

# EFFECTS OF PHARMACOLOGICAL TREATMENTS ON COGNITION

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Enabling Discovery, Development, & Translation for  
Cognitive Dysfunction in Depression:  
A Workshop

# FINANCIAL DISCLOSURES

PAST THREE YEARS

## **CONSULTANT/AD BOARD/SERVICE PROVIDER**

Abbvie, Akebia, Amgen, Astellas, Asubio, AviNeuro/ChemRar, Biogen Idec, BiolineRx, Biomarin, Boehringer-Ingelheim, Eli Lilly, EnVivo/FORUM, GW Pharmaceuticals, Helicon, Lundbeck, Merck, Mitsubishi, Novartis, Otsuka, Pfizer, Roche, Shire, Sunovion, Takeda, Targacept

## **RESEARCH FUNDING**

Department of Veteran's Affairs, Feinstein Institute for Medical Research, GlaxoSmithKline, NIMH, Novartis, Psychogenics, Research Foundation for Mental Hygiene, Singapore Medical Research Council

## **FOUNDER OF NEUROCOG TRIALS, INC.**

Providing rater training, data quality assurance and consultation to several pharmaceutical companies and other consortia

## **SHAREHOLDER**

Sengenix

## **ROYALTIES**

Brief Assessment of Cognition in Schizophrenia (BACS), MATRICS Consensus Cognitive Battery (MCCB), Virtual Reality Functional Capacity Assessment Tool (VRFCAT)

# INTRODUCTION & BACKGROUND

- Magnitude of the cognitive impairment approximately 0.5-.7 SDs
- Cognitive deficits and mood symptoms track with one another
- Determination of the magnitude of effect of antidepressant treatment on cognitive function is made difficult by
  - Wide variety of study designs, patient populations and assessment methodologies
  - A broad range of neuropsychological instruments used across studies
  - Findings have been reported in different formats even when similar instruments are used
  - Inconsistency in the manner by which these instruments have been categorized into specific domains of cognitive function
  - Treatment response of mood and cognition are rarely assessed for orthogonality

# REVIEW & META-ANALYSIS

## METHODS

- Effect sizes were calculated for all cognitive endpoints from trials that included a placebo control, healthy control, or active comparator and that adequately reported the data
- Cohen's  $d$  ( $[\text{active treatment} - \text{control}] / \text{pooled population standard deviation at end of study}$ ) for treatment differences in the change from baseline
- 43 reports were included in this review:
  - 15 reports on placebo-controlled studies (8 monotherapy, 7 augmentation)
  - 11 reports on active-comparator studies (all monotherapy)
  - 17 reports on open-label studies (12 monotherapy, 5 augmentation)
    - ✓ single-arm studies
    - ✓ studies of treated patients vs either healthy controls or untreated patients
    - ✓ time-course comparisons of treated patients without a control arm

Keefe RSE, McClintock SM, Roth RM, Doraiswamy PM, Tiger S, Madhoo M. Cognitive effects of pharmacotherapy for major depressive disorder: A systemic review. *Journal of Clinical Psychiatry*, 2014; 75(8): 864-876.

# STUDY PARTICIPANTS

- Individuals with mild to severe depression by entry criteria that included a minimum score on a depression symptom rating instrument
- Among all the studies included in this review, only Mahdoo et al, 2014, assessed a population defined by complete or partial remission of MDD (based on Montgomery-Asberg Depression Rating Scale score  $\leq 18$ )
- In 15 of the 43 reports, the populations were described as elderly
- An additional 3 studies assessed post-stroke patients
- Some studies dealt with depressive symptoms in the setting of comorbidities such as heart failure, alcohol dependence, stroke, or other conditions; 1 report dealt with psychotic depression

# SAMPLE SIZES

- 4,828 participants were evaluated:

	<b>n</b>
Monotherapy versus Placebo	2,149
Active versus Placebo Augmentation	384
Monotherapy versus Active Control	1,410
Open-label Monotherapy	745
Open-label Augmentation	140

- Sample size (N):

	<b>mean ± SD</b>	<b>median</b>	<b>range</b>
All studies	112 ± 151	50	11-776
Monotherapy studies	139 ± 169	63	12-776
Augmentation studies	44 ± 39	30	11-143

# STUDY DURATION

- Most of the studies were of relatively short duration.

	<b>mean <math>\pm</math> SD</b> weeks	<b>median</b> weeks	<b>mode</b> weeks	<b>range</b> weeks
All studies	13 $\pm$ 16	8	12	3-104
Monotherapy studies	11 $\pm$ 7	8		4-36
Augmentation studies	16 $\pm$ 28	6		3-104

# TREATMENTS

In most studies, treatment was with antidepressant agents, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and tricyclic antidepressants

Other psychotropic agents were also tested:

- Apomorphine
- lithium
- estrogen
- the serotonin-reuptake enhancer tianeptine
- aripiprazole
- amisulpride
- mineralocorticoid receptor modulators
- fludrocortisone
- spironolactone
- galantamine
- donepezil
- ketamine
- lisdexamfetamine dimesylate

# COGNITIVE ASSESSMENT

- Primary/co-primary outcome in 32 reports
- Secondary outcome in 9 reports
- Safety outcome in 2 reports

# PRIMARY COGNITIVE DOMAINS ASSESSED BY NEUROLOGICAL TESTS

- There are a lot of ways to assess cognitive function with neuropsychological tests in patients with MDD
- Comprehensive testing is informative but potentially burdensome

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			•								

Keefe et al. J Clin Psychiatry, 2014

# RESULTS

- In the majority of reports, there was statistically significant cognitive benefit with monotherapy or augmentation therapy
- Significant benefit was reported with:
  - active treatment versus placebo in 7 of 8 monotherapy studies
  - active augmentation versus placebo augmentation in 5 of 7 studies
- Of the 3 placebo-controlled studies that did not report significant benefit, all had relatively small treatment groups
- Depressive symptoms improved in almost all studies
- In 10 of 11 active-comparator monotherapy trials, significant between-treatment differences were reported, with sertraline having superior effects to nortriptyline in 3 studies and to fluoxetine in 2 studies

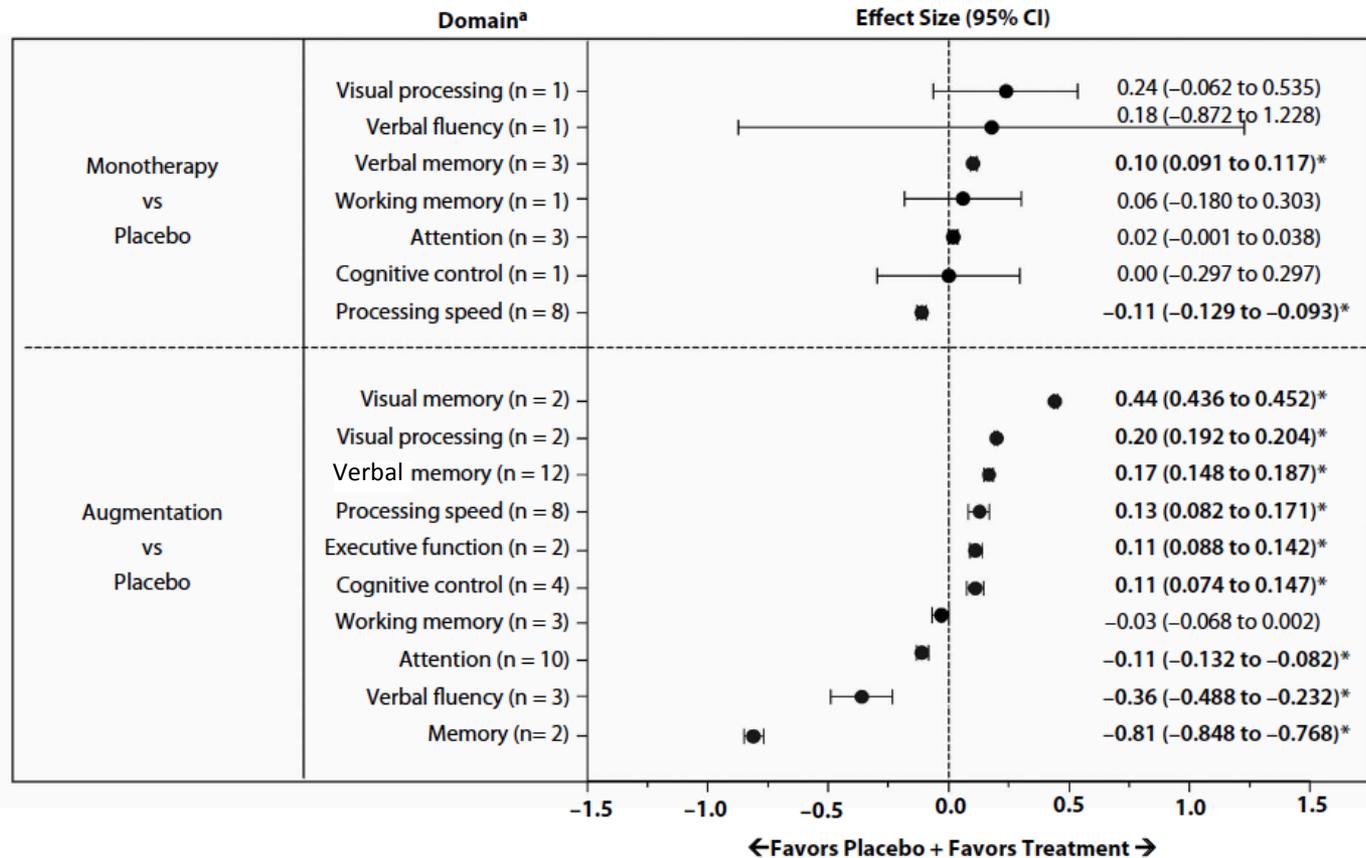
# RESULTS BY DOMAIN

- Cognitive testing most frequently included the domains of verbal memory, working memory, and processing speed
- Antidepressant pharmacotherapy was more likely than not to improve performance in those domains, but the reported estimates of improvement were relatively small
- Many studies included multiple tests for a given domain and only 7 of 43 studies corrected for multiple comparisons.
- Reported improvements:
  - verbal memory, 12 studies
  - working memory, 7 studies
  - processing speed, 8 studies
  - executive function, 5 studies

# EFFECT SIZES

- 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 9 monotherapy publications and 6 augmentation publications
- 20 of 168 (12%) analyses favored an active treatment over placebo or untreated healthy controls
- 7 of 168 (7%) favored placebo or untreated healthy controls over active treatment
- Does this difference exceed the file drawer problem?

# SAMPLE WEIGHTED EFFECT SIZES WITH 95% CI'S ACROSS COGNITIVE FUNCTION DOMAINS

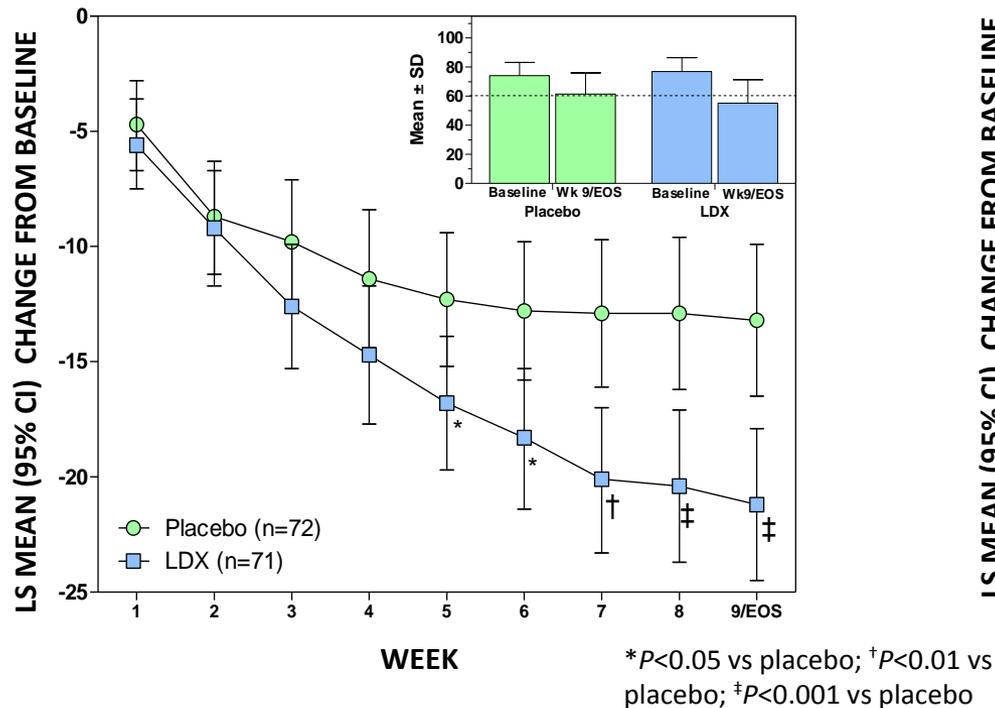


<sup>a</sup>Values in parentheses beneath each domain of function represent the number of cognitive assessments included in the analysis of each domain of function.

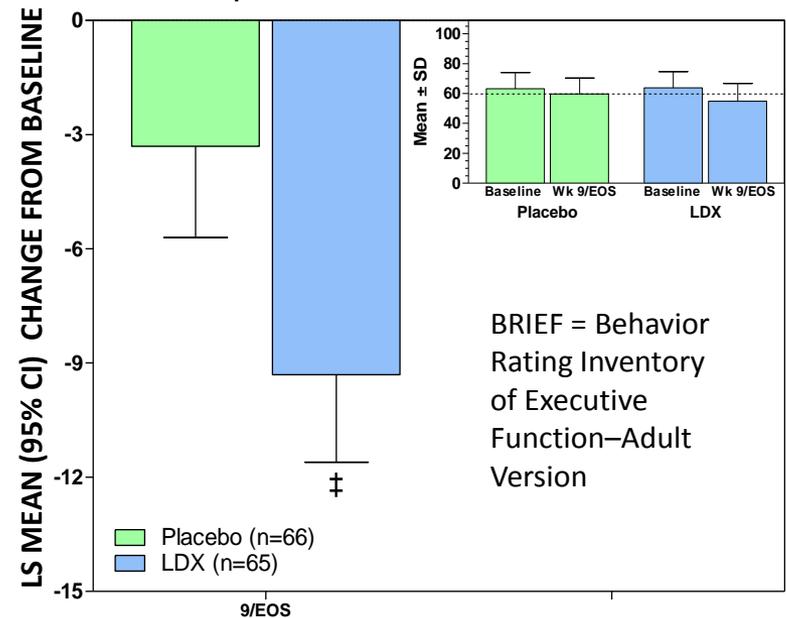
\*Assessments with 95% CIs not crossing 0.

# EFFECTS OF LISDEXMETHAMFETAMINE ON BRIEF SCORES

## SELF-REPORT



## INFORMANT REPORT



BRIEF = Behavior Rating Inventory of Executive Function—Adult Version

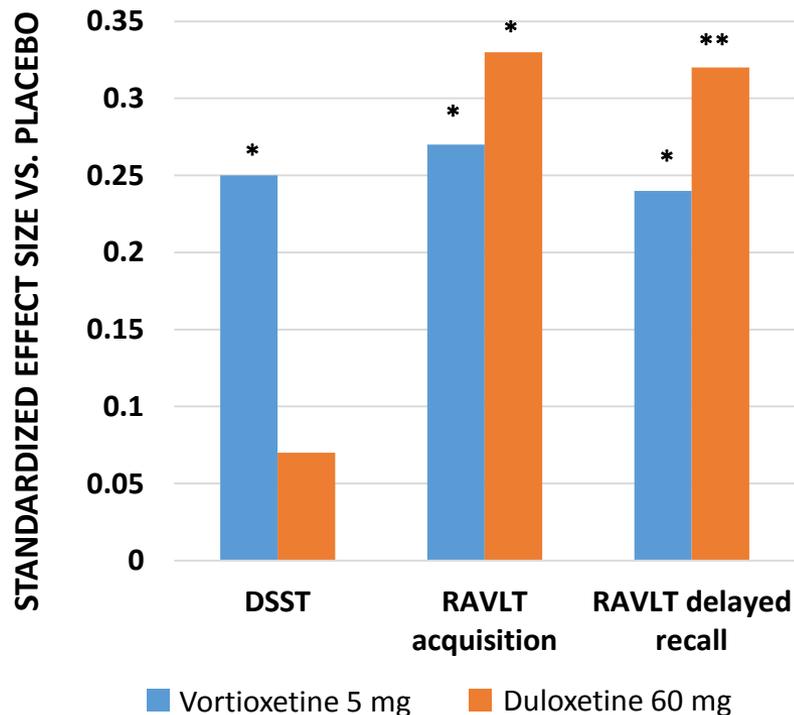
Lisdexamfetamine did not significantly improve performance on a computerized cognitive test battery

Madhoo M, Keefe RSE, Roth RM, Sambunaris A, Wu J, Trivedi MH, Anderson CS, Lasser R. *Neuropsychopharmacology*, 2014; 39(6): 1388-1398.

# VORTIOXETINE IMPROVED COGNITIVE DYSFUNCTION IN DEPRESSED ELDERLY PATIENTS

## ELDERLY STUDY

Vortioxetine improved cognitive performance as measured by both the DSST and RAVLT tests<sup>1</sup>



- Vortioxetine improved cognitive performance in both the RAVLT and DSST
- The active reference (duloxetine) improved cognitive performance in RAVLT, but not in DSST, confirming published data<sup>2</sup>

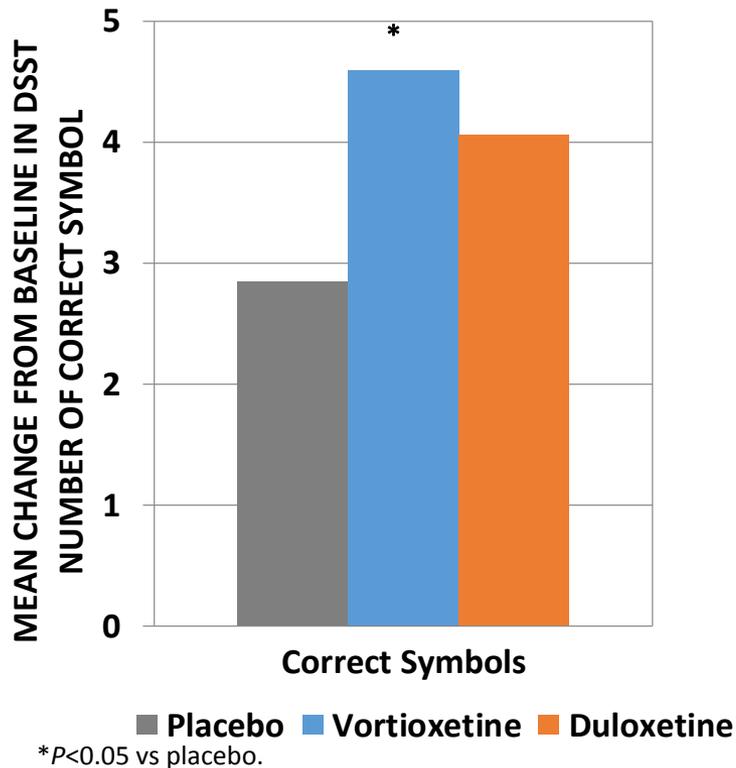
1. Katona C et al. *Int Clin Psychopharmacol.* 2012;27(4):215-23

2. Raskin J et al. *Am J Psychiatry* 2007;164(6):900-9

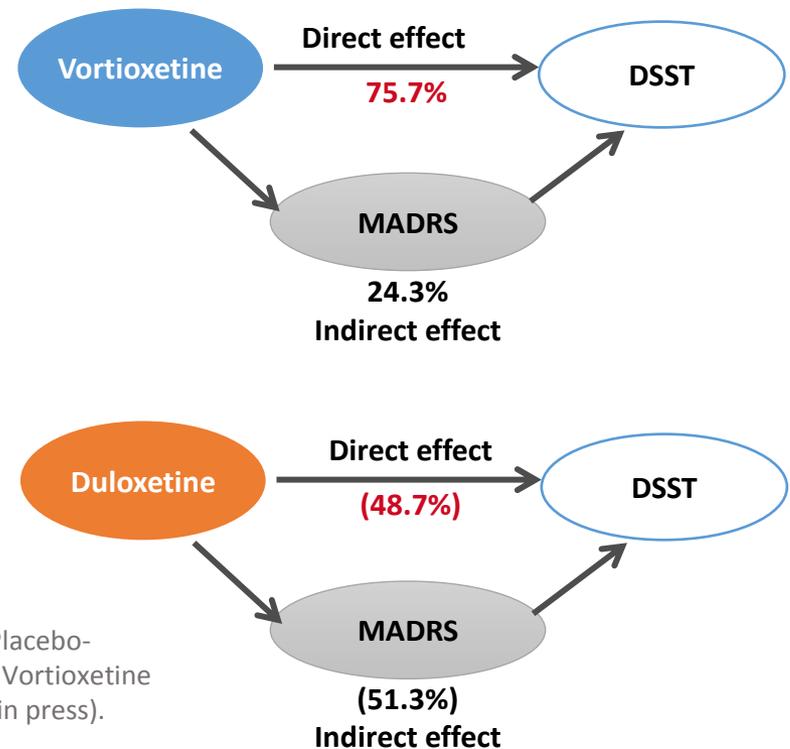
DSST, Digit Symbol Substitution Test; RAVLT, Rey Auditory Verbal Learning Test

# MEAN CHANGE FROM BASELINE IN DSST NUMBER OF CORRECT SYMBOLS AT WEEK 8

## CONNECT STUDY



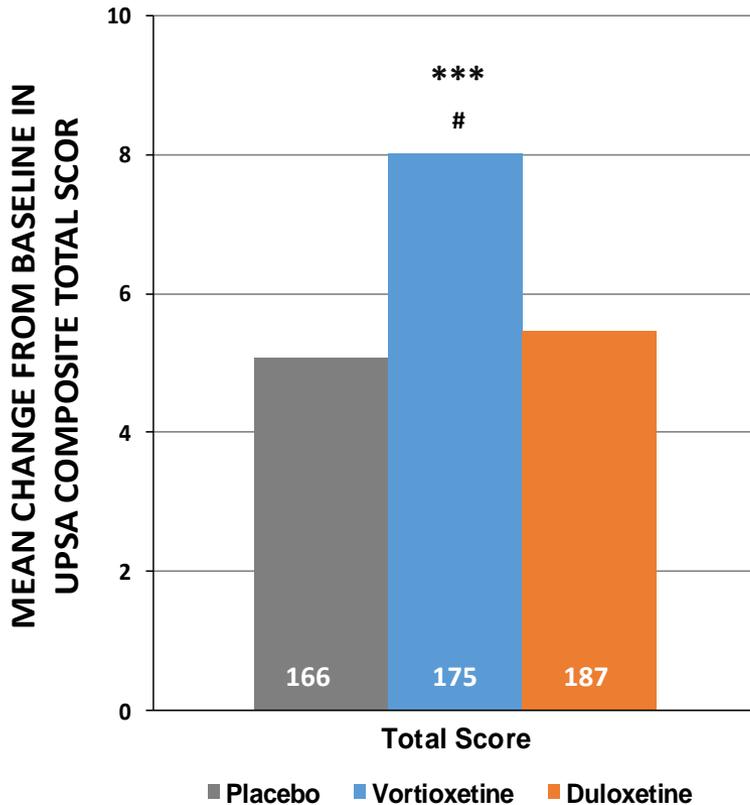
Proportion of the effect on cognitive performance attributed to an improvement of general depressive symptoms



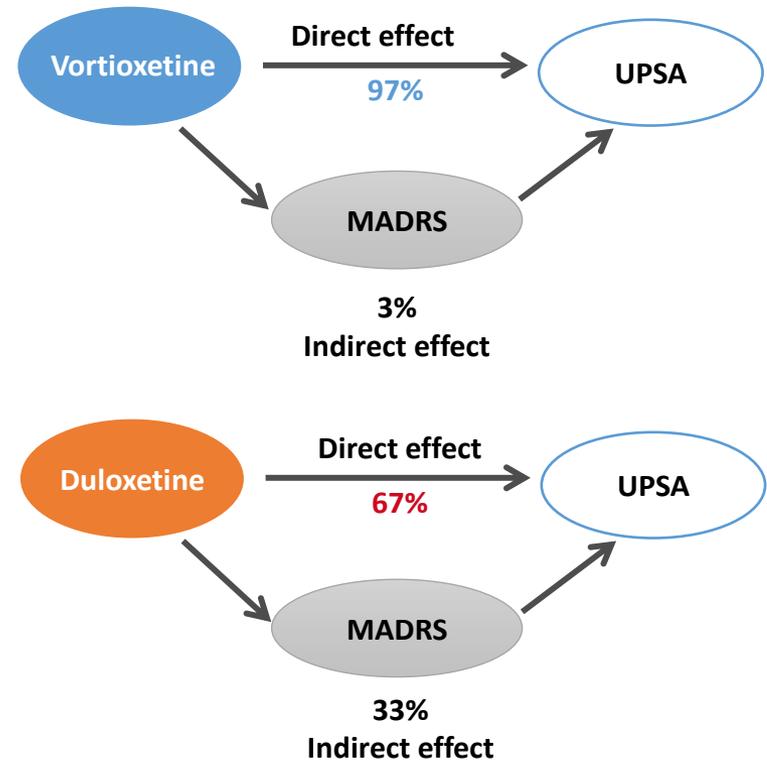
Mahableshwarkar AR, Zajecka J, Jacobson W, Chen Y, Keefe RSE. A Randomized, Placebo-Controlled, Active-Reference, Double-Blind, Flexible-Dose Study of the Efficacy of Vortioxetine on Cognitive Function in Major Depressive Disorder. *Neuropsychopharmacology* (in press).

# MEAN CHANGE FROM BASELINE IN UPSA COMPOSITE TOTAL SCORE AT WEEK 8

CONNECT STUDY



Baseline score ~ 78  
 (Range 0-100, where higher scores indicate better functional capacity)



P-value: \*\*\*P<0.001 vs placebo; #P=.001 vs DUL.

# CONCLUSIONS

- No firm conclusions regarding differential effects of antidepressant pharmacotherapy on various cognitive domains
- Tally of results from published research yielded no consistent patterns
- Some tentative trends that emerged:
  - Verbal memory was slightly improved with monotherapy
  - Visual and verbal memory were improved by augmentation therapy
  - Improved executive function and cognitive control with augmentation therapy
- Results may be interpreted cautiously as suggesting that antidepressant pharmacotherapy may have a slight beneficial effect on cognitive impairment associated with MDD

# LIMITATIONS

- High degree of variability in study design and data presentation
- Many of the studies were relatively small or assessed selected subgroups of the depressed populations
- It remains unclear whether the findings can be generalized to a larger and more heterogeneous population of depressed individuals
- Studies were generally of short duration, so long-term effects of treatment remain uncertain

# LIMITATIONS

## CONTINUED

- Almost all studies 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
- The potential impact of comorbid medical conditions on cognitive function was generally not addressed

# FUTURE DIRECTIONS

- Further research should seek to overcome substantial methodological limitations of prior investigations
- 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
- Study designs and statistical methods that maximize test validity and minimize confounding factors
- Assessment of treatment effects on specific domains of cognitive function would be valuable