



Cognition as a target in major depression: New developments



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Abstract

Major depressive disorder (MDD) is a highly prevalent and disabling psychiatric illness often accompanied by cognitive dysfunction which may persist even when patients achieve clinical remission. Currently, cognitive deficits emerge as a potential target because they compromise the functional outcome of depressed patients. The aim of this study was to review data for several potential pharmacological treatments targeting cognition in MDD, resulting from monotherapy or adjunctive treatment. An extensive and systematic Pubmed/Medline search of the published literature until March 2014 was conducted using a variety of search term to find relevant articles. Bibliographies of retrieved papers were further examined for publications of interest. Searches were limited to articles available in English language. We describe studies using modafinil, lisdexamfetamine, ketamine, lanicemine, memantine, galantamine, donepezil, vortioxetine, intranasal oxytocin, omega-3, s-adenosyl-methionine, scopolamine and erythropoietin. From these articles, we determined that there are a number of promising new therapies, pharmacological agents or complementary medicines, but data are just emerging. Drugs and therapies targeting cognitive dysfunction in MDD should prove effective in improving specific cognitive domains and functioning, while ruling out pseudospecificity.

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1. Introduction

Major depressive disorder (MDD) is a highly prevalent and disabling psychiatric disorder ranked as the first leading

cause of years lost due to disability (WHO, 2012; Catala-Lopez et al., 2013). This psychiatric condition is associated with higher rates of morbidity and mortality. In addition, the public health cost of this condition is quite high, in part due to both the limited effectiveness and the long delay (up to 12 weeks) of conventionally antidepressant treatments (Kessler et al., 2003; Jick et al., 2004). Different studies conclude that only 30-40% of patients that are optimally treated with first line antidepressants achieve remission (Trivedi et al., 2006; Rush et al., 2011) and more than one

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third of patients with depression are classified as treatment-resistant depression (TRD) (Souery et al., 2006), although the rates may vary depending on the criteria used to define TRD (Vieta and Colom, 2011; Posternak et al., 2004).

In this regard, most patients, including those considered as good responders to antidepressant treatment, continue suffering from residual subsyndromal symptomatology as well as presenting persistent functional impairment, being unable to achieving remission criteria. Some authors point out that sleepiness, fatigue as well as executive dysfunctions constitute some of the most common residual symptoms presented in this group of patients (Stahl and Grady, 2003). Hence, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) included some cognitive symptoms, such as a diminished ability to think or concentrate, or indecisiveness, in the diagnostic criteria for major depression, recognizing that cognitive impairment is a core feature associated to this condition. Nonetheless, it should be remarked that cognitive difficulties may persist in patients even when depressive symptoms have abated or disappeared, with small to medium effect sizes for memory and medium to severe effect sizes for attention and executive function (Bora et al., 2013; Rock et al., 2013).

Despite the main cognitive dysfunctions in MDD are related to executive functions, attention, processing speed and memory domains are also significantly impaired (Bora et al., 2013; Rock et al., 2013; McIntyre, 2013). These cognitive problems compromise the individual's coping abilities and the likelihood of successfully returning to work, which in turn exert a huge impact on functional recovery (Jaeger et al., 2006). In this sense, it is well known that cognitive function represents one of the best predictors of functional outcome in psychiatric patients (Baune et al., 2010; Bonnin et al., 2014). For this reason cognitive impairment emerges as a potential target for both pharmacological and psychosocial treatments, with the final goal of improving functioning.

In order to deal with the aforementioned limitations shown by current antidepressant drugs, the American Psychiatric Association (APA) treatment guidelines recommend augmentation strategies added to antidepressant treatment in those patients showing an inadequate response, since most of the proposed antidepressant monotherapy treatment strategies may not be effective enough to achieve full remission in a substantial group of patients.

So far, most of the widely prescribed antidepressants target the aminergic system, however, evidence suggests that depression is also associated with alterations in other neurotransmitter systems (such as glutamatergic transmission), as well as to a loss of synaptic plasticity in circuits involved in regulating mood and emotions (Sanacora et al., 2008; Kavalali and Monteggia, 2012). Therefore, it seems that the complexity of MDD entails more than the monoaminergic dysregulation. Currently, there is an increasing interest in the role of glutamatergic neurotransmitter system in the pathophysiology of mood disorders and the development of novel and rapid-acting antidepressant drugs. Additionally, there is an urgent clinical need for new treatments that target cognitive enhancement since most current antidepressant medications have no direct pro-cognitive effects - only indirect effects mediated by mood improvement. In this line, the conventional antidepressants available so far seem not to have enough robust

procognitive effects (McIntyre, 2013). The serotonergic-noradrenergic reuptake inhibitors (SNRIs) seem to have a better cognitive profile than serotonin reuptake inhibitors (SSRIs) (Herrera-Guzman et al., 2009). Nonetheless, Baune and Renger, in a preliminary study, found that cognitive effects of SSRIs and selective serotonin reuptake enhancers (SSREs) were similar. They also reported that SSRIs cognitive effects were superior to those observed in the group of patients treated with tricyclic antidepressants (Baune and Renger, 2014).

This systematic review focuses on those studies aimed to assess the cognitive effects resulting from both the combination of different pharmacological agents and current antidepressants, as well as monotherapy, in MDD. Although our main focus of interest are objective cognitive measures, we have included some studies using subjective cognitive measures if the study was considered of clinical relevance for testing new compounds that may influence cognitive variables. Even so, it is necessary to keep in mind the distinction between self-reported/objective cognitive measures given that the relationship between them in patients with affective disorders is controversial and several studies have found that these variables are not associated to a great extent (Svendsen et al., 2012). As Rosa and colleagues pointed out, probably, cognitive complaints are referred to subjective experience of general cognitive problems that are not well characterized when reported by patients (Rosa et al., 2013).

2. Experimental procedures

To identify relevant studies, we performed a PubMed search of new treatments for cognitive dysfunction in human studies with major depressive disorder until March 2014, using the following keywords: "depression" or "major depression" cross-referenced with "cognition" or "cogn*". The same keywords were cross-referenced with different pharmacological agents which were considered that could influence cognitive function as well as new agents that were found in articles reviewed, such as: "aniracetam", "bitopertin", "DHEA", "D-cycloserine", "donepezil", "D-serine", "dextromethorphan", "encelidine", "erythropoietin", "galantamine", "GLYX-13", "intranasal oxytocin", "ketamine", "lisdexamfetamine", "lanicemine", "lurasidone", "memantine", "metyrapone", "mifepristone", "MK-0657", "modafinil", "n-acetyl-cysteine", "NRX-1047", "omega-3", "pramipexole", "propofol", "riluzole", "rivastigmine", "s-adenosyl methionine", "ropinirole", "sarcosine", "scopolamine", "tamoxifen", "traxoprodil", "vilazodone", "vortioxetine". Complementing the database search, pertinent review articles and reference lists from identified articles were hand-searched for additional studies eligible for inclusion in this review not previously identified.

The inclusion criteria for studies were the following:

1. Studies conducted on humans where participants were adults with diagnoses of MDD.
2. Exploring changes in cognitive functions as primary or secondary outcome.
3. A randomized, or quasi-randomized controlled trial or an open study assessing any cognitive measure or social cognition.
4. English language original articles.

The exclusion criteria were:

1. Preclinical studies (such as animal studies).
2. Studies with participants with a diagnosis of depression

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