BACKGROUND

• Patients with major depressive disorder (MDD) often exhibit impairment in cognitive function, including executive function, processing speed, concentration/attention, learning and memory.

• Cognitive dysfunction has been identified as a target of pharmacological treatments in patients with MDD.

• Nevertheless, only few reviews describe the effect of antidepressants (ADs) on cognitive dysfunction in MDD, focusing mostly on comparisons versus placebo.

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 registers, 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 appropriateness 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 ANDA 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

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 was excluded due to the absence of a common link with the other antidepressants included in the network.

• The 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.

• 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 (8 RCTs).

• 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

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

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

Table 1: Treatment effect estimates

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Standardised Effect Size</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vortioxetine</td>
<td>-0.18</td>
<td>(-0.32; -0.04)</td>
<td>0.004</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>-0.17</td>
<td>(-0.30; -0.05)</td>
<td>0.005</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.00</td>
<td>(-0.17; 0.17)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Table 2: Treatment effect estimates

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Standardised Effect Size</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vortioxetine</td>
<td>-0.20</td>
<td>(-0.35; -0.04)</td>
<td>0.007</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>-0.19</td>
<td>(-0.33; -0.05)</td>
<td>0.008</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.00</td>
<td>(-0.19; 0.19)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

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 differences versus placebo.

• Vortioxetine was numerically better than all included antidepressants with statistically significant differences versus escitalopram and norryptiline in 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.

• 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.

Acknowledgements:

B. T. Baune, M. Brignone, K. Groes Larsen

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

CONCLUSIONS

• Some of the ADs assessed demonstrated a detrimental effect on cognitive dysfunction in patients with MDD (Figure 4).

• Similarly, some of the ADs assessed demonstrated a detrimental effect on cognitive dysfunction in patients with MDD (Figure 4).

• Similarly, some of the ADs assessed demonstrated a detrimental effect on cognitive dysfunction in patients with MDD (Figure 4).

• Similarly, some of the ADs assessed demonstrated a detrimental effect on cognitive dysfunction in patients with MDD (Figure 4).