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REVIEW

Systematic review of randomized controlled trials of candidate treatments for cognitive impairment in depression and methodological challenges in the field

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Abstract
Cognitive impairment is a core feature of Major Depressive Disorder (MDD) but treatments targeting cognition are lacking. Numerous pre-clinical and clinical studies have investigated potential cognition treatments, but overall the evidence is conflicting. We conducted a systematic search following the PRISMA guidelines on PubMed and PsychInfo to evaluate the extant evidence and methodological challenges in randomized controlled trials (RCTs) of biological, psychological and behavioural candidate treatments targeting cognition in MDD. Inclusion criteria were RCTs with a placebo control assessing potential pro-cognitive effects of candidate treatments in MDD. Two independent authors reviewed the studies and assessed their risk of bias with the Cochrane Collaboration's Risk of Bias tool. Twenty-eight eligible studies (24 biological and four psychological or behavioural studies) were identified. Cognition was the primary treatment target in ten (36%) trials and an additional treatment outcome together with mood symptoms in 18 (64%) trials. The risk of bias was high or unclear in 93% of trials due to potential selective outcome reporting or 'pseudospecificity' (*unspecific* cognitive improvement due to reduced depression severity), and/or insufficient details on how the allocation sequence was generated or how blinding was maintained. Several promising treatments were identified, including vortioxetine, erythropoietin, transcranial direct current stimulation and cognitive remediation. However, several common methodological challenges may impede advances in the field. In particular, future trials should select one cognitive composite score as primary

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outcome, screen for cognitive impairment before inclusion of participants and address 'pseudospecificity' issues. Together, these strategies may improve the success of future cognition trials in MDD.

1. Introduction

Patients with Major Depressive Disorder (MDD) present with non-specific cognitive impairment across psychomotor speed, attention, learning and memory and executive functioning (Lee et al., 2012; Rock et al., 2014; Snyder, 2013). Cognitive deficits are present already at depression onset (Lee et al., 2012) and seem to increase with the burden of past depressive illness (Gorwood, et al., 2008; Hasselbalch et al., 2013) and number of episodes (Kessing, 1998), which points to a neurodegenerative component (Maes et al., 2009; Myint and Kim, 2003). Cognitive deficits are typically of medium to large effect sizes during acute episodes (Rock et al., 2014; Snyder, 2013) with about 20% of patients showing severe global impairment (performance ≥ 2 standard deviations below the norm) across several cognitive domains (Gualtieri and Morgan, 2008). Patients with recurrent depression show persistent cognitive impairment in periods of remission which is most pronounced within attention and executive function, while memory deficits are somewhat milder (Bora et al., 2013; Hasselbalch et al., 2011; Rock et al., 2014). This is consistent with meta-analytic evidence for only weak correlation between depression severity and deficits in processing speed, memory and executive function (McDermott and Ebmeier, 2009) and meta-analytic results showing that residual depressive symptoms were not associated with cognitive impairment in euthymic MDD (Bora et al., 2013). Cognitive impairment in MDD may thus be an at least partially separate illness dimension with its own developmental trajectory. Further, detrimental effects of persistent cognitive impairment have been observed on patients' illness prognosis and chances of functional recovery (Jaeger et al., 2006; Judd et al., 1998). Indeed, cognitive impairment has been identified as one of the principal contributors to reduced workforce capacity in MDD *independent* of mood symptoms (McIntyre et al., 2013). Since loss of work productivity constitutes the greatest socio-economic cost of MDD (Olesen et al., 2012), there is an urgent need for novel treatments to target cognitive impairment in MDD.

The past decade has witnessed an intense and increasing research interest into candidate treatments targeting cognition in MDD. Numerous preclinical studies have investigated the potential pro-cognitive effects of pharmacological treatments that act on multiple neurotransmitter systems involved in mood and cognition. These studies showed potential beneficial effects of antidepressant treatments that modulate the monoamine systems, including the new multimodal antidepressant, vortioxetine (Pehrson et al., 2015). Other experimental treatments, including erythropoietin (EPO), insulin, minocycline, angiotensin-converting enzyme (ACE) inhibitors, S-adenosyl methionine (SAMe) and N-acetylcysteine (NAC) have also shown encouraging effects on depression-relevant cognitive deficits in preclinical studies (Bortolato et al., 2016; Carvalho et al., 2014; Miskowiak et al., 2012). However, the translation of the preclinical effects into efficacy on cognition in clinical populations has proven difficult.

A recent meta-analysis assessing the effect of monoaminergic antidepressants versus placebo in nine studies demonstrated small beneficial effects on psychomotor speed and delayed recall, with no significant differences between drug classes (Rosenblat et al., 2016). Another systematic review of the effects of antidepressant monotherapy or new pharmacological augmentation treatments on cognition in acute depression identified treatment-related cognitive improvement in most studies (Keefe et al., 2014). In particular, antidepressant monotherapy seemed to improve verbal memory (which was not possible to assess in Rosenblat et al. (2016)), while augmentation therapy led to broader cognitive improvements across several domains (Keefe et al., 2014). Importantly, however, 'pseudospecificity' of the observed cognitive improvements (i.e., *unspecific* cognitive improvement due to reduced depression severity) cannot be ruled out given patients' concomitant treatment-related reduction in depressive symptoms (Keefe et al., 2014). Consequently, it is difficult to determine whether these interventions had any *direct* pro-cognitive properties. Notably, meta-analytical findings indicate that antidepressant medication may also be associated with poorer executive function (even after adjustment for depression severity) (Snyder, 2013). However in general, antidepressants seem to exert beneficial albeit possibly pseudospecific effects on cognition (Baune and Renger, 2014; McIntyre et al., 2013; Solé et al. 2015). A range of *non-pharmacological* interventions have also shown encouraging cognitive effects including neuromodulatory treatments, exercise and cognitive remediation (CR) (Baune and Renger, 2014; McIntyre et al., 2015). However, a substantial part of this evidence is not derived from randomized controlled trials (RCTs) and its validity is therefore unclear. The present systematic review aims to: (i) critically evaluate and synthesise the evidence from RCTs of biological, psychological and behavioural candidate treatments targeting cognition in MDD, (ii) examine the methodological challenges in the field and (iii) provide suggestions for how to address such challenges in order to advance treatment development targeting cognition.

2. Experimental procedures

2.1. Data sources

Systematic searches following the PRISMA guidelines were performed in the electronic databases PsycINFO and Pubmed in March 2016. In PsycINFO, the following keywords were used: ("Unipolar

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