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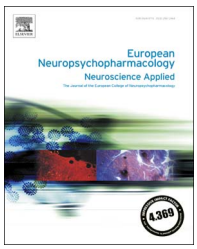

REVIEW

Cognitive enhancement treatments for bipolar disorder: A systematic review and methodological recommendations

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Abstract
Cognitive dysfunction is an emerging treatment target in bipolar disorder (BD). Several trials have assessed the efficacy of novel pharmacological and psychological treatments on cognition in BD but the findings are contradictory and unclear. A systematic search following the PRISMA guidelines was conducted on PubMed and PsychInfo. Eligible articles reported randomized, controlled or open-label trials investigating pharmacological or psychological treatments targeting cognitive dysfunction in BD. The quality of the identified randomized controlled trials (RCTs) was evaluated with the Cochrane Collaboration's Risk of Bias tool. We identified 19 eligible studies of which 13 were RCTs and six were open-label or non-randomized studies. The findings regarding efficacy on cognition were overall disappointing or preliminary, possibly due to several methodological challenges. For the RCTs, the risk of bias was high in nine cases, unclear in one case and low in three cases. Key reasons for the high risk of bias were lack of details on the randomization process, suboptimal handling of missing data and lack of a priori priority between cognition outcomes. Other challenges were the lack of consensus on whether and how to screen for cognitive impairment and on how to assess efficacy on cognition. In conclusion, methodological problems are likely to impede the success rates of cognition trials in

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BD. We recommend adherence to the CONSORT guidelines for RCTs, screening for cognitive impairment before inclusion of trial participants and selection of one primary cognition outcome. Future implementation of a 'neurocircuitry-based' biomarker model to evaluate neural target engagement is warranted.

1. Introduction

Cognitive deficits are common in bipolar disorder (BD) and occur across several domains including sustained attention, verbal memory, and executive function (Bourne et al., 2013). These cognitive deficits persist after clinical remission from mood episodes and are not reversed by antipsychotic or mood-stabilizing treatments (Bourne et al., 2013). The pattern of non-specific cognitive deficits in BD is similar to the profile of cognitive dysfunction in schizophrenia (Barch, 2009) although generally less pronounced (Reichenberg et al., 2009; Schretlen et al., 2007). However, emerging evidence points to global cognitive deficits that are as severe as in schizophrenia in 40–50% BD patients (with performance between −1 to −2 standard deviations below the norm across multiple domains) (Burdick et al., 2014; Jensen et al., 2016). This highlights cognitive dysfunction as a common illness dimension across distinct neuropsychiatric disorders (Millan et al., 2012).

Meta-analytic evidence has shown mild to moderate cognitive dysfunction in individuals at genetic risk for BD (Bora et al., 2009) and we have demonstrated that cognitive impairment in at-risk individuals increases their risk of illness onset (Vinberg et al., 2013). Trait-related cognitive deficits are also present already at the onset of BD and are more severe at later illness stages (Rosa et al., 2014). These findings indicate that the cognitive deficits may reflect both genetic abnormalities and neurotoxic effects of affective episodes, although this 'cognitive neuroprogression hypothesis' remains controversial since only few longitudinal studies have investigated the association between mood episodes and cognitive deficits (Kessing and Andersen, 2004).

Persistent cognitive dysfunction in BD is among the strongest contributors to patients' functional disability and high unemployment rates (Bonnin et al., 2010; Torrent et al., 2012; Tse et al., 2014). Indeed, recent meta-analytic evidence indicated that cognitive deficits together with the illness progression had larger effects on unemployment rates in BD than symptomatology or sociodemographic factors (Tse et al., 2014). Nevertheless, there are no available treatments targeting cognitive dysfunction in BD. Pharmacological treatments may, in fact, have detrimental effects on cognition due to their anticholinergic, extrapyramidal, sedative, and/or blunting effects (Dias et al., 2012). Cognition is therefore emerging as a new important treatment target to enhance patients' functional recovery. In schizophrenia, cognitive deficits and candidate cognition treatments have been studied extensively for several decades, whereas this is a relatively new field in BD (Vreeker et al., 2015). Accordingly, cognition trials in BD still lack methodological consensus and evidence for efficacy of new candidate treatments is unclear (Martinez-Aran and Vieta, 2015).

Burdick and colleagues (2015) recently published an expert opinion paper on methodological challenges in BD cognition trials and how these can be tackled. In the current paper, we conduct a systematic review of the extant evidence from randomized controlled trials (RCTs) and open label studies of novel pharmacological and psychological treatments for cognitive dysfunction in BD and evaluate the quality of the identified RCTs with the Cochrane Collaboration's Risk of Bias tool (Higgins and Green, 2011). Based on this, we discuss a number of key methodological challenges in this emerging field – with focus on the screening of participants and selection of cognition outcomes for tracking treatment efficacy - and provide some methodological recommendations for future cognition trials.

2. Experimental procedures

2.1. Data sources

Studies were identified by searching the PubMed and PsychInfo in February 2016. For PubMed, the following MESH terms were used: "Cognition Disorders" AND "Bipolar Disorder" with following filters activated: Clinical Study, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase IV, Clinical Trial, Phase III, Clinical Trial. For PsychInfo, the following search terms were used: "Bipolar Disorder" AND "Cognitive Impairment" AND ("Clinical trials" OR "Drug Therapy" OR "Intervention").

Only articles written in English were included. Eligible articles reported randomized, controlled or open-label trials investigating potential *pro-cognitive* effects of pharmacological or psychological treatments in patients in bipolar disorder. Conference abstracts were not included. Studies were excluded if they investigated the degree of potential *adverse* cognitive effects of interventions or the effects of interventions on *cognitive side-effects* of electroconvulsive treatment (i.e., not cognitive dysfunction associated with BD *per se*). The reference lists of relevant articles were hand-searched for other studies fulfilling inclusion criteria.

2.2. Study selection and quality assessment

Following the PRISMA guidelines, two authors (KWM and LVK) identified and screened the articles using the above search terms and criteria. Two authors (KWM and LVK) also independently performed the quality assessment of the identified articles. Disagreements were discussed and consensus was reached in all cases.

The risk of bias within and across the included randomized controlled studies was assessed according to the following criteria outline in the Cochrane Collaboration's Risk of Bias tool (Higgins and Green, 2011): (i) generation of an allocation sequence, (ii) adequate allocation concealment, (iii) blinding of participants, personnel and outcome assessors, (iv) incompleteness of outcome data, (v) selective reporting and (vi) other sources of bias.

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