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Effects of remission speed and improvement of cognitive functions of depressed patients

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ABSTRACT

Major depressive disorder (MDD) presents neuropsychological alterations which improve after the treatment, but it might be mediated by clinical variables. Our goal is to study whether the speed of remission of MDD bears any relation to the improvement of the patients' cognitive functioning after a successful treatment. We carried out clinical and neuropsychological assessments of 51 patients with MDD. After these procedures they underwent a 24-week treatment with fluoxetine, and were assessed again with the same battery used prior to treatment. They were arranged into three groups according to how rapid their symptoms remitted. The patients with a rapid remission presented improvements in working memory, speed of information processing, and some executive functions, unlike the other groups. Rapid remitters also improved in episodic memory and executive functions more than the other patients.

1. Introduction

Patients with major depressive disorder (MDD) frequently suffer from alterations in a broad spectrum of cognitive functions including attention deficits (Porter et al., 2003; Weiland-Fielder et al., 2004), alterations in mental processing speed and motor performance (Gualtieri et al., 2006), memory deficit (Gallassi et al., 2006), and executive dysfunctions (Gualtieri et al., 2006; Snyder, 2013). These cognitive alterations could be seen from the first depressive episode (Lee et al., 2012).

This disease is often treated with antidepressants, which increase the synaptic levels of one or more monoamines (Millan, 2004), and these neurotransmitters play a crucial role in modulating affection and cognition (Millan, 2004). For this reason antidepressants could ameliorate the cognitive functions of depressed patients. Several studies with selective serotonin reuptake inhibitors (SSRI) support this idea. Sertraline can also improve memory in depressed patients (Finkel et al., 1999; Bondareff et al., 2000; Doraiswamy et al., 2003; Newhouse et al., 2000), as well as mental processing speed (Finkel et al., 1999; Newhouse et al., 2000), attention and executive functions (Devanand et al., 2003; Rocca et al., 2005; Constant et al., 2005). Other papers suggest that citalopram and escitalopram can improve memory and executive functions in depressed patients (Zobel et al., 2004; Wroolie et al., 2006; Herrera-Guzmán et al., 2009, 2010; Diaconescu et al., 2011; Göder et al., 2011). Cognitive improvements have been reported after MDD pharmacological treatment with fluvoxamine (Koetsier et al., 2002) and paroxetine (Battista-Cassano et al., 2002; Nickel et al., 2003). Fluoxetine, the same SSRI used in this study, can improve memory and mental processing speed (Battista-Cassano et al., 2002; Levkovitz et al., 2002; Finkel et al., 1999; Newhouse et al., 2000; Gallassi et al., 2006). Nevertheless, not all studies found an association between antidepressant treatment and improvement in cognitive functions in depressed patients. The paper by Fergusson et al. (2003), for example, cannot demonstrate cognitive improvements in depression after paroxetine treatment. For their part, Culang et al. (2009) suggested that citalopram does not improve memory and mental processing speed in depressed patients who responded adequately to the treatment. Nebes et al. (2002) suggested that neither nortriptilyne nor the paroxetine SSRI could improve cognition in depression. The work by Gorenstein and Johnson (2006) showed that sertraline could improve cognition in depressed patients, but not fluoxetine. A recent work by Bastos et al. (2013) randomized a large sample to three treatments: psychodinamic psychotherapy, fluoxetine treatment, and combined treatment. Interestingly their results suggest that the psychodinamic psychotherapy and the combination of

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this therapy with fluoxetine can improve several cognitive functions in depressed patients, but this effect was not observed in the group treated with fluoxetine only.

In addition, it should be noted that only between 50% and 70% of the patients respond to the initial treatment with antidepressants (Thase and Rush, 1995), and only about 40% remit with this pharmacological therapy (Warden et al., 2007).In addition, some original studies and meta-analyses suggest that cognitive deficits in MDD tend to remain after the remission of depressive symptoms, at least to some degree (Douglas and Porter, 2009; Herrera-Guzmán et al., 2010).

The effect of antidepressant treatment on the cognitive functions of MDD patients might be mediated by several clinical or response-to-treatment variables. Some papers suggest that clinical variables such as the presence of depressive symptoms after the treatment may be related to a worse neuropsychological performance. The severity of major depressive disorder has been positively related to the severity of the illness's neuropsychological alterations in some original works, reviews, and meta-analyses (McDermott and Ebmeier, 2009; McClintock et al., 2010).The time course of improvement in MDD patients is another clinically relevant variable because remission in MDD implies wellness (Keller, 2004), and some studies suggest that patients who respond rapidly and fully to antidepressant treatment are more likely to sustain treatment gains such as a better prognosis of Axis III disorders, better psychosocial and professional functioning, and continuing wellness (see Keller (2004) for a review). For these reasons some authors consider that remission should be the goal of antidepressant treatment (Judd et al., 2000a, 2000b; Keller, 2004), and that clinicians, patients, and caregivers need to know the probability and the time of onset of antidepressant response and remission (Husain et al., 2004). However, remission speed in itself, and its possible relation to the neuropsychological alterations of MDD, are two scarcely studied topics. A recent paper by Gudayol-Ferré et al. (2013) suggests that the patients with MDD who remit after a pharmacological treatment can be classified into three groups, so that some patients present a rapid remission pattern, others a slow remission pattern, and a third group presents an oscillating remission pattern. Each of the three remission patterns is established according to the form of the remission that the patients present in the Hamilton scale values during the treatment weeks. Rapid remission is understood as the presence of small values in the Hamilton scale rapidly and sustainedly, the slow remission pattern is characterized by a sustained delay in the decrease of scores in the Hamilton scale, but when it does, it is maintained. Finally, oscillating remission is understood as patients who present a mild decrease in the Hamilton scale, followed by a period of stability, then another phase of small increase, then another phase of stability, and so on until they reach remission values in the Hamilton scale similar to the other two groups. That same paper suggests that the patients presenting a slow remission of MDD had a more severe initial depressive symptomatology and worse baseline scores in some neuropsychological variables of speed of information processing and executive functions.

Despite this data, to our knowledge, there are no papers relating the speed of remission to the cognitive improvement experienced by patients with MDD after the pharmacological treatment. In our previous work (Gudayol-Ferré et al., 2013) we studied the possible relationship between the remission speed of MDD and pretreatment clinical, genetic, and neuropsychological measures. Our current hypothesis is that the different patterns of remission in depression may be associated also to the neuropsychological improvements experienced by depressed patients after pharmacological treatment. For that reason, the goal of our paper is to study whether the time pattern of remission shown by the patients in the work by Gudayol-Ferré et al. (2013) after 12 weeks' treatment with fluoxetine is related to the improved cognitive functioning of those same patients after 24 weeks' treatment.

2. Methods

2.1. Participants

The protocol was approved by the Ethics Committee of the Mental Health Center of Michoacán. All the participants signed a written informed consent. The sample included 51 outpatients recruited between April 2007 and September 2008. The sample comprises MDD patients who remained outpatients for the entire study duration and who were in remission after 12 weeks' treatment with fluoxetine, and is a sub-sample of the same sample used in our previous works (Gudayol-Ferré et al., 2010, 2012, 2013). The patients were diagnosed according to DSM-IV criteria for major depressive disorder. The inclusion criteria were diagnostic confirmation with the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) were determined by means of the MINI. This instrument was also used to determine Axis I comorbidities. A score of 18 points or higher in the Hamilton Depression Rating Scale (HAM-D-17) (Hamilton, 1967), age comprised between 20 and 50 years. This age range was chosen to avoid the potential confounding effect of developmental and aging-related variables on neuropsychological scores. The patients must also be free of antidepressants and other psychopharmacological compounds for at least the past four months. The subjects were excluded if they met the DSM-IV criteria or had a history of the following diseases: post-traumatic, obsessive-compulsive, schizophrenia, psychotic, delusional, bipolar, or substance-abuse disorders. The MINI was used to exclude these Axis I comorbid disorders, and also for clinical assessment. Likewise, the subjects with any present or past disease involving the central nervous system, with presence of diabetes, hypertension, cardiac, hepatic, pulmonary, or renal diseases, and systemic infectious diseases were also excluded. Women entering the trial could not be pregnant and had to be oral-contraconceptive-free. Laboratory tests were carried out for the presence of any of the illnesses listed in the exclusion criteria when these ailments required laboratory tests to be diagnosed and their presence was suspected.

2.2. Clinical assessment

All the subjects were clinically assessed through a clinical history and the MINI. The clinical variables measured with the clinical history used in statistical analysis were the number of past depressive episodes, the age at the first depressive episode, and the duration of the present depressive episode in weeks. The MINI was used to assess the presence or absence of melancholic symptoms, suicidal ideation, panic disorder, social phobia, agoraphobia, and generalized anxiety disorder. Also, derived from the MINI, we computed the number of anxiety disorders comorbid with MDD of every patient. The HAM-D-17 was used to assess depression severity at baseline, and biweekly from weeks 2 to 24.

2.3. Neuropsychological instruments

The subjects were assessed with a neuropsychological battery containing traditional instruments and tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB). A comprehensive description and the authorship of these tests are found elsewhere (Robbins et al., 1994; Lezak et al., 2004). The tests administered to the participants and the rest of variables recorded are described below.