Journal of Affective Disorders 221 (2017) 205–221

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Review article

Treatment of neurocognitive symptoms in unipolar depression: A systematic review and future perspectives

E. Salagre[a], B. Solé[a], Y. Tomioka[a], B.S. Fernandes[b,c], D. Hidalgo-Mazzei[a], M. Garriga[a], E. Jimenez[a], J. Sanchez-Moreno[a], E. Vieta[a,*], I. Grande[a]

[a] Bipolar Disorders Unit, Hospital Clinic, Institute of Neurosciences, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalonia, Spain
[b] Deakin University, IMPACT Strategic Research Centre, School of Medicine, Barwon Health, Geelong, Australia
[c] Laboratory of Calcium Binding Proteins in the Central Nervous System, Department of Biochemistry, Federal University of Rio Grande do Sul, Porto Alegre, Brazil

ARTICLE INFO

Keywords:
Cognition
Major depressive disorder
Adjuvant treatment
Monotherapy
Systematic review

ABSTRACT

Background: Cognitive symptoms in Major Depressive Disorder (MDD) are persistent and commonly entail neurocognitive impairment and a decline in quality of life. This systematic review gathers the current scientific evidence on therapeutic strategies for neuropsychological impairment in MDD.
Method: A systematic search on PubMed, PsycINFO and Clinicaltrials.gov was carried out on December 2016 according to PRISMA using Boolean terms to identify interventions for the treatment of cognitive dysfunction in MDD. Only English-written articles providing original data and focusing in adults with MDD were included with no time restrictions.
Results: A total of 95 studies reporting data on 40 pharmacological and non-pharmacological interventions were included. Interventions were grouped into the following categories: 1) Pharmacological Therapies (antidepressants, stimulants, compounds acting on NMDA receptors, compounds acting on the cholinergic system, compounds showing anti-inflammatory or antioxidant properties, other mechanisms of action), 2) Physical Therapies and 3) Psychological Therapies, 4) Exercise. There are some promising compounds showing a positive impact on cognitive symptoms including vortioxetine, lisdexamfetamine or erythropoietin.
Limitations: The studies included showed significant methodological differences in heterogeneous samples. The lack of a standardized neuropsychological battery makes comparisons between studies difficult.
Conclusion: Current evidence is not sufficient to widely recommend the use of procognitive treatments in MDD although promising results are coming to light.

1. Introduction

Major Depressive Disorder (MDD) is a chronic and multifactorial disease that presents with depressed mood, anhedonia and somatic symptoms such as lack of appetite or sleep disturbances (Otte et al., 2016). It affects more than 300 million people worldwide (WHO, 2012) and it is a leading cause of disability among young people (World Health Organization, 2014).

Neuroimaging studies have shown that MDD is associated with cerebral volume alterations and functional changes in brain networks related to emotional processing and cognition (Zhang et al., 2016). This is not merely a radiological finding, but it has important implications from a clinical point of view. Indeed, patients with MDD often present with cognitive dysfunction in domains like attention, executive functions, memory or psychomotor speed (Clark et al., 2016), which has been classically considered to be secondary to affective symptoms. Nowadays, however, this traditional view is changing since cognitive dysfunction has proved to be a central and lasting feature of MDD (Bartfai et al., 1991; Hammar et al., 2010), as previously seen in schizophrenia or bipolar disorder (BD) (Martinez-Aran et al., 2002). In addition, the cognitive impairment has been discarded as being exclusive of elderly depression and has been described in patients with first-episode depression (Lee et al., 2012).

Current treatments for MDD present remission rates around 30–40% (Trivedi et al., 2006). Moreover, patients with remitted depression show residual cognitive dysfunction (Hasselbalch et al., 2011), leading to impairment in psychosocial functioning (Al-Sukhni et al., 2015; Hasselbalch et al., 2011). Considering that one of the main targets in the treatment of MDD is achieving a functional recovery besides symptomatic recovery (Hasselbalch et al., 2011; Trivedi et al., 2006), there is growing interest about efficacious treatments for MDD and in particular for cognitive dysfunction in MDD.

* Correspondence to: Bipolar Disorders Unit, Clinical Institute of Neurosciences, Hospital Clinic, Villarroel 170, 08036 Barcelona, Spain.
E-mail address: evieta@clinic.ub.es (E. Vieta).

http://dx.doi.org/10.1016/j.jad.2017.06.034
Received 3 March 2017; Received in revised form 10 May 2017; Accepted 17 June 2017
Available online 19 June 2017
0165-0327/

The aim of this review is to systematically review current scientific evidence on therapeutic strategies for neuropsychological impairment in MDD.

2. Methods

With the aim of identifying all eligible peer-reviewed articles assessing treatments focused on residual cognitive symptoms on MDD we performed a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and guidelines from the Cochrane Collaboration (Higgins and Green, 2011). The systematic search was conducted on December 2016 using Pubmed, PsycINFO and ClinicalTrials.gov databases. The Boolean terms used were: ("major depression" OR "unipolar depression" OR "major depressive disorder") AND ("cogn*" OR "cognition") AND ("treatment" OR "therapy" OR "intervention"). Only studies published in English were included, with no time restriction. Search was completed by manually searching the reference list of the identified articles and reviews related to the topic.

We included studies meeting the following inclusion criteria: 1) studies conducted on human adults with diagnosis of MDD; 2) studies exploring changes in cognitive performance as primary or secondary outcome; 3) open-label, randomized or quasi-randomized controlled trials. The exclusion criteria were: 1) preclinical studies (as animal studies); 2) studies conducted in subjects with a diagnosis of depression secondary to other illnesses (i.e. Parkinson's disease, bipolar depression, post-stroke depression…); 3) comorbid substance abuse; 4) case-report studies; 5) studies evaluating the short-term effects (< 1 month) of electroconvulsive therapy on cognition.

Following these inclusion and exclusion criteria 95 studies were identified (Fig. 1). The results have been organized according to the neurobiological mechanism of action of the compound or intervention.

3. Results

3.1. Pharmacological therapies

3.1.1. Antidepressants

The cognitive tolerability profile of selective serotonin reuptake inhibitors (SSRIs) in the long-term still remains to be clarified (Gorenstein et al., 2006; Popovic et al., 2015). In the short-term, their effects on cognition differ between young (Constant et al., 2005; Gudayol-Ferre et al., 2015; Herrera-Guzman et al., 2010; Wroolie et al., 2006) and elderly (Beheydt et al., 2015; Culang et al., 2009; Culang-Reinlieb et al., 2012; Marano et al., 2015, 2013; Martocchia et al., 2014; Nebes et al., 2003) patients with MDD (Table 1). In the elderly, most of the studies failed to find significant effects of SSRIs on cognition (Beheydt et al., 2015; Culang et al., 2009; Culang-Reinlieb et al., 2012; Marano et al., 2015, 2013; Martocchia et al., 2014; Nebes et al., 2003). For instance, Beheydt et al. (2015) evaluated the effect of escitalopram on cognition and psychomotor speed at 12 weeks in geriatric depressive patients and found a moderate effect on depressive symptoms but scarce changes on cognition and fine motor performance. Bearing in mind the possible slower effect of antidepressants in elderly populations, the authors recommend a longer follow-up to detect changes in cognitive and affective symptoms. On the contrary, positive results in younger patients with MDD have been reported (Herrera-Guzman et al., 2010). Improvements in psychomotor slowing and executive functions have been reported with sertraline after the first 3–7 weeks of treatment (Constant et al., 2005). Similarly, a sample of middle-age women treated with escitalopram for 12 weeks showed statistically significant improvements both in depressive symptoms and in cognitive domains such as cognitive flexibility or information recall (Wroolie et al., 2006). Regarding the serotoninergic-noradrenergic reuptake inhibitors (SNRIs), they have proved to be effective enhancing cognitive performance in domains like executive functions, verbal learning, attention, working memory or verbal processing speed (Lam et al., 2016; Reddy et al., 2016; Tian et al., 2016), even in elderly populations (Raskin et al., 2007; Trick et al., 2004). Herrera-Guzman et al. (2010) found that duloxetine and escitalopram were equally efficient treating cognitive and depressive symptoms, but according to results of exploratory analyses, it has been suggested that duloxetine would exert its pro-cognitive effects regardless of mood improvement (Greer et al., 2014). Currently, several clinical trials focusing on the cognitive effects of escitalopram (NCT00343070), duloxetine (NCT00933439, NCT00062673) and desvenlafaxine (NCT01468610) are being carried out. They will help to provide further evidence on the impact of SNRIs and SSRIs on cognition.

No negative effects on cognition have been found with vortioxetine (Theunissen et al., 2013) and a recent meta-analysis supports its short-term efficacy in MDD (Thase et al., 2016). It has been found that patients with moderate to severe MDD receiving vortioxetine 5–20 mg performed significantly better than the placebo or duloxetine groups (active comparator), regardless of dosage, in tests assessing executive function and attention (Katona et al., 2012; Mahableshwarkar et al., 2015; McIntyre et al., 2014) and also learning and memory (McIntyre et al., 2014). Improvements in cognition were accompanied by an improvement in functional capacity (Mahableshwarkar et al., 2015). Vortioxetine seems to have a multi-domain beneficial effect on cognitive performance (Harrison et al., 2016) and these effects seem to be independent of its effect on depressive symptoms (McIntyre et al., 2016). Ongoing clinical trials will provide further data on the effect of vortioxetine on cognition (NCT02332954; NCT02272517; NCT02234362).

Concerning the rest of antidepressants, the noradrenergic reuptake inhibitor (NRI) reboxetine has shown positive effects on attention and cognitive functioning speed (Ferguson et al., 2003). Bupropion has demonstrated to be as effective as SSRIs improving cognitive performance (Gorlyn et al., 2015; Herrera-Guzman et al., 2008; Soczynska et al., 2014), global function and work productivity (Soczynska et al., 2014). Tianeptine improved cognitive impairment in subjects with moderate to severe MDD (Klasik et al., 2011; Saiz-Ruiz et al., 1998) and, compared to SSRIs, it showed superiority over escitalopram (Jeon et al., 2014) but not over paroxetine (Nickel et al., 2003). As for the monoamine oxidase inhibitors (Roth et al., 1996) or tricyclic antidepressants (Bartfai et al., 1991), evidence remains unclear.

To sum up, evidence supports a beneficial effect of SNRIs, NRIs or bupropion on cognition and suggests that SSRIs would be especially useful treating cognitive symptoms in young patients. Special attention should be paid to vortioxetine and duloxetine, whose action over cognition seems independent of mood improvements. As for the rest of antidepressants, further studies are required.

3.1.2. Stimulants

Modafinil would exert antidepressant effects apparently by modulating the dopaminergic system (Mahmoudi et al., 2015) whilst it has been hypothesized that its possible cognitive-enhancing effects would depend on its noradrenergic action (Müller et al., 2004). Current evidence supports its efficacy as an adjunctive treatment of MDD (Goss et al., 2013), especially in those patients exhibiting fatigue and sleepiness as residual symptoms (DeBattista et al., 2003; Fava et al., 2007), and trials performed in healthy volunteers suggest a procognitive effect (Minzenberg and Carter, 2008). In MDD, one prospective open-label trial assessed the effects of modafinil as an adjunctive treatment on cognitive dysfunction (DeBattista et al., 2004). In this trial, modafinil did not negatively impact on neurocognitive function and secondary analyses pointed out that it could even improve executive function, as seen in healthy subjects (Franke et al., 2017). Recently, modafinil appeared to improve episodic memory and working memory performance in a randomized study including 60 individuals with remitted depression (Kaser et al., 2016) (Table 2).

The utility of lisdexamfetamine (LDX) augmentation in MDD has not