend to show the most severe impairment, especially in elderly people with MDD.[1]

For most people with MDD, it is unclear whether cognitive impairment varies with the severity of depressive symptoms or persists during times of euthymia. The degree of correlation between the severity of cognitive impairment and the severity of depressive symptoms has been reported to vary widely.[4–6] However, it is known that in some individuals, cognitive impairment can persist during periods of remission from depressive symptoms.[7] Moreover, prior research suggests that persistent cognitive deficits (including cognitive inefficiency) can have detrimental effects on coping ability[8] and execution of basic and instrumental activities of daily living.[9]

The US Food and Drug Administration has not approved any pharmaceuticals for the treatment of cognitive impairment in MDD, nor is there an expert clinical and scientific consensus on this issue. Nevertheless, numerous antidepressant therapy studies have included endpoints to detect treatment-associated cognitive improvement as a therapeutic benefit or treatment-associated cognitive impairment as an adverse event.

Determination of the magnitude of effect of antidepressant treatment on cognitive function is made difficult by the wide variety of study designs and assessment methodologies that have been implemented. A broad range of neuropsychological instruments has been used across studies; findings have been reported in different formats even when similar instruments are used; and there is considerable inconsistency in the manner by which these instruments have been categorized in terms of assessing specific domains of cognitive function.

In addition, because antidepressant monotherapy is effective in only some individuals with MDD, and only a minority achieve complete remission with initial monotherapy,[10] many patients have residual depressive symptoms, including decreased concentration,[11] which can interfere with higher-order cognitive function. Therefore, MDD treatment often requires augmentation of antidepressant monotherapy. However, relatively little is known about the effects of augmentation therapy on cognitive function in individuals with MDD.

Clinical Points

- Individuals with major depressive disorder (MDD) may exhibit deficits across a range of cognitive function domains, which can persist during depressive symptom remission.
- No current pharmacotherapy is approved for treating cognitive dysfunction in MDD, but pharmacotherapy may have beneficial effects in this area.
- Based on the biomedical literature review, antidepressant monotherapy or augmentation of antidepressant monotherapy can help improve cognitive dysfunction in MDD; however, cautious interpretation is warranted because of intrinsic study limitations and variability in study designs.

This systematic review reports on the cognitive effects of antidepressant monotherapy and augmentation pharmacotherapy on cognitive function in individuals with MDD. The goals of the review were (1) to summarize the published studies and conference presentations that have assessed the effects of antidepressant pharmacotherapy for MDD on cognitive impairment, with attention to identifying the domains of cognitive function most likely to be affected by treatment; and (2) to describe the impact of augmentation pharmacotherapy on cognitive function in people with MDD whose depressive symptoms are stable or in remission after monotherapy.

METHOD

Literature Searches

We performed a series of literature searches on the effects of therapy on cognitive function in MDD on July 30, 2013. The first PubMed search, focused on monotherapy, was conducted using the following search string: (*major depressive disorder* OR *unipolar depression*) AND (*executive function* OR *cognitive function* OR *cognition* OR *cognitive impairment* OR *cognitive dysfunction* OR *executive dysfunction*). The search was limited to humans, clinical trials, meta-analyses, randomized controlled trials, and English language. The second search, focused specifically on augmentation therapy, was conducted using the following search string: (*major depressive disorder* OR *MDD* OR *unipolar depression*) AND (*augmentation* OR *augment* OR *adjunct* OR *adjunctive* OR *combination therapy* OR *add-on*) AND (*therapy* OR *treatment*). The same search parameter limits described above were applied. To confirm and coordinate these searches, a final search was conducted using the following string: (*major depressive disorder* OR *unipolar depression*) AND (*executive function* OR *cognitive function* OR *cognition* OR *cognitive impairment* OR *cognitive dysfunction* OR *executive dysfunction*) AND (*augmentation* OR *augment* OR *adjunct* OR *adjunctive* OR *combination therapy* OR *add-on*) AND (*therapy* OR *treatment*). Again, the same search parameter limits were applied.

We obtained full-text versions of all potentially pertinent references from these 3 independent searches. These articles were reviewed to confirm their relevance to the topic. During this review, we obtained publications cited in the selected papers that appeared to be relevant and had not already been identified in the independent literature searches. Duplicates (reports that came up on more than one search) were eliminated. Also, reports on nonpharmacologic treatment modalities (such as transcranial magnetic stimulation) were excluded so that this review could focus on the effects of pharmacotherapy.

Finally, a search of EMBASE was conducted to identify recent conference presentations of relevance to this topic that were not yet published as peer-reviewed manuscripts. This search, conducted on July 30, 2013, used the terms *major depressive disorder* AND (*cognition* OR *cognitive*) AND (*drug* OR *treatment* OR *pharmacotherapy* OR *pharmacotherapeutic*) NOT (*magnetic* OR *electromagnetic* OR *transcranial* OR *electroconvulsive*); the limits were English language, human subjects, years 2010–2013; publication type: conference presentation/abstract/review.

Statistical Analyses

Effect sizes for the treatment differences in the change from baseline (end-of-study values – baseline values) for all cognitive endpoints from trials that included a placebo control, healthy control, or active comparator and that adequately reported the data were calculated using Cohen *d* ([active treatment – control]/pooled population standard deviation at end of study). The pooled standard deviation at end of study was chosen for this analysis because it may better approximate the standard deviation for the individual changes from baseline for each study. In addition, sample weighted mean effect sizes with 95% CIs were calculated for each cognitive function domain across studies assessing monotherapy versus placebo or augmentation therapy versus placebo augmentation. As clinical improvement is associated with increased values for some measures and decreased values for others, all analyses were conducted so that positive effect sizes favor active treatment. The 95% CI of the effect size was based on the normal distribution of the estimators of effect size. Due to the lack of a rigorous peer-review process, published abstracts were not included in the assessment of effect size.

Literature Review Results

The 4 searches on the cognitive effects of antidepressant monotherapy and augmentation therapy in MDD yielded a total of 1,032 hits (PubMed, n = 759; EMBASE, n = 273). hits. After exclusion of duplicates, items deemed not relevant and items not reporting cognition data, and the selection of additional articles identified from the reference lists of included publications, 43 research reports were identified. These reports included 31 monotherapy studies[12–42] (26 published articles, 5 abstracts for one of which[40] additional study design information was obtained from a reference[43] cited in the published abstract) and 12 augmentation studies[44–55] (10 published articles, 2 abstracts). Three reports present pooled data,[17,19,36] 2 represent a primary study and its extension,[22,33] and 2 are separate assessments of a single study population.[25,30]

RESULTS

Descriptive Analysis

Supplementary eTable 1 summarizes the main characteristics of the 43 reports included in this review. In terms of study design, there are 15 reports on placebo-controlled studies (8 monotherapy, 7 augmentation therapy), 11 reports on active-comparator studies (all monotherapy), and 17 reports on open-label studies (single-arm studies or studies of treated patients vs either healthy controls or untreated patients, or time-course comparisons of treated patients without a control arm; 12 monotherapy, 5 augmentation therapy).

Study participants were individuals with mild to severe depression; entry criteria in all studies included a minimum score on a depression symptom rating instrument to verify the level of severity of depression. Among all the studies included in this review, only 1[44] assessed a population defined by complete or partial remission of MDD (based on Montgomery-Asberg Depression Rating Scale score ≤ 18). In 15 of the 43 reports, the populations were described as elderly (including 3 studies in which age ≥ 50 years was an entry criterion). An additional 3 studies assessed poststroke patients (mean ages, 58, 65, and 67 years). Most of the reports described cognitive effects of pharmacotherapy in participants with MDD. However, some dealt with depressive symptoms in the setting of comorbidities such as heart failure,[12] alcohol dependence,[15] stroke,[27–29] or other conditions[30]; 1 report dealt with psychotic depression.[50]

Across all 43 studies, 4,828 participants were evaluated: monotherapy versus placebo, n = 2,149; active versus placebo augmentation, n = 384; monotherapy versus active control, n = 1,410; open-label monotherapy, n = 745; open-label augmentation, n = 140. Population size ranged from 12 to 776 participants per monotherapy study (mean ± SD, 139 ± 169; median, 63) and from 11 to 143 participants per augmentation therapy study (mean ± SD, 44 ± 39; median, 30). The mean ± SD number of participants across all studies was 112 ± 151 but the median was only 50 (interquartile range, 21–143), indicating that the distribution was skewed toward smaller populations.

Most of the studies were of relatively short duration. Excluding single-observation studies[13,21,40] and a long-term extension,[33] study duration ranged from 4 to 36 weeks in monotherapy studies (mean ± SD, 11 ± 7 weeks; median, 8 weeks) and from 3 to 104 weeks in augmentation therapy studies (mean ± SD = 16 ± 28 weeks; median, 6 weeks). Across all studies, mean ± SD study duration was 13 ± 16 weeks, but the distribution was skewed toward shorter lengths; the median study duration was 8 weeks (interquartile range, 6–12 weeks). The most frequent study durations were 8 weeks (10 studies) and 12 weeks (11 studies).

In most studies, antidepressant pharmacotherapy consisted of commonly used antidepressant agents (selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, or tricyclic antidepressants). In some studies, other psychotropic agents were tested: apomorphine,[13] lithium,[48] estrogen,[49] the serotonin-reuptake enhancer tianeptine,[24] the antipsychotics aripiprazole[54] and amisulpride,[50] the mineralocorticoid receptor modulators fludrocortisone and spironolactone,[53] the cognition-enhancing drugs galantamine[46] and donepezil,[51] the dissociative anesthetic/*N*-methyl-D-aspartate antagonist ketamine,[40] and the *d*-amphetamine prodrug lisdexamfetamine dimesylate.[44]

Assessment of cognitive function was described as a primary/coprimary assessment in 32 reports (24 monotherapy*; 8 augmentation[44,46,47,49,51–54]) and as a secondary assessment in 9 reports (6 monotherapy[14,20,23,36,39,40]; 3 augmentation[45,50,55]). In contrast, it was a safety assessment in only 2 reports (1 monotherapy[21]; 1 augmentation[48]).

Numerous cognitive assessment tools were employed (see Supplementary eTable 1 at PSYCHIATRIST.COM). The most frequently used instrument was the Digit-Symbol Substitution Test (DSST, 13 studies); versions of this test also appear as part of the revised Wechsler Adult Intelligence Scale (WAIS-R, where it is called Digit Symbol), the third-edition WAIS (WAIS-III, where it is called Digit Symbol Coding), and the Brief Assessment of Cognition for Affective Disorders (BAC-A, where it is called Symbol Coding). Other frequently used instruments included the Mini-Mental State Examination (MMSE, 10 studies), Trail Making Test (9 studies), and the Stroop test (6 studies).

The cognitive domains assessed included processing speed, psychomotor function, attention, verbal learning and memory, verbal fluency, visuospatial awareness, and executive function. In some of the reports, the assessment instruments used are identified as measures of one or more specific domains of cognitive function. However, such identification was inconsistent. For example, in different studies, the Stroop test was described as a measure of executive function,[31,33,35,42,45,51] information processing speed,[22,31] or attention[31]; similarly, DSST was described as a measure of attention,[13,25,30,32] psychomotor function,[17,20,21,42] information processing speed,[20,39] or visuospatial awareness.[17,51]

Table 1 lists the neurocognitive measures used in the studies that are included in this review, with the present authors' own assignment of the primary cognitive domain assessed by each test. It is recognized that many tests assess multiple domains and that there may be disagreement with these assignments. In some cases, our assignment of primary cognitive domain was based on the codification by Strauss et al (2006),[56] and as such may differ from that of the authors of the reviewed publication. For example, we labeled the Stroop test as a measure of cognitive control, a domain not named in the publications included in this review.

Data on the cognitive effects reported in the 43 studies of pharmacotherapy for depression included in this review are summarized in Supplementary eTable 2. In 6 studies, cognitive effects were specifically reported as a function of treatment response (defined by prespecified improvement in depressive symptoms) versus nonresponse; among these

*References 12, 13, 15–19, 22, 24–35, 37, 38, 41, 42.

Table 1. Primary Cognitive Domains Assessed by Neuropsychological Tests[a]

Test	Attention	Cognitive Control	Executive Function	Naming	Processing Speed	Verbal Fluency	Verbal Memory	Verbal/ Nonverbal Intelligence	Visual Memory	Visual Processing	Working Memory
Animal naming/category fluency						●					
Boston Naming Test				●							
BRIEF-A			●								
Buschke SRT							●				
Continuous Performance Test	●										
COWAT						●					
CVLT							●				
DSST					●						
Digit cancellation	●										
Digit span forward	●										
Digit span backward											●
Executive Interview			●								
Extradimensional shift			●								
Intradimensional shift			●								
Judgment of line orientation										●	
Letter cancellation	●										
Letter fluency						●					
Letter-number sequencing											●
Logical memory delayed recall							●				
Match-to-sample											●
Paired associations							●				
Purdue Pegboard					●						
Raven's Progressive Matrices								●			
RAVLT							●				
RBANS	●						●		●	●	●
Rey-Osterreith Delayed Recall									●		
Rey-Osterreith Complex Figure Test										●	
Ruff Selective Attention Test	●										
Shape cancellation	●										
Shopping list task							●				
Spatial span											●
Spatial working memory											●
Stockings of Cambridge			●								
Stroop test		●									
Test of Attentional Performance	●										
TMT-A					●						
TMT-B		●									
TMT-B/TMT-A Ratio			●								
TMT difference (B – A)			●								
Vienna System Tests					●						
Visual recall									●		
Visual reproduction									●		
Voluntary inhibitory control		●									
WAIS Vocabulary								●			
WAIS Similarities			●								
Wisconsin Card Sorting Test			●								

[a]Many of the tests listed assess more than 1 cognitive domain, and the list does not include general tests that are not classifiable by any particular domains (notably, the Mini-Mental State Examination, which was one of the most frequently used tests, and the cognitive section of Cambridge Mental Disorders of the Elderly Examination). The method of categorization used in this report is generally consistent with the codification of Strauss et al[56] but also reflects our own collective understanding of these tests and the constructs they measure.

Abbreviations: BRIEF-A = Behavior Rating Inventory of Executive Function–Adult Version; COWAT = Controlled Oral Word Association Test (verbal fluency test on letters F, A, S or C, F, L); CVLT = California Verbal Learning Test; DSST = Digit-Symbol Substitution Test; RAVLT = Rey Auditory Verbal Learning Task; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; SRT = Selective Reminding Test (Buschke Selective Reminding Test); TMT-A, TMT-B = Trailmaking Test parts A and B; WAIS = Wechsler Adult Intelligence Scale.

6 studies, there was no reported correlation with treatment response in 1 open-label study[16] and 1 active-comparator study[35] but treatment responders tended to perform better than nonresponders in 2 active-comparator studies,[17,24] 1 placebo-controlled study,[42] and 1 open-label study.[32]

In the majority of reports, there was statistically significant cognitive benefit with monotherapy* or augmentation therapy.[44,45,47,51–55] As might be expected, significant benefit was reported frequently with active treatment versus placebo (7 of 8 monotherapy studies[19,25,30,34,36,39,42]) and with active augmentation versus placebo augmentation (5 of 7 studies[44,47,51,52,55]). Of the 3 placebo-controlled studies that did not report significant benefit, all had relatively small treatment groups.[13,46,49] Significant improvement from baseline appeared to be less consistent in open-label studies (7 of 12 monotherapy,[12,27–29,31,32,41] 3 of 5 augmentation[45,53,54]). In 10 of 11 active-comparator trials (all monotherapy),† significant between-treatment differences were reported, with sertraline consistently having superior effects to nortriptyline in 3 studies[14,17,35] and to fluoxetine in 2 studies.[20,23]

In many reports, benefit was seen on certain cognitive measures but not others, or in certain subpopulations (eg, treatment responders vs nonresponders) but not others, or during the course of the study but not at study end. In a minority of reports, no statistically significant cognitive benefit was seen with monotherapy[13,15,16,18,21] or augmentation therapy.[46,48–50] Across all studies, clear descriptions of the use of statistical procedures to adjust for multiple comparisons or time course analyses was found in only 7 reports.[12,18,23,29,33,45,48]

Based on the present authors' assignment of the primary cognitive domain assessed by each test (Table 1), the cognitive tests most frequently used in the reports included in this review assessed the domains of verbal memory, working memory, and processing speed. Antidepressant pharmacotherapy was more likely than not to help improve performance in those domains, but the reported estimates of improvement were relatively small compared with the magnitude of the deficits. Keeping in mind that many studies included multiple tests for a given domain and that relatively few studies clearly stated that correction for multiple comparisons was conducted, verbal memory improved in 12 studies,‡ working memory improved in 7 studies,[19,22,31,33,51,53,54] and processing speed improved in 8 studies.[17,19,20,23,32,39,41,53] Executive function, sometimes considered a key clinical and functional indicator, showed statistically significant improvement in 2 monotherapy studies[33,37] and 3 augmentation therapy studies.[44,51,54]

Effect Size Analysis

Based on data from 15 of the 43 identified publications, it was feasible to calculate an effect size for 168 cognitive measures. Assessments were based on data from 8 monotherapy publications[13,17,19,20,24,33,35,42] and 4 augmentation publications[47,52,53,55] and on data requested from the authors of 1 monotherapy publication[25] and 2 augmentation publications.[46,51] The 95% CI of the effect size did not cross 0 in 27 of these analyses (16%), indicating an effect favoring one of the treatment arms (Figures 1–3; see values with asterisks), but did cross 0 in the remaining 141 analyses (84%). Of those analyses with 95% CIs that did not cross 0, 20 favored an active treatment (12% of all analyses [20/168]) over placebo or untreated healthy controls; the remaining analyses favored placebo or untreated healthy controls over active treatment (4% of all analyses [7/168]).

In monotherapy studies that included a placebo control, the 95% CIs did not cross 0 for 3 effect sizes from 2 studies.[13,25] Small to large effect sizes indicated that improvements from baseline in the processing speed domain were greater with placebo than with apomorphine or duloxetine (Figure 1). The remaining effect sizes (n = 20) in monotherapy studies with a placebo control had 95% CIs that crossed 0; these effect sizes generally favored active treatment and tended to be of small to moderate magnitude (Figure 1).

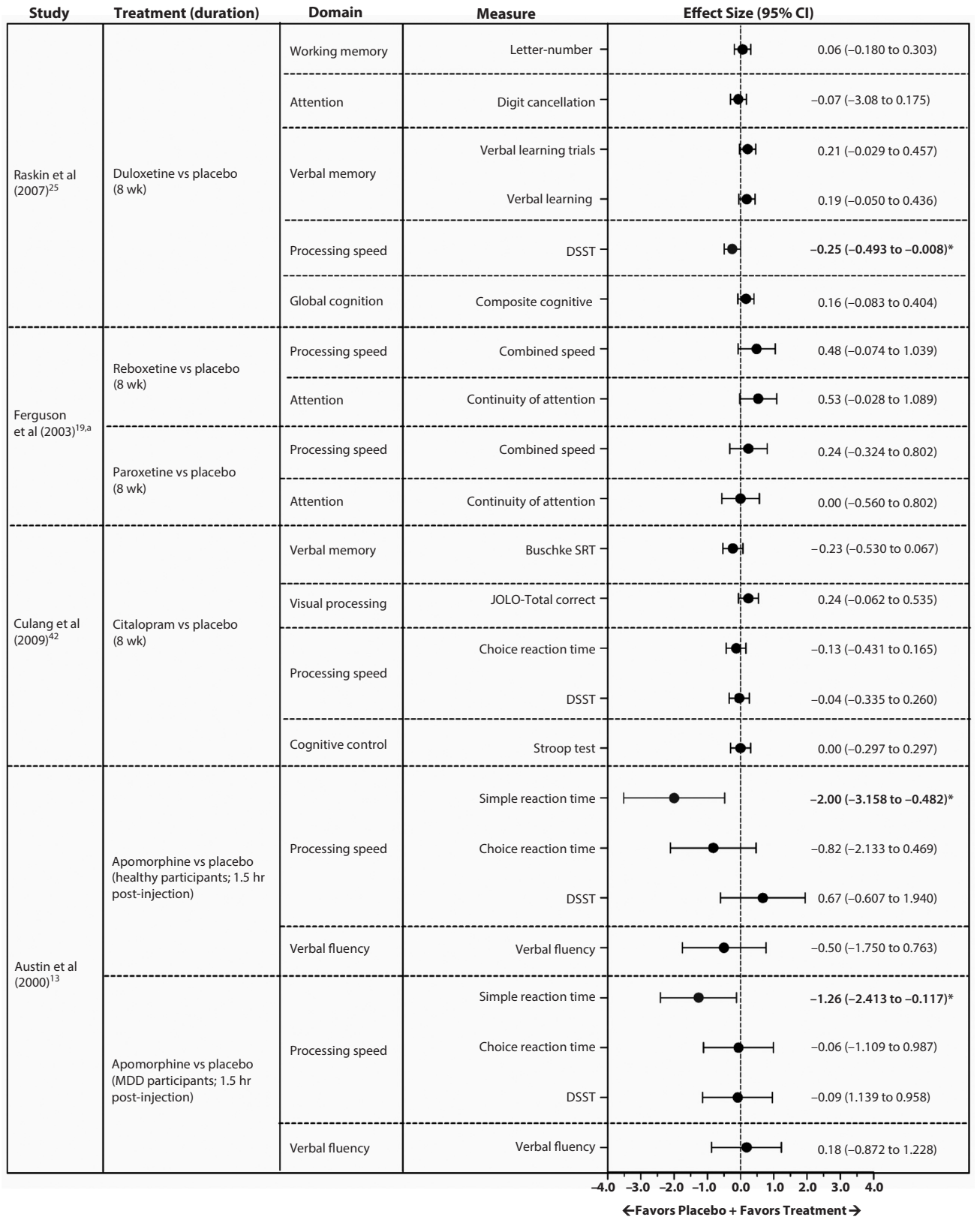
In 1 monotherapy study that included healthy controls,[33] 10 effect sizes had 95% CIs that did not cross 0 (Figure 2). The large effect sizes indicated that improvement from baseline in individuals with MDD treated with duloxetine was greater than in untreated healthy controls in the working memory domain and that improvement in individuals with MDD treated with escitalopram was greater than in untreated healthy controls in the executive function domain. Additionally, large effect sizes indicated that improvement from baseline in untreated healthy controls in the executive function domain was greater than in individuals with MDD treated with duloxetine. The remaining effect sizes (n = 23) in monotherapy studies with healthy controls had 95% CIs that crossed 0; these effect sizes generally favored active treatment and tended to be of small to moderate magnitude (Figure 2).

In 3 monotherapy trials that included active comparators,[17,24,35] 5 effect sizes had 95% CIs that did not cross 0 (Figure 2). In 1 study,[35] a large effect size indicated that improvement from baseline in the verbal memory domain was greater with sertraline than with nortryptiline. In a second study,[17] moderate to large effect sizes indicated that improvement in the verbal memory domain was greater with fluoxetine than with nortryptiline and that improvement in the verbal memory and processing speed domains were greater with sertraline than with nortriptyline. In a third study,[24] large effect sizes indicated that improvement from baseline in the attention domain was greater with tianeptine than with paroxetine. The remaining effect sizes (n = 22) in monotherapy studies with active treatment comparators had 95% CIs that crossed 0; across these assessments, effect sizes tended to be of small to moderate magnitude (Figure 2).

In augmentation therapy studies that included a placebo control, 9 effect sizes from 3 studies[47,51,53] had 95% CIs that did not cross 0 (Figure 3). In 1 study,[47] large effect sizes indicated that improvements from baseline in the verbal

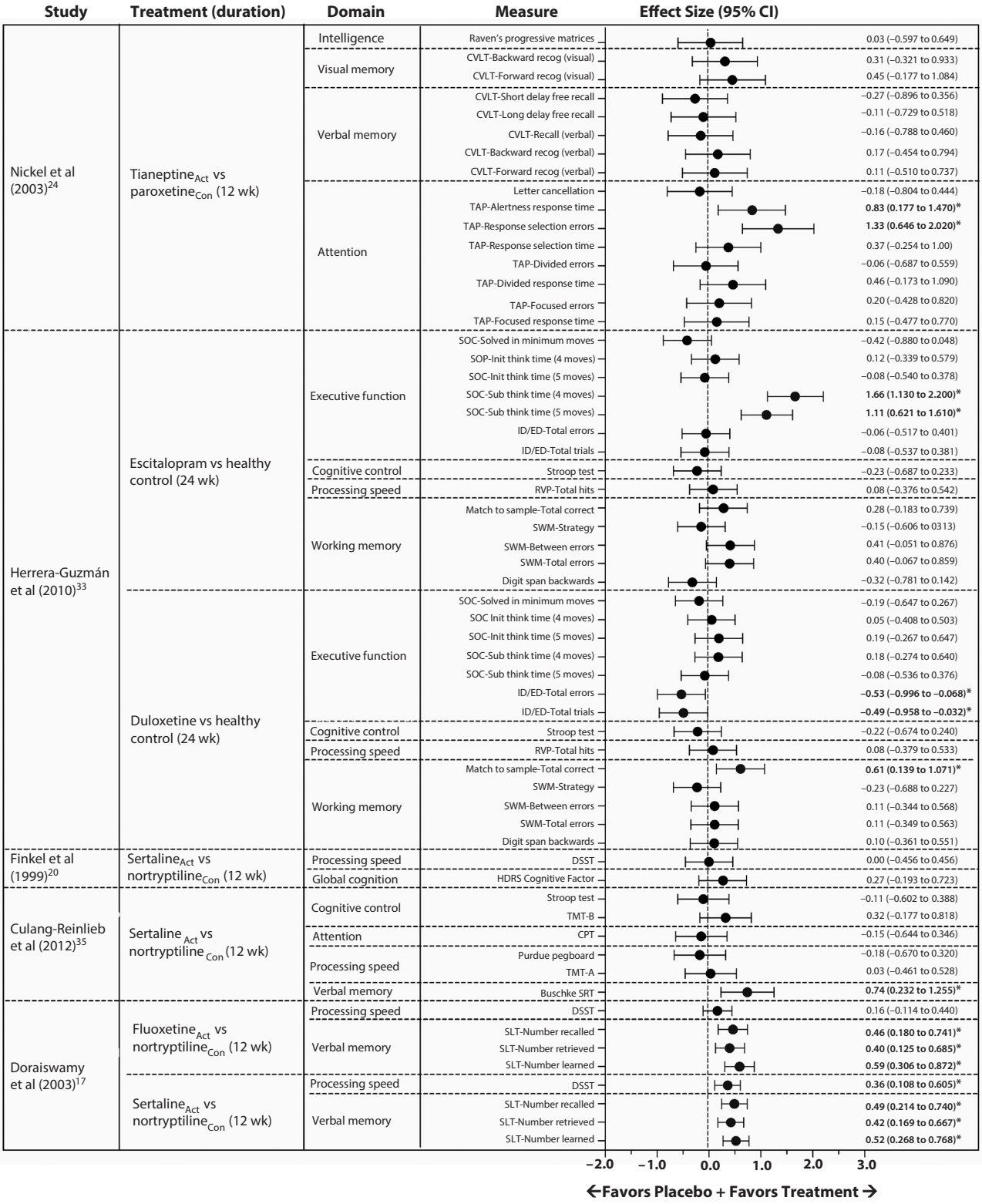
*References 12, 14, 17, 19, 20, 22–39, 41, 42.
†References 14, 17, 20, 22–24, 26, 33, 35, 38.
‡References 14, 17, 22, 23, 25, 26, 31, 32, 35, 39, 41, 52.

Figure 1. Effect Sizes With 95% CIs for Monotherapy Versus Placebo



[a]Effect size based on change from baseline data reported in the primary publication rather than on the estimated change from baseline calculated from baseline and end of study data.
*Assessments with 95% CIs not crossing 0.
Abbreviations: DSST = Digit Symbol Substitution Test, JOLO = Judgment of Line Orientation, MDD = major depressive disorder, SRT = selective reminding test.

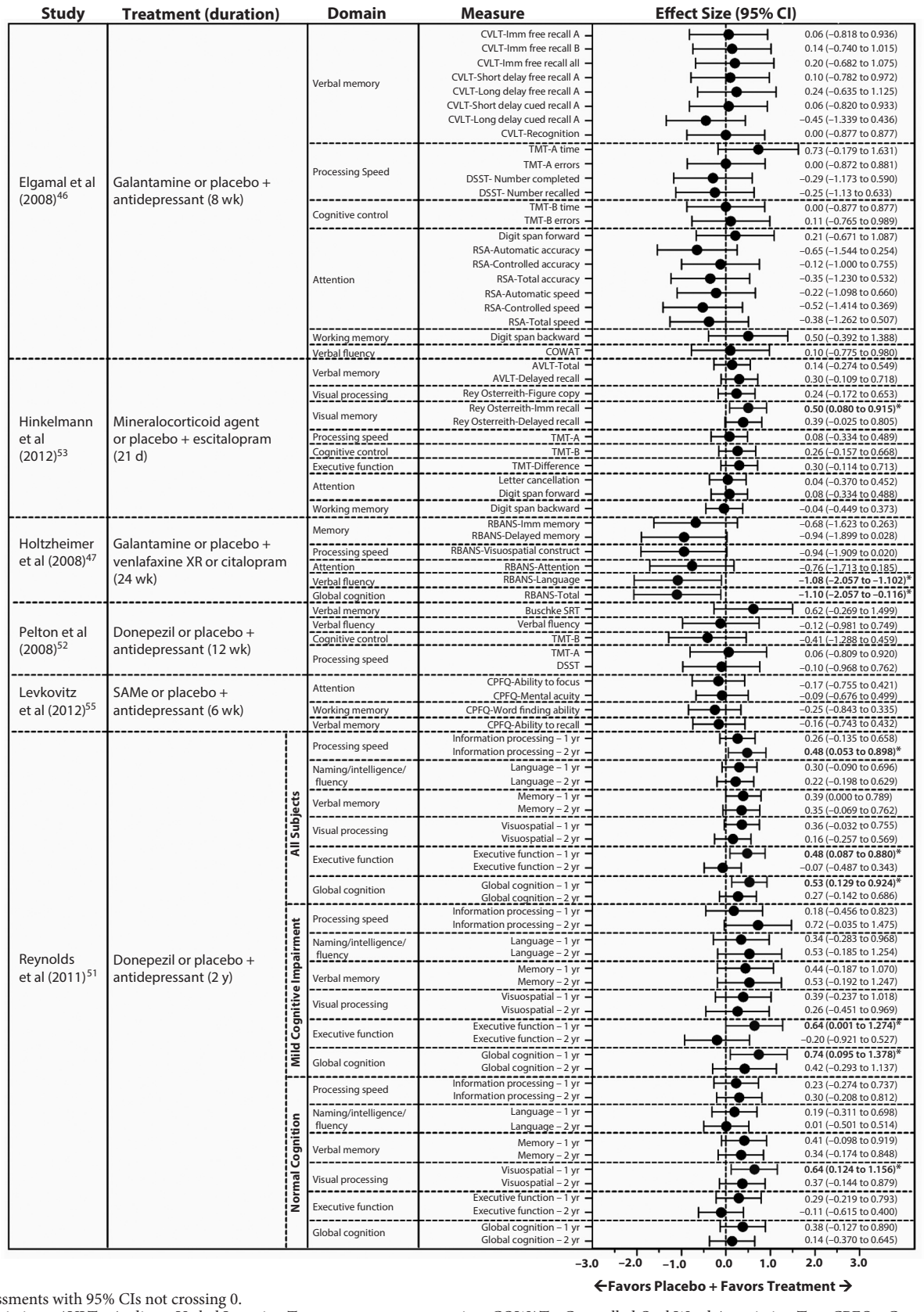
Figure 2. Effect Sizes With 95% CIs for Monotherapy Versus Untreated Healthy Controls or Active Controls



*Assessments with 95% CIs not crossing 0.

Abbreviations: Act = active, Con = control, CPT = Continuous Performance Test, CVLT = California Verbal Learning Test, DSST = Digit Symbol Substitution Test, HDRS = Hamilton Depression Rating Scale, ID/ED = Intradimensional/Extradimensional, Init = initial; recog = recognition, RVP = Rapid Visual Processing, SLT = Shopping List Test, SOC = Stockings of Cambridge, SRT = Selective Reminding Test, Sub = subsequent, SWM = Spatial Working Memory, TAP = Test of Attentional Performance, TMT-A = Trail Making Test-A, TMT-B = Trail Making Test-B.

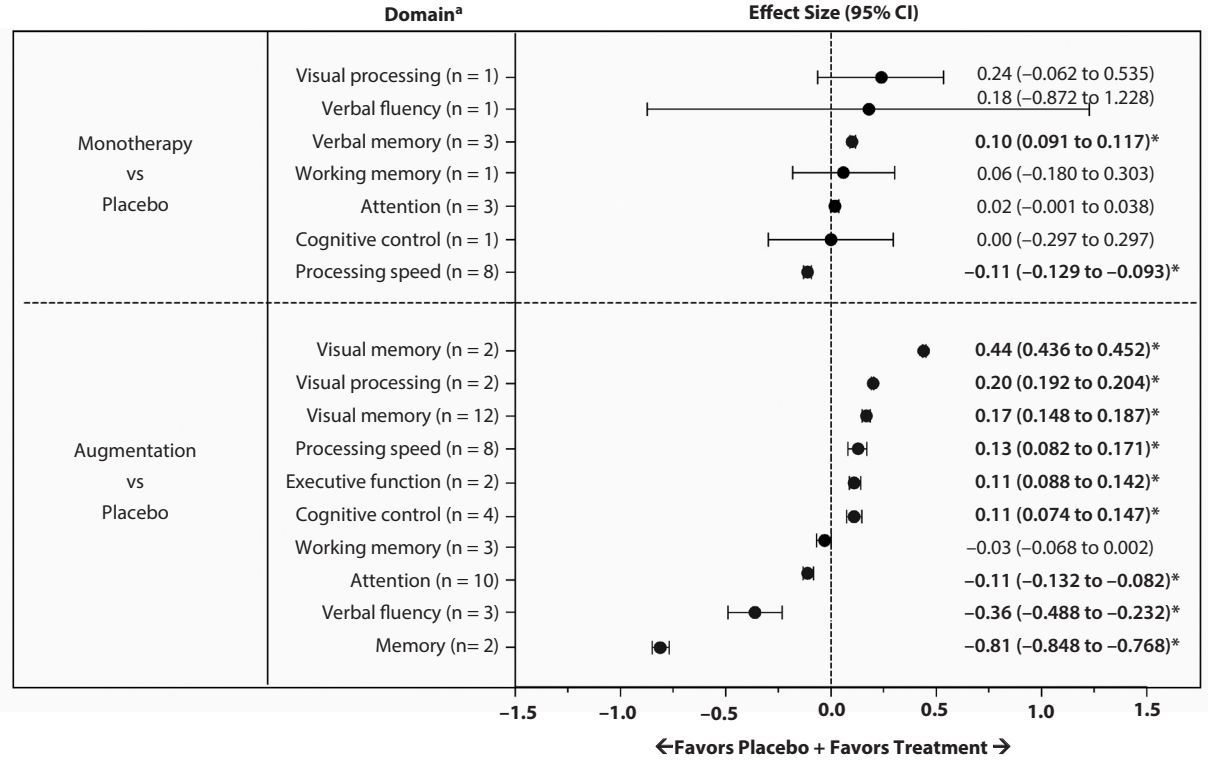
Figure 3. Effect Sizes With 95% CIs for Augmentation Therapy Versus Placebo



*Assessments with 95% CIs not crossing 0.

Abbreviations: AVLT = Auditory Verbal Learning Test, construct = construction, COWAT = Controlled Oral Word Association Test, CPFQ = Cognitive and Physical Symptoms Questionnaire, CVLT = California Verbal Learning Test, DSST = Digit Symbol Substitution Test, Imm = immediate, RBANS = Repeatable Battery for the Assessment of Neuropsychological Status, RSA = Ruff Selective Attention Test, SAMe = S-adenosylmethionine, SRT = Selective Reminding Test, TMT-A = Trail Making Test-A, TMT-B = Trail Making Test-B, XR = extended release.

Figure 4. Sample-Weighted Effect Sizes With 95% CIs Across Cognitive Function Domains



[a]Values in parentheses beneath each domain of function represent the number of cognitive assessments included in the analysis of each domain of function.
*Assessments with 95% CIs not crossing 0.

fluency domain and for global cognition were greater with placebo than with galantamine augmentation. In a second study,[53] a large effect size indicated that improvement in the visual memory domain was greater with augmentation with a mineralocorticoid agonist or antagonist than with placebo. In the third study,[51] moderate to large effect sizes for the executive function domain, visual spatial domain, information processing domain, and for global cognition indicated that improvements in performance were greater with donezepil augmentation than with placebo. The remaining effect sizes (n = 76) in augmentation therapy studies with a placebo control had 95% CIs that crossed 0; these effect sizes generally favored active treatment and tended to be of small to moderate magnitude (Figure 3).

An examination of the cognitive domains across studies indicated that the 95% CIs for the sample weighted mean effect sizes did not cross 0 for 2 domains in monotherapy studies and for 9 domains in augmentation therapy studies (Figure 4, see values with asterisks). In monotherapy studies, a small effect size favoring active treatment was observed for verbal memory and a small effect size favoring placebo was observed for processing speed (Figure 4, top). In augmentation therapy trials, a moderate effect size favoring active treatment was observed for visual memory and small effect sizes favoring active treatment were observed for visual processing, verbal memory, processing speed, executive function, and cognitive control; a large effect size favoring placebo was reported for memory and small to moderate effect sizes favoring placebo were reported for attention and verbal fluency (Figure 4, bottom).

DISCUSSION

Although it is known that cognitive dysfunction is associated with MDD, the data regarding the cognitive effects of antidepressant pharmacotherapy are relatively limited. Overall, the reports included in this review suggest that antidepressant monotherapy or augmentation therapy can have beneficial effects on cognitive function. This interpretation is partially supported by the effect size analyses included in this review. Although the effect size analyses based on individual measures within studies indicated that there was a tendency for monotherapy and augmentation therapy to be favored over placebo across a range of cognitive domains, improvement with pharmacotherapy versus placebo or untreated healthy controls was meaningful (95% CI of the effect size not crossing 0) for only a minority (approximately 12%) of the analyzed cognitive assessments. Examination of sample weighted mean effect sizes for cognitive domains across studies indicated that only verbal memory was improved with monotherapy versus placebo; multiple domains of function improved with augmentation therapy versus placebo, with the largest effect size observed for visual

memory. In regard to the effect size analyses reported in this review, it is important to note that the magnitude of the effects should be interpreted with caution because they represent estimates based on the pooled standard deviation at the end of each study. These effect sizes may overestimate or underestimate the "true" effect size based on the pooled standard deviation of the individual changes from baseline for each study. Furthermore, the number of measures included for each sample weighted mean effect size was ≤ 3 for all but 1 domain in monotherapy trials and was ≤ 4 in 7 of 9 domains. Another reason for caution is the high degree of variability in study design and data presentation among the studies included in this review.

Because many of the studies were relatively small or assessed selected subgroups of the depressed populations (eg, elderly patients or those with specific comorbidities), it remains unclear whether the findings can be generalized to a larger and more heterogeneous population of depressed individuals. Furthermore, the studies were generally of short duration, so long-term effects of treatment remain uncertain. Finally, it should be noted that in the trials comparing multiple active treatments, cognitive benefit with treatment versus lack of treatment was suggested but not confirmed.

With the exception of the report by Madhoo et al,[44] which used a population of individuals in partial remission (MADRS total scores of 10–18) or full remission (MADRS total scores < 10), the studies included in this review assessed cognitive function in the presence of mild to severe depressive symptoms, which makes it difficult to establish whether cognitive improvement was an independent outcome or a consequence of clinical response and remission. Studies in elderly individuals generally did not draw clear distinctions between cognitive decline due to aging versus cognitive inefficiency and impairment due to depression. Similarly, except for the report by Wise et al,[30] the potential impact of comorbid medical conditions on cognitive function were generally not addressed.

Statistical methodology was inconsistent, and some of the included reports were incomplete or unclear in this area. Examples include outcomes reported as interaction statistics without data on within-group changes from baseline and between-group differences at study end[24,27,51] and drug effects described in words but not substantiated with specific data.[46,48–50] Moreover, few of the reports specifically stated whether any type of correction for multiple comparisons was made; 7 reports[12,18,23,29,33,45,48] stated that such corrections were made and 6 reports[24,25,30,31,41,55] stated or described the analyses in such a manner as to indicate that corrections were not made. In addition, some neurocognitive measures were used more frequently than others, potentially increasing the likelihood that a positive outcome would be observed in these domains by chance.

A major issue in the interpretation of our findings in this review is the specific instruments used for assessment of cognitive function in the included studies. Several of the studies relied solely on the MMSE for assessment of cognitive function, but this scale is a poor choice for this purpose because it broadly measures global cognitive function, has no alternate form, and has extreme ceiling effects. In addition, many instruments assess multiple cognitive domains, and categorization was inconsistent across studies. For example, the Controlled Oral Word Association Test (COWAT) has been classified as a test of phonemic verbal fluency, which falls within the cognitive domain of language function,[31] but it has also been deemed a measure of processing speed or executive function.[57] The method of categorization used in this report is generally consistent with the codification of Strauss et al[56] but also reflects our own collective understanding of these tests and the constructs they measure. Furthermore, different versions of the same assessment tool could have been used in different studies, which could influence the consistency of findings across studies. Lastly, many of the assessment tools used were developed to assess cognitive function in healthy individuals or in those with specific neurologic deficits. As such, their use in individuals with MDD may imply that there is a more complex array of deficits in depression when, in fact, there is a simpler factor structure associated with depression.

One method to ensure consistency across studies would be to use a cognitive battery specific and sensitive to MDD. This approach is reflected in the Measurement and Treatment Research to Improve Cognition in Schizophrenia[58] (MATRICS) initiative directed by the National Institutes of Mental Health (NIMH), which recognized that lack of consensus on the optimal tools for assessing cognitive function was a barrier to the development of effective treatments for cognitive impairment in schizophrenia. Thus, a standardized test battery, developed in accordance with criteria suggested by the MATRICS participants, could facilitate interpretation across separate studies; however, a limitation of this approach is that researchers may feel obligated to use the standard battery even in situations for which other tests might be more appropriate.

The complexities of research in this area are illustrated by assessing the similarities and differences between the present review and that of a recently published meta-analysis (with a psychological rather than pharmacotherapeutic focus) of executive function impairment in MDD.[59] Both publications suggest that MDD is associated with deficits across a wide range of cognitive domains, that cognitive impairment may correlate with depressive symptom severity on some measures, and that impairments may persist despite remission of depressive symptoms. However, the focus on the role of pharmacotherapy in MDD differed between publications. The present review examined the impact of pharmacotherapy on cognitive dysfunction and found some evidence for a positive effect. In contrast, the meta-analysis of Snyder focused on identifying the nature of the cognitive deficits in MDD and their possible mediators, which included detrimental effects of pharmacotherapy on cognitive function (although the author acknowledged that this finding may reflect the profile of patients using antidepressant drugs rather than adverse effects of the drugs). In addition, the categorization of neurocognitive tests offered in the meta-analysis sometimes

differed from our own, again indicating the need for greater understanding of and consensus on the various domains of cognition, their interrelationships, and the optimal means by which they may be measured.

It should be noted that this literature review was restricted to searches of PubMed and EMBASE, which are databases that include publications from the most methodologically rigorous journals and congresses. However, utilization of other databases might have provided additional information. In addition, the inclusion of abstracts in the review can be viewed as a limitation because the peer-review process is less rigorous for abstracts than it is for published manuscripts. As such, data from these abstracts were not included in the assessment of effect sizes. However, as presentations at biomedical congresses represent the most recent data that is available, a description of these studies and their findings is relevant to this topic. Lastly, although several negative findings were reported in the studies we included in our review, it should be noted that publication bias could influence these findings as negative findings are less likely to be published.

The common occurrence of cognitive impairment in individuals with MDD may be related to the shared neurobiologic systems and processes that can modulate cognitive function and mood. Although a detailed review of these neurobiologic mechanisms is beyond the scope of the current review, an improved understanding of how common neurobiologic substrates and processes, including those related to cortical and subcortical structure and function and neurogenesis,[60,61] mediate cognition and mood will be critical to furthering the field's development of treatments for cognitive impairment in depression. Because the methods for studying cognition in MDD has varied substantially been studied differently, the construct of cognition has been deemed important enough for the National Institutes of Health to consider it a key component of the Research Domain Criteria initiative.

Considering all these concerns, it is difficult to draw any firm conclusions regarding differential effects of antidepressant pharmacotherapy on various cognitive domains. Our own tally of results from the individual studies included in this review yielded no consistent patterns. However, a review of the sample weighted mean effect size data for cognitive domains across studies suggested that verbal memory was slightly improved with monotherapy and that visual and verbal memory were improved by augmentation therapy. Additionally, there was evidence for improved executive function and cognitive control with augmentation therapy. Overall, the results summarized in this review may be interpreted cautiously as suggesting that antidepressant pharmacotherapy may have a beneficial effect on cognitive impairment associated with MDD.

CONCLUSIONS

There is a need for more systematic examination of the cognitive effects of pharmacotherapy in MDD, similar to the examination already underway in schizophrenia. Larger-scale, longer-term, placebo-controlled studies are warranted to assess drug effects on cognitive function in populations representative of the general MDD population. Furthermore, study designs and statistical methods that maximize test validity and minimize the influence of confounding factors should be used. Finally, more rigorous research into treatment effects on specific domains of cognitive function would be valuable.

Based on a literature review and effect size analysis, it appears that some antidepressant pharmacotherapies can help improve cognitive deficits associated with MDD, including augmentation therapies when the response to antidepressant monotherapy is inadequate, with certain types of memory showing the most consistent improvement with pharmacotherapy. As in other clinical conditions in which an appropriate regimen of monotherapy has resulted in only partial response, augmentation therapy, especially with an agent that employs a different mechanism of action, may be a more sensible strategy than dose escalation (which could increase the incidence and/or severity of adverse effects) or drug switching (which could yield results no better than those obtained with the initial drug and which could incur adverse events not seen with the initial drug). Further research should seek to overcome substantive methodological limitations of prior investigations and to confirm whether pharmacotherapy would be beneficial for the treatment of cognitive deficits associated with MDD.

Drug names: apomorphine (Apokyn), aripiprazole (Abilify), donepezil (Aricept and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), galantamine (Razadyne), ketamine (Ketalar and others), lisdexamfetamine (Vyvanse), lithium (Lithobid and others), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), spironolactone (Aldactone and others).

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Supplementary Material

Article Title: Cognitive Effects of Pharmacotherapy for Major Depressive Disorder: A Systematic Review

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List of Supplementary Material for the article

1. eTable 1 Key Characteristics of Studies Describing Cognitive Effects of Pharmacotherapy in MDD
2. eTable 2 Key Findings on Cognitive Effects From Studies of Pharmacotherapy for Depression

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Supplementary eTable 1. Key Characteristics of Studies Describing Cognitive Effects of Pharmacotherapy in MDD

Reference	Design	Treatment Groups	Depressive Symptom Level Inclusion Criterion	Cognitive Assessments
MONOTHERAPY				
Placebo-controlled studies				
Alev et al (2011)[36] [Abstract]	Pooled analysis of data from 2 separate 9-month studies; patients with MDD	Duloxetine 60 mg/d (n=518) vs placebo (n=258)	Not specified	CPFQ
Austin et al (2000)[13]	Single-dose, crossover; depressed/melancholic patients and controls	Apomorphine injection vs placebo in depressed/melancholic patients (n=7) vs controls (n=5)	HDRS-21: >16	DSST, COWAT, reaction time (simple and complex), RAVLT (learning, recall, recognition)
Culang et al (2009)[42]	8 wk; age ≥75 y with MDD	Citalopram 20 mg/d adjustable to 40 mg/d (n=84) vs placebo (n=90)	HDRS-24: ≥20	MMSE, DSST, Stroop test, Choice Reaction Time, Judgment of Line Orientation, Buschke SRT
Ferguson et al (2003)[19]	2 identical 8-wk trials; patients with MDD	Pooled data on reboxetine 8–10 mg/d (n=25) vs paroxetine 20–40 mg/d (n=23) vs placebo (n=26)	HDRS-17: >20	Cognitive Drug Research battery (comprising tasks of attention, working memory, episodic secondary memory, and critical flicker fusion) assessed at baseline, day 14, day 56
Katona et al 2012[39] [Abstract]	8 wk, double-blind, randomized, controlled study; age≥65 y with MDD	Vortioxetine (Lu AA21044) 5 mg/d vs duloxetine 60 mg/d vs placebo	MADRS: ≥26	DSST, RAVLT
Raskin et al (2007)[25]	8 wk; elderly with MDD with or without medical comorbidity	Duloxetine 60 mg/d (n=207) vs placebo (n=104)	HDRS-17: ≥18	Composite score from Verbal Learning and Recall Test (adapted from RAVLT), DSST, Digit Cancellation, Letter-Number Sequencing Test
Reilly et al (2012)[34] [Abstract]	12 wk; patients with nonpsychotic depression	Cognitive behavioral therapy (n=14), placebo + supportive care (n=13), sertraline titrated to mean 137.5 mg/d + supportive care (n=12)	HDRS >15 (version not specified)	Tests of psychomotor functions, working memory, and voluntary inhibitory control, plus neuropsychological test battery
Wise et al (2007)[30] (substudy of Raskin et al 2007)	See Raskin et al	See Raskin et al	See Raskin et al	See Raskin et al
Active-comparator studies				
Bondareff et al (2000)[14]	12 wk; age ≥60 y with MDD	Sertraline 50–150 mg/d (n=74) vs nortriptyline 25–100 mg/d (n=70); double-dummy to maintain blinding	HDRS-24: >18	MMSE, DSST, Shopping List Task, WAIS

Reference	Design	Treatment Groups	Depressive Symptom Level Inclusion Criterion	Cognitive Assessments
Chang et al (2012)[37]	6 wk; patients with MDD	Fluoxetine 20–80 mg/d (n=73) vs venlafaxine 37.5–225 mg (n=72)	Not specified (baseline HAM-D score of 23.9)	Continuous Performance Test, WCST
Culang-Reinlieb et al (2012)[35]	12 wk; elderly with MDD	Sertraline 50 mg/d x 1 wk then 100 mg/d, adjustable to 150 mg/d at week 5 and 200 mg/d at week 9 as needed (n=33) vs nortriptyline 1 mg/kg/d adjustable to maintain stable plasma concentration (n=30); double-blinding maintained	HDRS: ≥16 (version not specified)	MMSE, TMT-A, TMT-B, Continuous Performance Test, Purdue Pegboard, Buschke SRT, Stroop test
Doraiswamy et al (2003)[17]	Two 12-wk studies; elderly with MDD	Pooled data on sertraline 50 mg/d (n=185) vs either fluoxetine 20 mg/d (n=105) or nortriptyline 25 mg/d (n=96)	HDRS-24: ≥18	Shopping List Task, DSST, MMSE
Finkel et al (1999)[20]	12 wk; age ≥70 y with MDD	Sertraline 50–100 mg/d (n=42) vs fluoxetine 20–40 mg/d (n=33); double-dummy to maintain blinding	HDRS-24: ≥18	DSST, Shopping List Task, MMSE
Hashemian et al (2011)[38] [Abstract]	4 wk; patients with MDD	Bupropion 200 mg/d vs fluoxetine 20 mg/d (population size not specified)	Not specified	Validated computer-generated reaction time tasks
Herrera-Guzman et al (2009)[22]	24 wk; patients with MDD	Escitalopram 10 mg/d (n=36) or duloxetine 60 mg/d (n=37)	HDRS-17: ≥18	WAIS Vocabulary and Digit Span Backward, RAVLT, simple and 5-Choice Reaction Times, Stroop test, Match-To-Sample, Paired Associates
Herrera-Guzman et al (2010)[33] (continuation of Herrera-Guzman 2009)	24 wk; patients with MDD	Escitalopram 10 mg/d (n=36) vs duloxetine 60 mg/d (n=37); untreated controls (n=104)	HDRS-17: ≥18	WAIS vocabulary and Digit Span Backward, Stroop test, Match-To-Sample, Rapid Visual Processing, Extradimensional Shift, Intradimensional Shift, Stockings of Cambridge
Newhouse et al (2000)[23]	12 wk; age ≥60 y	Sertraline 50 mg/d adjustable to 100 mg/d at week 4 (n=119) vs fluoxetine 20 mg/d adjustable to 40 mg/d at week 4 (n=117)	HDRS-24: ≥18	Shopping List Task, DSST
Nickel et al (2003)[24]	6 wk; inpatients with MDD	Tianeptine 37.5 mg/d adjustable to 75 mg/d at week 3 (n=22) vs paroxetine 20 mg/d adjustable to 40 mg/d at week 3 (n=18)	HDRS-21: >18	Test for Attentional Performance, letter cancellation, CVLT (German version), Raven's Progressive Matrices

Reference	Design	Treatment Groups	Depressive Symptom Level Inclusion Criterion	Cognitive Assessments
Richardson et al (1994)[26]	6 wk; patients with MDD	Amitriptyline (n=19) vs fluoxetine (n=18)	HDRS: >20 (version not specified)	RAVLT
Open-label studies				
Alves et al (2007)[12]	8 wk; patients with heart failure (HF) or HF + MDD	Healthy controls (n=18) HF only (n=23) HF + MDD treated with citalopram starting at 20 mg/d or sertraline starting at 50 mg/d (n=20)	HDRS: ≥18 (version not specified)	CAMCOG (11 subscales and global score)
Boeker et al (2012)[41]	Inpatients with acute or remitted MDD	Treatment regimens not specified; agents used included SSRIs, TCAs, MAOIs, and atypical antidepressants	HDRS-21: ≥24 BDI: ≥24	CANTAB (paired associates learning, pattern recognition memory,spatial working memory, rapid visual information processing, and intra-extradimensional set shift)
Brown et al (2003)[15]	12 wk, single-arm; alcohol-dependent with MDD	Nefazodone, monotherapy, or add-on therapy, 100 mg BID increased biweekly to 200 and then 300 mg BID (n=13)	HDRS: ≥18 (version not specified)	RAVLT
Deuschle et al (2004)[16]	5 wk with >1 y follow-up, single-arm; depressed patients	Amitriptyline 150 mg/d or paroxetine 40 mg/d (n=24)	HDRS: ≥18 (version not specified)	CVLT
Devanand et al (2003)[32]	12 wk, single-arm; age >50 y with depression and cognitive impairment	Sertraline 200 mg/d (n=39)	HDRS-17: ≥8	MMSE, Digit Span Forward and Backward, Buschke SRT, Animal Naming, Boston Naming Test, Revised WAIS Digit Symbol and Similarities, COWAT, Letter Cancellation, Shape Cancellation
Farabaugh et al (2006)[18]	8 wk, single-arm; patients with MDD	Fluoxetine 20 mg/d (n=310)	HDRS-17: ≥16	Cognitions Questionnaire (overall measure of depressive cognition)
Gorenstein et al (2006)[21]	Patients on MDD therapy for ≥6 mo	Clomipramine mean 219 mg/d (n=9) or imipramine mean 230 mg/d (n=15) or sertraline mean 157 mg/d (n=18) or fluoxetine mean 54 mg/d (n=14); each treated patient was matched (sex, age, education) to a healthy control subject	Not specified (baseline mean Beck Depression Inventory: 12–20; baseline mean Hamilton Depression Inventory: 7–10)	Selective Memory Questionnaire, Verbal Recall, Word Appreciation Task, Digit Span Forward and Backward, Word Stem Completion, Visual Recall, DSST, Digit Cancellation, Symbol Copying, Vienna System tests (tapping, inserting pins), reaction times
Murrough et al (2012)[40] [Abstract]	Randomized, double-blind, single-dose open-label; (mean age, 49 y)	Single dose of lamotrigine (300 mg) or placebo, followed by a single 40-min intravenous ketamine (0.5 mg/kg) infusion	IDS-C30: >32	MATRICS battery (TMT-A, TMT-B, Spatial Span, Letter-Number Sequencing, Hopkins Verbal Learning Test, Brief Visual Memory Test, Category Fluency, and Continuous Performance Test)

Reference	Design	Treatment Groups	Depressive Symptom Level Inclusion Criterion	Cognitive Assessments
Sato et al (2006)[27]	Approximately 3 mo, nonrandomized trial; patients (ages 41–75 y) with poststroke MDD	Milnacipran 30–60 mg/d (n=10) vs untreated controls (n=8)	Not specified (mean baseline HDRS-21: 19–21)	MMSE
Spalletta & Caltagirone (2003)[28]	8 wk, single-arm; inpatients (mean age, 66.7 y) with poststroke depression	Sertraline, 50 mg/d adjustable to 100 mg/d at day 28 (n=20)	HDRS-17: >14	MMSE
Spalletta et al (2006)[29]	8 wk; patients (mean age, 64.9 y) with poststroke MDD, with or without alexithymia	Sertraline 50 mg/d adjustable to 100 mg/d at day 28 (n=21) or fluoxetine 20 mg/d adjustable to 40 mg/d at day 28 (n=29)	Not specified (mean baseline HDRS-17: 21–22)	MMSE
Wroolie et al (2006)[31]	12 wk, single-arm; women aged 45–65 y (mean age, 55.9 y) with midlife MDD	Escitalopram 10 mg/d adjustable to 20 mg/d at week 5 (n=17)	Not specified (mean baseline HDRS-17: 21)	CVLT, Stroop test, TMT-A, TMT-B, COWAT, Wechsler Memory Scale tests (Digit Span, Spatial Span, Logical Memory, Letter-Number Sequencing, Visual Reproduction)
AUGMENTATION THERAPY (add-on to background antidepressant therapy)				
Placebo-controlled studies				
Elgamal & MacQueen (2008)[46] (letter to the editor)	8 wk; patients with MDD	Galantamine 8 mg/d x 4 wk, then 16 mg/d (n=10) vs placebo (n=10) add-on to various antidepressant regiments	Not specified	CVLT, Ruff 2 and 7 Selective Attention Test, Digit Span Forward and Backward, TMT-A, TMT-B, DSST, COWAT
Holtzheimer et al (2008)[47]	24 wk; age ≥50 y	Galantamine 8 mg/d x 1 mo, then 16 mg/d (n=19) vs placebo (n=18) add-on to titrated venlafaxine XR or citalopram	HDRS-17: >17	Repeatable Battery for the Assessment of Neuropsychological Status, assessed at baseline, 12 wk, and 24 wk
Levokovitz et al (2012)[55]	Secondary analysis of a 6-week, double-blind, randomized placebo-controlled trial of adjunctive oral SAMe	S-adenosylmethionine 1600 mg QD (n=27) vs placebo (n=19)	HDRS-17: ≥16	CPFQ
Madhoo et al (2012)[44] [Abstract]	9 wk, patients with mild MDD and executive dysfunction (BRIEF-A T-score ≥60)	LDX 20–70 mg/d (n=71) vs placebo (n=72) add-on to SSRI	MADRS ≤18	BRIEF-A

Reference	Design	Treatment Groups	Depressive Symptom Level Inclusion Criterion	Cognitive Assessments
Morgan et al (2005)[49]	6 wk; perimenopausal women aged 40–60 y with MDD in partial remission	Estrogen 0.625 mg/d (n=11) vs placebo (n=6) add-on to background antidepressant	HDRS >7 and ≤14 (version not specified)	Buschke SRT, Digit Span
Pelton et al (2008)[52]	12 wk, with 8-mo open-label extension; age ≥50 y with depression and cognitive impairment	Donepezil 5 mg/d x 4 wk, then 10 mg/d (n=12) vs placebo (n=9); open-label extension, donepezil (n=6) vs no treatment (n=6) add-on to titrated doses of sertraline or "doctor's choice"	HDRS-24: ≥14	Buschke SRT, DSST, TMT-A, TMT-B, COWAT at weeks 8, 20, and 52 (or at time of early discontinuation)
Reynolds et al (2011)[51]	2 y; maintenance in patients age ≥65 y	Donepezil 5–10 mg/d (n=67) vs placebo (n=33) add-on to escitalopram ≤20 mg/d with option to switch as needed to duloxetine ≤120 mg/d and to augment with aripiprazole ≤15 mg/d	HDRS-17: ≥15	Processing speed (TMT-A, DSST, pegboard); visuospatial (Rey-Osterreith Complex Figure Test, Simple Drawings, Block Design); language (Boston Naming Test, Spot-the-Word, Letter Fluency, Animal Fluency); delayed memory (Logical Memory Delayed Recall, Rey-Osterreith Figure Delayed Recall, CVLT Delayed Recall); executive function (Stroop test, Executive Interview, TMT-B/TMT-A ratio, Wisconsin Card Sorting Test errors)
Open-label studies				
Greer et al (2011)[54] [Abstract]	6 wk, patients with MDD	Aripiprazole (n=17) add-on to escitalopram, citalopram, or sertraline	Not specified; response defined as HDRS-17 reduced ≥50%, remission defined as HDRS ≤7	CANTAB (including these tests of cognitive function: Stockings of Cambridge Mean Initial Thinking Time, Spatial Working Memory Between Errors, and Spatial Working Memory Strategy score)
DeBattista et al (2004)[45]	4 wk, single-arm; patients with MDD	Modafinil 100–400 mg/d (n=31)	HDRS: >16 (version not specified)	Stroop test, Letter-Number Sequence, Digit Span, TMT-A, TMT-B
Hinkelmann et al (2012)[53]	3 wk, patients with MDD and matched healthy controls	Mineralocorticoid-receptor (MR) agonist fludrocortisone (n=19) vs MR antagonist spironolactone (n=22) vs placebo (n=11) add-on to escitalopram 10–20 mg/d	HDRS-17: ≥18	RAVLT, TMT-A, TMT-B, Digit Span Forward and Backward, Rey-Osterreith Complex Figure Test, Raymond Complex Figure Test, Letter Cancellation Test
Kok et al (2007)[48]	6 wk, randomized, and 2-year follow-up; age ≥60 y with MDD	Lithium 200 mg/d (titrated to maintain plasma levels) add-on to TCA or venlafaxine (n=15) vs switch to phenelzine 30–60 mg/d (n=14)	MADRS: ≥20	CVLT (Dutch version), TMT (not specified as to TMT-A and/or TMT-B)
Politis et al (2008)[50]	5 wk, single-arm; elderly with psychotic depression	Amisulpride 75–100 mg/d (n=11)	Not specified (HDRS score range, 17–26; version not specified)	MMSE

BDI=Beck Depression Inventory; BID= twice daily; BRIEF-A=Behavior Rating Inventory of Executive Function–Adult Version; CAMCOG=cognitive section of Cambridge Mental Disorders of the Elderly Examination; CANTAB=Cambridge Neuropsychological Test Automated Battery; COWAT=Controlled Oral Word Association Test (verbal fluency test on letters F, A, S or C, F, L); CPFQ=Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire; CVLT=California Verbal Learning Test; DSST=Digit-Symbol Substitution Test; HDRS=Hamilton Depression Rating Scale; Inventory of Depressive Symptomatology – Clinician Rated=IDS-C30; LDX=lisdexamfetamine dimesylate; MADRS=Montgomery-Asberg Depression Rating Scale; MAOI=monoamine oxidase inhibitor; the Measurement and Treatment Research to Improve Cognition in Schizophrenia; MDD=major depressive disorder; MMSE=Mini-Mental State Examination;RAVLT=Rey Auditory Verbal Learning Task; SRT=Selective Reminding Test (Buschke Selective Reminding Test); SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant; TMT, TMT-A, TMT-B=Trailmaking Test parts A and B; WAIS=Wechsler Adult Intelligence Scale; WCST=Wisconsin Card-Sorting Test.

Supplementary eTable 2. Key Findings on Cognitive Effects From Studies of Pharmacotherapy for Depression

Reference	Cognitive Effects	Notes
MONOTHERAPY		
Placebo-controlled studies		
Alev et al (2011)[36] [Abstract]	Duloxetine Significantly greater improvement from baseline with duloxetine vs placebo on the CPFQ using MMRM (P<.001) and LOCF (P–value not reported)	
Austin et al (2000)[13]	Apomorphine DSST: Melancholic patients showed significant (P<0.016) deficit pretreatment and significant deficit vs controls after placebo (P<0.02 covarying for age) ANCOVA showed no effect of drug, time, or drug × time interaction in either group; MANCOVA controlling for age showed that apomorphine caused significant impairment on COWAT, DSST, and reaction time tests compared with placebo (P=0.007 averaging across diagnosis [melancholic and control], P=0.009 for diagnosis × drug interaction); effects were more severe in controls	Conclusions were limited by small sample size, minimal pretreatment task impairment in depressed patients vs control subjects, mild sedation during task performance, and lack of serum apomorphine levels
Culang et al (2009)[42]	Citalopram Judgment of Line Orientation: Citalopram responders performed significantly better than citalopram or placebo nonresponders (both P=0.01) but not better than placebo responders (P=0.08) Citalopram nonresponders showed significant declines from baseline on Buschke SRT (P=0.05) and DSST (P=0.04)	Detrimental effects on memory and psychomotor speed among nonresponders suggest that treatment should not be continued in these patients
Katona et al 2012[39] [Abstract]	Vortioxetine (Lu AA21004) Superiority over placebo reported on cognitive assessments of processing speed and verbal learning and memory in elderly patients with recurrent MDD	
Ferguson et al (2003)[19]	Reboxetine Reboxetine: significant improvements from baseline to day 56 in Continuity of Attention (derived from choice reaction time accuracy and digit vigilance correct and wrong responses; P=0.023) and Combined Speed (derived from simple and choice reaction time speeds, digit vigilance speed of correct responses, and numeric working memory and word recognition speed of responses; P=0.024); nonsignficantly better than placebo on Continuity of Attention (P=0.07) and Combined Speed (P=0.10) at day 56 Paroxetine: significant improvement from baseline to day 14 in Combined Speed (P=0.02), but this effect was not sustained through day 56 For all treatment groups combined, changes in HDRS-17 total score showed correlation with Combined Speed (P=0.04) but not with Continuity of Attention	

Reference	Cognitive Effects	Notes
Raskin et al (2007)[25]	Duloxetine Composite score: improvement significantly greater with duloxetine vs placebo among all randomized patients and among those with baseline HDRS <24 (both $P<0.02$); no significant between-group difference among patients with baseline HDRS ≥24 ($P=0.13$); no significant treatment × HDRS interaction ($P=0.82$) Individual tests: Improvement significantly greater score with duloxetine vs placebo on Verbal Learning and Recall learning trials ($P=0.03$) and delayed recall ($P=0.03$); no significant between-group differences on other tests	Lack of statistical significance with duloxetine vs placebo among patients with baseline HDRS ≥24 might be due in part to small numbers in this subgroup (n=16)
Wise et al (2007)[30] (substudy of Raskin et al)	Duloxetine Subanalysis in those with medical comorbidity (75% of population) vs those without comorbidity (25%): composite score was significantly better with duloxetine vs placebo for the whole population ($P=0.013$) and for the subgroup with medical comorbidity ($P=0.006$); no significant between-group difference in patients without comorbidity ($P=0.724$); no significant treatment × comorbidity interaction ($P=0.266$)	Comorbidities were vascular disease, diabetes, or arthritis
Reilly et al (2012)[34] [Abstract]	Sertraline Patients receiving sertraline showed greatest improvements in terms of reduced psychomotor slowing, improved ability to plan and initiate behavior, and improved performance on some neuropsychological tests	Little or no cognitive impairment at baseline, so improvement may represent practice effects
Active-comparator studies		
Bondareff et al (2000)[14]	Sertraline vs nortriptyline Significant between-group differences favoring sertraline at study end (Confusion Factor and MMSE, both $P=0.01$; WAIS, $P=0.002$; Shopping List Task, $P\leq0.02$); in general, there was a beneficial effect with sertraline vs mildly negative effect with nortriptyline	No information relating to possible correlation between cognitive outcomes and clinical response
Chang et al (2012)[37]	Fluoxetine vs venlafaxine No significant differences in the cognitive effects of fluoxetine and venlafaxine; overall, significant improvement from baseline on the neuropsychologic function domain of the HAM-D ($P < 0.001$) after 6 weeks of treatment and CPT: Significant improvement in performance in the masked vesion of the test ($P< 0.001$) WCST: Significant improvement for completed categories ($P=0.027$)	
Culang-Reinlieb et al (2012)[35]	Sertraline vs nortriptyline Buschke SRT: Significant improvement from baseline with sertraline ($P=0.001$); change did not depend on response status; improvement was significantly greater with sertraline than with nortriptyline among all treated patients ($P=0.02$) and among responders on each treatment ($P=0.01$); no other significant differences reported	
Doraiswamy et al (2003)[17]	Sertraline vs fluoxetine or nortriptyline Shopping List Task and DSST: Significantly better performance on both tests with sertraline vs nortriptyline and with fluoxetine vs nortriptyline for total group and for treatment responders (all $P<0.05$) but not for treatment responders with baseline cognitive impairment DSST: Significantly better performance with sertraline vs fluoxetine for total group ($P<0.05$)	Male sex and older age were significantly associated with poorer cognitive performance at baseline
Finkel et al (1999)[20]	Sertraline vs fluoxetine DSST: Significantly greater improvement from baseline with sertraline than with fluoxetine ($P=0.0008$)	

Reference	Cognitive Effects	Notes
Hashemian et al (2011)[38] [Abstract]	Bupropion vs fluoxetine With both treatments, correct responses to visual stimuli significantly increased ($P<0.05$), a the number of correct responses was significantly greater with bupropion compared with fluoxetine after 2 and 4 weeks Significant improvement from baseline at end of study for the auditory task was observed with only with bupropion compared to the baseline No significant difference in mean reaction times between treatments	
Herrera-Guzman et al (2009)[22]	Escitalopram vs duloxetine RAVLT: Significant improvement from baseline ($P=0.000$); no significant between-group difference ($P>0.2$) Paired associates: Significant improvement in first-trial memory ($P=0.045$), total errors adjusted ($P=0.042$), and total trials ($P=0.026$); no significant between-group differences (all $P>0.4$) Delayed match-to-sample: No significant improvement in total correct ($P=0.125$) or total correct delayed ($P=0.477$); significant between-group difference in total correct ($P=0.031$ favoring duloxetine) Pattern recognition: Significant improvement in latency ($P=0.000$); no significant between-group difference ($P=0.880$) 5-choice movement time: Significant improvement ($P=0.001$); no significant between-group difference ($P=0.893$) Digit Span Backward: Significant improvement ($P=0.022$); no significant between-group difference ($P=0.589$) Spatial span: Significant improvement ($P=0.032$); no significant between-group difference ($P=0.524$) Spatial working memory: Significant improvements in between errors, total errors, and strategy (all $P<0.04$); no significant between-group differences (all $P>0.3$) Stroop test: Significant improvements in words read ($P=0.000$) and colors named ($P=0.003$); no significant between-group differences ($P=0.695$ for words read, $P=0.207$ for colors named) Significant treatment × time interaction for RAVLT ($P=0.000$); paired associates total errors adjusted ($P=0.045$), total trials adjusted ($P=0.004$), and mean trials to success ($P=0.014$); and Digit Span Backward ($P=0.014$)	Improvements in memory were generally greater with the SNRI duloxetine than with the SSRI escitalopram No information relating to possible correlation between cognitive outcomes and clinical response

Reference	Cognitive Effects	Notes
Herrera-Guzman et al (2010)[33] (substudy of Herrera-Guzman 2009)	Escitalopram vs duloxetine Digit Span Backward: Significant improvement from baseline (P=0.015); significant between-group difference (P<0.001) Spatial working memory: Significant improvements in between-errors, total-errors, and strategy (all P≤0.004); significant between-group difference in total errors (P<0.001) Rapid visual processing: Significant improvement (P<0.001); significant between-group difference (P=0.010) Match-to-sample: No significant improvement (P=0.286); significant between-group difference (P<0.001) Stroop test: Significant improvement (P=0.001); significant between-group difference (P<0.001) Extradimensional shift and intradimensional shift: Significant improvements in total trials and total errors (both P=0.005); significant between-group differences in total trials and total errors (P<0.001) Stockings of Cambridge: Significant improvements in initial thinking time 4 moves, subsequent thinking time, and problems solved with minimal moves (all P≤0.004); significant between-group differences in initial thinking time, subsequent thinking time 5 moves, and problems solved (all P≤0.02) No significant treatment × time interactions	Results may vary from Herrera-Guzman 2009 because untreated controls as third group performed better than either treatment group No information relating to possible correlation between cognitive outcomes and clinical response
Newhouse et al (2000)[23]	Sertraline vs fluoxetine Shopping List Task: Performance significantly better with sertraline vs fluoxetine on increase in number of items recalled at week 6 (P=0.022); borderline significant advantage in number of items recalled at week 8 (P=0.051) DSST: Significant improvement from baseline at weeks at 4–12 with sertraline (P<0.01), but only at week 12 with fluoxetine (P<0.05); sertraline significantly better than fluoxetine at weeks 6 (P=0.019) and 12 (P=0.037)	
Nickel et al (2003)[24]	Tianeptine vs paroxetine Both treatment groups showed improvement at day 42, with significant time effects for alertness response time (P=0.032), selective attention (P=0.000), and correctly solved problems Time × treatment: borderline significant for divided attention response time (P=0.051) Time × response status: significant for selective attention (P=0.025) Performance was generally better among responders vs nonresponders	Unlike SSRIs (eg, paroxetine), which block the presynaptic 5-HT transporter to *increase* synaptic serotonin, tianeptine enhances presynaptic reuptake to *reduce* serotonergic transmission Lack of significant between-group difference may be due to group differences in pretreatment scores
Richardson et al (1994)[26]	Amitriptyline vs fluoxetine RAVLT: Repeated measures ANOVA with verbal learning at baseline as a covariate: significant effects for drug (P=0.004) and assessment (P=0.004). Post hoc analysis shows performance significantly better with fluoxetine than with amitriptyline at week 3 (P=0.03) and week 6 (P=0.004); recall of new words (intrusion list) at week 6 was also better with fluoxetine than with amitriptyline (P=0.03); clinical improvement was similar for both treatments	Amitriptyline group showed higher serum anticholinergic activity, supporting the concept that muscarinic blockade impedes working memory
Open-label studies		

Reference	Cognitive Effects	Notes
Alves et al (2007)[12]	Citalopram or sertraline CAMCOG: Treatment in HF + MDD group resulted in significant improvement in global score (P<0.001) and on 5 of 11 subscales: attention (P=0.001), remote memory (P=0.046), calculation (P=0.009), language expression (P=0.006), abstract reasoning (P=0.026)	Subscale for language comprehension described as showing significant improvement but P value is shown as 0.44
Boeker et al (2012)[41]	Various antidepressants After remission of depressive symptoms, the paired associate learning memory score improved (P< 0.05) and the number of total errors decreased (P<0.05); in addition, pattern recognition memory response time significantly improved (P< 0.05) No differences between the acute and the remitted state were observed for intra-extradimensional shift, rapid visual processing, or spatial working memory	
Brown et al (2003)[15]	Nefazodone RAVLT: assessment of declarative memory was low to average at baseline; improvement from baseline was not statistically significant (P=0.215)	Lack of statistically significant improvement could be due in part to small sample size
Deuschle et al (2004)[16]	Amitriptyline or paroxetine CVLT: no significant changes from baseline to day 35 in remitters, responders, or nonresponders, although remitters were significantly less impaired than nonresponders at baseline (P<0.05); no significant differences by response category at day 35 or at long-term follow-up	
Devanand et al (2003)[32]	Sertraline Data from 26 completers (17 responders, 9 nonresponders): responders were younger than nonresponders (mean age 67 vs 82 y, P<0.001), and younger patients had better baseline scores on Buschke SRT delayed recall (P<0.05); more education was associated with better baseline scores on WAIS similarities, DSST and COWAT; ANCOVA with response status as between-patients factor and age and education as covariates showed significant effect for response status on DSST (P<0.03), with percentage change improving for responders but worsening for nonresponders (P<0.02); percentage changes in HDRS inversely correlated with percent changes in Buschke SRT total recall (P<0.03), DSST (P<0.01), and letter cancellation (P<0.01)	Patients had MCI, not dementia; entry criterion for HDRS-17 was substantially lower (more inclusive of milder depression) than in most other studies
Farabaugh et al (2006)[18]	Fluoxetine Cognition Questionnaire: with Bonferroni correction, no significant differences between patients with "true drug response" (TDR; persistent improvement after 2-week delay) vs those with "placebo pattern response" (PPR; early transient improvement) in scores at baseline or at endpoint (both P=0.06); however, measured stress was significantly lower with PPR than with TDR at study end (P=0.0009)	Focus of study is not treatment-related cognitive change per se, but changes classified as TDR vs PPR
Gorenstein et al (2006)[21]	Clomipramine or imipramine or sertraline or fluoxetine Memory: Patients in all treatment groups scored significantly poorer than matched controls on Selective Memory Questionnaire (P<0.01 for clomipramine, P<0.001 for the other treatments) regardless of remission status; patients taking sertraline scored poorer than controls on visual recall (P<0.05) Psychomotor function: Patients taking imipramine scored poorer than controls on inserting pins and visual reaction time (P<0.05)	Comparisons were treated patients vs healthy matched controls, not treatment vs treatment and not change from baseline On some tests with some drugs, difference vs controls was reduced at higher dosages

Reference	Cognitive Effects	Notes
Murrough et al (2012)[40] [Abstract]	Ketamine infusion preceded by pretreatment with lamotrigine No significant effect of ketamine alone on verbal learning or semantic fluency on the HVLT (both $P>0.05$) at 40 minutes post infusion; ketamine significantly worsened delayed recall on the HVLT at 40 minutes post-infusion ($P=0.04$). Pretreatment with lamotrigine significantly decreased the likelihood of observing ketamine associated cognitive impairment ($P=0.04$).	
Sato et al (2006)[27]	Milnacipran MMSE: Among patients with major depression (treatment, n=3; control, n=3) or minor depression (treatment, n=7; control, n=5), there was a significant time × treatment interaction ($P=0.034$) and significant time effect ($P=0.009$) favoring the SNRI milnacipran vs no treatment No significant change in HDRS in either group and no evidence that cognitive response depended on affective response	Controls refused or could not take treatment; therefore, assignment to treatment was not randomized; however, there were no significant between-group differences in demographics, stroke location or type, or neurological symptoms
Spalletta & Caltagirone (2003)[28]	Sertraline MMSE: Statistically significant improvement from baseline starting at day 28 ($P<0.05$ vs day 0)	
Spalletta et al (2006)[29]	Sertraline or fluoxetine MMSE: For the whole population, no significant effect after Bonferroni correction; significant time × alexithymia status interaction ($P=0.0003$; significant improvement from baseline only among patients without alexithymia); among those without alexithymia, improvement vs baseline was significant at week 2 ($P=0.0271$), week 4 ($P=0.0015$), week 6 ($P=0.0158$), and week 8 ($P=0.0001$) Because MMSE is language-oriented and affected by left hemisphere lesions, whereas alexithymia is associated with right hemisphere lesions, patients were stratified by location of stroke: significant time × laterality interaction ($P=0.0001$); among those with left hemisphere injury and without alexithymia, improvement vs baseline was significant at week 2 ($P=0.0222$), week 4 ($P=0.0011$), week 6 ($P=0.0042$), and week 8 ($P=0.0003$)	Focus was not sertraline vs fluoxetine but effects of treatment among patients with vs without alexithymia (difficulty in identifying and describing feelings, elaborating fantasies, and using externally oriented thinking)
Wroolie et al (2006)[31]	Escitalopram Significant improvement on Wechsler Memory Scale Logical Memory and Visual Reproduction tests ($P<0.05$) and on TMT-B ($P=0.004$), but significant worsening on COWAT ($P=0.004$)	
AUGMENTATION THERAPY (add-on to background antidepressant therapy)		
Placebo-controlled studies		
Elgamal & MacQueen (2008)[46] (letter to the editor)	Galantamine Numerically greater improvement with galantamine vs placebo on CVLT, Ruff 2 and 7 Selective Attention Test, Digit Span Backward, TMT-A, COWAT, but no statistically significant differences	Lack of statistically significant between-group differences could be attributed to small sample size

Reference	Cognitive Effects	Notes
Holtzheimer et al (2008)[47]	Galantamine Significant advantage with galantamine vs placebo: group effect on tests of language (P=0.020) and delayed memory (P=0.028); time effect on tests of immediate memory (P=0.0002), visuospatial/construction (P=0.019), language (P=0.011), attention (P=0.033), delayed memory (P<0.0001), and total score (P=0.0001); no significant group × time interactions	
Levkovitz et al (2012)[55]	S-adenosyl methionine (SAMe) Significantly greater improvement on the CPFQ for "ability to recall information" (P<0.04) with adjunctive SAMe than with placebo; no treatment differences were observed for "ability to focus" (P<0.74), "word finding ability"(P<0.09), or "sharpness/mental acuity" (P=0.026).	
Morgan et al (2005)[49]	Estrogen Buschke SRT: Performance was generally better with estrogen vs placebo but difference was not statistically significant In both treatment groups, decreased FSH was associated with significantly better performance on Delayed Recall in Buschke SRT (P=0.021) and on Digit Span Backward (P=0.026)	
Pelton et al (2008)[52]	Donepezil Weeks 8–20: Within-group improvement with donepezil on Buschke SRT (P=0.05) but no significant between-group difference; group × time interaction (P=0.06) on ANCOVA with age, education, and week 8 HDRS as covariates; no benefit on other tests, which measured nonmemory domains Weeks 8–52: Group × time interaction (P<0.01) on ANCOVA with age, education, and week 8 HDRS as covariates	Add-on therapy came after 8 wk of open-label sertraline or other antidepressant
Reynolds et al (2011)[51]	Donepezil Significant at 2 years: Information processing speed: Time effect (P=0.004), MCI (P<0.001) Visuospatial domain: Time effect (P<0.001), MCI (P<0.001) Language: treatment × time × MCI interaction (P=0.047), MCI (P<0.001) Memory: Treatment effect (P=0.02), treatment × time interaction (P=0.02), MCI (P<0.001) Executive function: Treatment × time interaction (P=0.001), time × MCI interaction (P=0.02), MCI (P<0.001) Global: Time effect (P=0.002), treatment × time interaction (P=0.03), MCI (P<0.001)	Cognition was studied to assess ability of treatment to prevent, delay, or minimize onset or worsening of cognitive impairment MCI was a significant factor in all domains Donepezil had no benefit in patients with intact cognition
Madhoo et al (2012)[44] [Abstract]	Lisdexamfetamine Mean reduction on BRIEF-A Global Executive Composite T-score was greater with LDX than with placebo (–21.2 vs –13.2; P=0.0009)	
Open-label studies		

Reference	Cognitive Effects	Notes
Greer et al (2011)[54] [Abstract]	Aripiprazole Significant improvement with aripiprazole on Stockings of Cambridge Mean Initial Thinking Time for 3- and 5-move problems (both $P<0.02$), Spatial Working Memory Between Errors for 6-move problems ($P<0.01$), and Spatial Working Memory Strategy score ($P<0.04$)	Improvement in cognition showed greater correlation with changes in psychosocial function than with the large reductions in depressive symptoms occurring earlier
DeBattista et al (2004)[45]	Modafinil Stroop test: Significant improvement at week 4 ($P<0.004$)	
Hinkelmann et al (2012)[53]	Fludrocortisone or spironolactone Improvement greater in patients than in healthy controls in verbal ($P=0.02$) and nonverbal memory ($P<0.01$), but patients still performed worse than controls on Digit Span Forward ($P=0.02$), Rey-Osterreith and Taylor Complex Figure tests ($P<0.01$), and letter-cancellation test ($P<0.01$); no significant between-group differences over time Reduction in cortisol significantly associated with improved performance on TMT-A ($P<0.01$) and TMT-B ($P=0.03$), and trend toward improved performance on RAVLT, TMT-difference (B – A), Digit Span Backward, and the Complex Figure tests	Antidepressant treatment reduced salivary cortisol in MDD patients to normal levels, and reduction in cortisol was associated with improved performance on certain cognitive tests
Kok et al (2007)[48]	Lithium add-on to TCA or venlafaxine; or switch to phenelzine CVLT and TMT: No significant between-group difference at baseline on either measure (both groups showed baseline impairment on TMT); no significant change at week 6 in either group on either measure; no significant between-group difference at study end on either measure Memory impairment at study end with switch from TCA or venlafaxine to phenelzine ($P=0.002$ vs lithium add-on) was classified as an adverse event but was not a finding on either cognitive test	
Politis et al (2008)[50]	Amisulpride MMSE: No significant changes	

ANCOVA= analysis of covariance; ANOVA=analysis of variance; BRIEF-A=Behavior Rating Inventory of Executive Function–Adult Version; CAMCOG=cognitive section of Cambridge Mental Disorders of the Elderly Examination; COWAT=Controlled Oral Word Association Test; CPFQ=Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire; CPT=Continuous Performance Test; CVLT=California Verbal Learning Test; CVLT=California Verbal Learning Test; DSST=Digit-Symbol Substitution Test; FSH=follicle-stimulating hormone; HDRS=Hamilton Depression Rating Scale; HF=heart failure; HVLT=Hopkins Verbal Learning Test; LDX=lisdexamfetamine dimesylate; LOCF= last observation carried forward; MANCOVA= multivariate analysis of covariance; MCI=minimal cognitive impairment; MDD=major depressive disorder; MMRM=mixed-effects model repeated measures; MMSE =Mini-Mental State Examination; RAVLT=Rey Auditory Verbal Learning Task; SNRI=serotonin-norepinephrine reuptake inhibitor; SRT=Selective Reminding Test (Buschke Test); SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant; TMT, TMT-A, TMT-B=Trailmaking Test, parts A and B; WAIS=Wechsler Adult Intelligence Scale; WCST=Wisconsin Card-Sorting Test.