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Supplementary Material

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

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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.