Efficacy of vortioxetine versus other antidepressants on cognitive dysfunction in patients with major depressive disorder

Bernhard T Baune[1], Mélanie Brignone[2], Klaus Groes Larsen[3]

[1]School of Medicine, University of Adelaide, Australia; [2]Lundbeck SAS, Issy-les-Moulineaux, France;
[3]H. Lundbeck A/S, Valby, Denmark

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BACKGROUND

- Patients with major depressive disorder (MDD) often exhibit impairment in cognitive function, including executive function, processing speed, concentration/attention, learning and memory[1]
- Cognitive dysfunction has been identified as a target of pharmacological treatments in patients with MDD[2]
- Nevertheless, only few reviews describe the effect of antidepressants (ADs) on cognitive dysfunction in MDD, focusing mostly on comparisons versus placebo[3-5]

Aims

- To conduct a systematic literature review and network meta-analyses (NMA) to assess the relative effect of different antidepressants on cognitive dysfunction in MDD patients

METHODS

Systematic literature review

- MEDLINE®, Embase®, Cochrane, CDSR, PsychINFO® databases, clinical trial registries, and relevant conference abstracts were searched from database inception date to 13 November 2014
- The review focused on evidence from randomised controlled trials (RCTs) assessing pharmacological interventions and placebo in adult patients with MDD, with no restrictions on gender or race, or publication language
- Included studies underwent a two-stage screening and data extraction process conducted by two independent reviewers, with discrepancies reconciled by a third independent reviewer
- Studies were critically appraised using a comprehensive assessment criteria based on the recommendations in the NICE guidelines
- A feasibility assessment was carried out for determining the approach to assess the relative effect of antidepressants on cognitive dysfunction in MDD

Network meta-analysis (NMA)

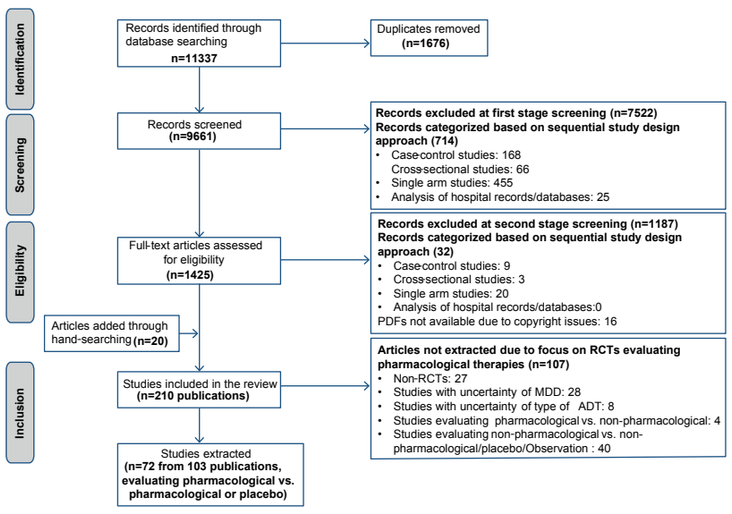
- The relative treatment effects were estimated through the evaluation of the standardised effect size in an NMA taking inter-trial heterogeneity into account
- The statistical model was a two-way ANOVA with random effects and known residual variances varying between treatment groups within studies
- Potential inconsistency was addressed through the concept of node-splitting, i.e. comparing if evidence from direct comparisons are consistent with evidence from indirect comparisons

RESULTS

Systematic literature review

- The database search retrieved 11,337 citations of which 72 RCTs from 103 publications met the inclusion criteria (Figure 1)
- The interventions assessed included ADs of the following therapeutic classes: selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and other non-SSRI/SNRI antidepressants such as monoamine oxidase inhibitors, tricyclic antidepressants (TCAs), and tetracyclic antidepressants.
- Amongst the included studies there was a high rate of variability in trial design and methods, with few studies completed to a high quality level
- The review identified 86 cognitive scales used to assess antidepressants effect on cognitive functioning, most of which were used in only one study
- A total of 12 scales were reported in four or more studies, with the Mini Mental State Examination (MMSE) and Digit Symbol Substitution Test (DSST) being the most commonly reported outcomes in 13 studies each

Figure 1: Flow diagram for identification and selection of studies



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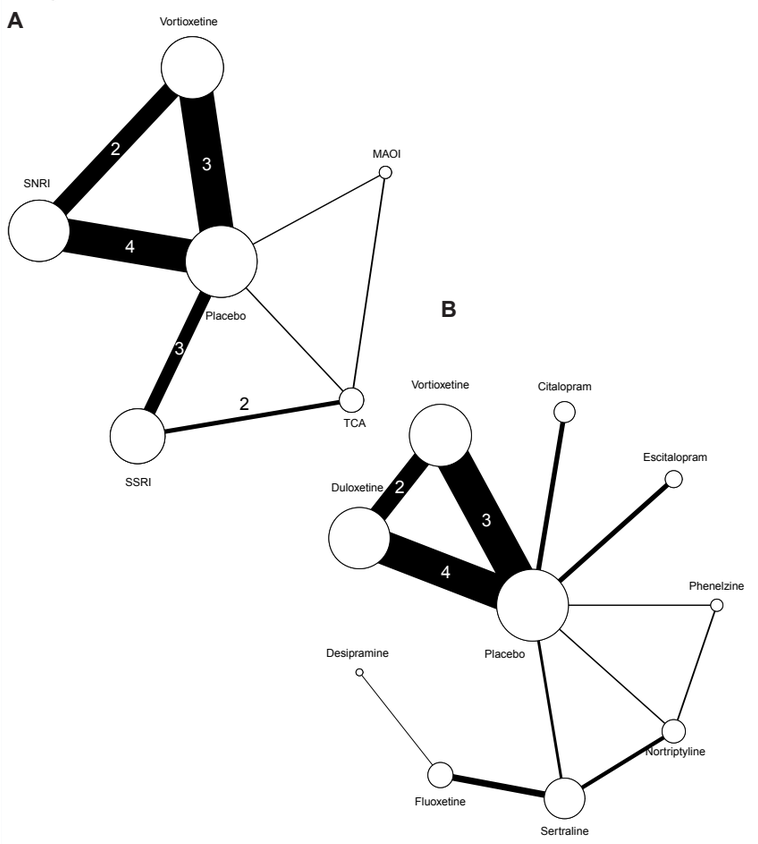
NMA

Networks of evidence

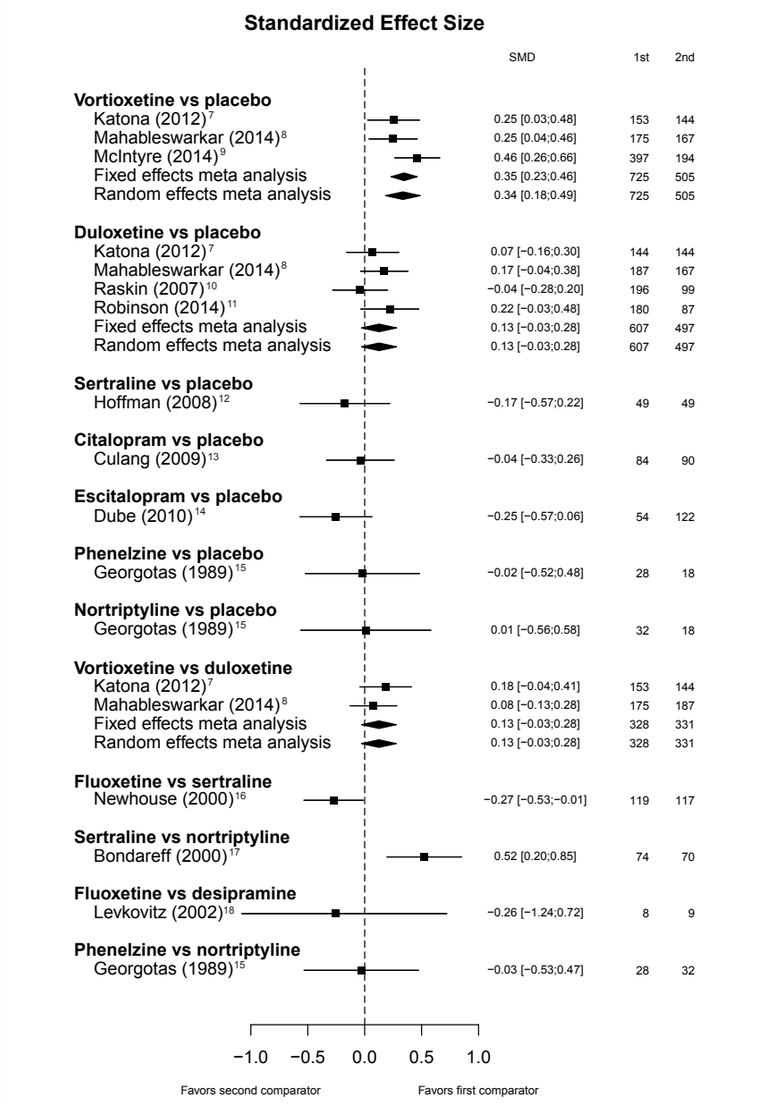
- The DSST was used across 13 of the included RCTs, allowing for a network of evidence to be generated comparing vortioxetine with other antidepressants. One study[6] was excluded in the absence of a common link with the other antidepressants included in the network
- DSST is a recognised measure of cognitive dysfunction as it assesses several of the cognitive domains that are the most impaired in MDD patients (executive function, processing speed and attention) and is recognised as being sensitive to change if treatment is effective[2]
- The number of patients in the included studies ranged from 27 to 602, and the time of DSST assessment varied from 4 weeks to 24 weeks with the majority of studies reporting DSST data at 8 weeks (n=8)
- Two networks were developed: one network by drug class and another by individual antidepressant (Figure 2)
- Meta-analysis of the effect of antidepressants on DSST based on direct evidence from clinical studies included in the DSST network is shown in Figure 3

Figure 2: Network for the A) by AD class analysis and B) by treatment analysis



Note: The size (area) of the nodes is proportional to the number of patients receiving the treatment. The width of lines are proportional to the number of patients in trials with direct comparison between the nodes. The numbers on the lines indicate how many trials with direct comparisons, if there are more than one.

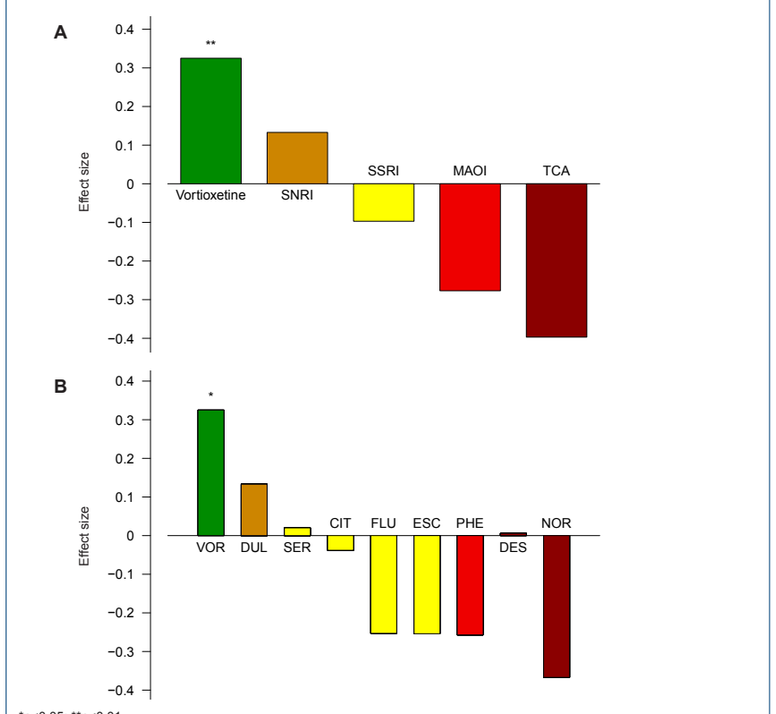
Figure 3: Meta-analysis of the effect of antidepressants on DSST based on direct evidence from clinical studies included in the network of evidence



Effect of ADs on DSST vs. placebo

- Vortioxetine was the only antidepressant showing a statistically significant effect versus placebo in improving cognitive dysfunction as assessed on DSST in MDD patients (standardised effect size on change from baseline compared with vortioxetine: 0.325 [95% CI=0.120; 0.529]) (Figure 4)
- Some of the ADs assessed demonstrated a detrimental effect on cognitive dysfunction in patients with MDD (Figure 4)

Figure 4: Standardised effect size relative to placebo by A) AD therapeutic classes and B) individual ADs



*p<0.05; **p<0.01

Abbreviations: VOR=vortioxetine, DUL=duloxetine, SER=sertraline, CIT=citalopram, FLU=fluoxetine, ESC=escitalopram, PHE=phenelzine, DES=desipramine, NOR=nortriptyline.

Relative effect of ADs on DSST

- Vortioxetine was also either numerically or statistically more efficacious than other included AD classes or individual therapies (Table 1)
- This difference was statistically significant versus SSRIs and TCAs (standardised effect size: 0.423 [95% CI=0.147; 0.698] and 0.722 [95% CI=0.316; 1.129], respectively)
- When comparisons were made between individual antidepressants, vortioxetine was numerically better than all included antidepressants with statistically significant differences versus escitalopram and nortriptyline (standardised effect size on change from baseline compared with vortioxetine: 0.579 [95% CI=0.117; 1.041] and 0.691 [95% CI=0.165; 1.217], respectively)

Table 1: Treatment effect estimates

VOR / VOR	0.193 (-0.013; 0.398)	**0.325 (0.135; 0.516)**	**0.423 (0.147; 0.698)**				0.602 (-0.008; 1.213)	**0.722 (0.316; 1.129)**
0.192 (-0.027; 0.411)	SNRI / DUL	0.133 (-0.032; 0.298)	0.230 (-0.041; 0.502)				0.410 (-0.199; 1.018)	**0.530 (0.126; 0.934)**
0.325 (0.120; 0.529)	0.133 (-0.043; 0.308)	PBO / PBO	0.097 (-0.129; 0.323)				0.277 (-0.313; 0.867)	0.397 (0.022; 0.771)
0.305 (-0.168; 0.777)	0.112 (-0.358; 0.582)	-0.020 (-0.460; 0.420)	SER	SSRI				
0.362 (-0.079; 0.804)	0.170 (-0.268; 0.608)	0.038 (-0.368; 0.443)	0.058 (-0.540; 0.656)	CIT			0.180 (-0.411; 0.770)	0.300 (-0.037; 0.636)
0.578 (-0.018; 1.173)	0.386 (-0.208; 0.979)	0.253 (-0.317; 0.823)	0.273 (-0.089;0.635)	0.215 (-0.484; 0.914)	FLU			
0.579 (0.117; 1.041)	0.387 (-0.073; 0.846)	0.254 (-0.174; 0.682)	0.274 (-0.340; 0.888)	0.216 (-0.374; 0.806)	0.001 (-0.712; 0.714)	ESC		
0.582 (-0.103; 1.267)	0.390 (-0.293; 1.072)	0.257 (-0.405; 0.919)	0.277 (-0.395; 0.950)	0.219 (-0.557; 0.996)	0.004 (-0.760; 0.768)	0.003 (-0.786; 0.792)	MAOI / PHE	0.120 (-0.437; 0.677)
0.319 (-0.984; 1.621)	0.127 (-1.175; 1.428)	-0.006 (-1.297; 1.285)	0.014 (-1.199; 1.228)	-0.044 (-1.397; 1.309)	-0.259 (-1.417; 0.900)	-0.260 (-1.620; 1.100)	-0.263 (-1.650; 1.125)	DES / TCA
0.691 (0.165; 1.217)	0.499 (-0.025; 1.023)	0.367 (-0.130; 0.863)	0.387 (-0.008; 0.781)	0.329 (-0.313; 0.970)	0.114 (-0.422; 0.649)	0.112 (-0.544; 0.768)	0.109 (-0.501; 0.720)	0.372 (-0.904; 1.648) / NOR

Treatment effect estimates in terms of Standardsed effect size with corresponding 95% confidence intervals based on a network meta analysis by treatment (lower triangle) and by AD class (upper triangle). The order of the treatments in the diagonal is based first on the relative efficacy of the AD classes and second on the relative efficacy of the treatments within the classes. A positive estimate indicates that the treatment/AD class to left is numerically better than the one to the right and vice versa. Statistically significant differences in the relative effect estimates are highlighted. Abbreviations: VOR=vortioxetine, DUL=duloxetine, PBO=placebo, SER=sertraline, CIT=citalopram, FLU=fluoxetine, ESC=escitalopram, PHE=phenelzine, DES=desipramine, NOR=nortriptyline.

Ranking

- Based on the NMA by class, the probability of vortioxetine being better than all other classes of ADs and placebo is 97%

Consistency analysis

- Consistency was addressed by node-splitting. There were mild inconsistencies regarding the vortioxetine/SNRI comparison and the placebo/SSRI/TCA comparisons, although none were significant (p=0.085 and p=0.132, respectively)
- Heterogeneity was mainly found in the comparison between vortioxetine and placebo, and was accounted for by the random effects in the NMA model

CONCLUSIONS

- A comprehensive overview of studies assessing the relative effect of antidepressants on cognitive dysfunction in MDD found a high degree of variability in the reporting of cognitive outcomes in RCTs
- Focusing on DSST, which was used across 12 of the studies included in the network, NMA showed vortioxetine to be the only antidepressant demonstrating statistically significant difference versus placebo
- Vortioxetine was numerically better than all included antidepressants with statistically significant differences versus escitalopram and nortriptyline
- The findings of this study support the effect of vortioxetine in improving cognitive function in MDD patients as assessed using the DSST; consistent with findings from clinical studies and meta-analyses[2]

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