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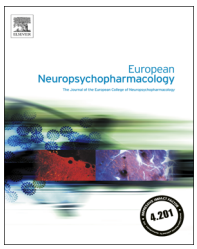

Ondansetron augmentation in patients with obsessive-compulsive disorder who are inadequate responders to serotonin reuptake inhibitors: Improvement with treatment and worsening following discontinuation

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Abstract
Object: The aim of this study was to evaluate low-dose ondansetron as an augmentation strategy in patients with obsessive-compulsive disorder (OCD) who do not adequately respond to serotonin reuptake inhibits (SRIs). *Methods*: Twenty-one OCD patients who had not responded adequately to an SRI received 12 weeks of single-blind ondansetron augmentation initiated at 0.25 mg BID for 2 weeks, and titrated to 0.5 mg BID for an additional 10 weeks. Patients were rated every two weeks using the Yale-Brown Obsessive Compulsive Scale (YBOCS) and Clinical Global Impressions Scale (CGI). Treatment response was defined as an additional 25% reduction in YBOCS score from the score at the initiation of ondansetron augmentation, an end of treatment YBOCS score of ≤ 24 and a CGI-Improvement (CGI-I) score of ≤ 2. Upon completion of treatment course patients were followed for 4 weeks. *Results*: At week 12, twelve of the 21 (57%) patients were responders. The average reduction in the YBOCS score for the overall group was 27.2%. Responders had an average 44% YBOCS score reduction and 76.9% CGI-I reduction. After discontinuation of ondansetron the YBOCS worsened an average of 15.5% in the entire sample and 38.3% in the responder subsample. No clinically meaningful side effects were reported. *Conclusion*: OCD patients who do not adequately respond to an SRI may benefit from

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augmentation with a low-dose of ondansetron. This may provide an alternative approach to augmentation with atypical antipsychotic agents, with a more favorable safety profile.

1. Introduction

Obsessive-compulsive disorder (OCD) is characterized by intrusive thoughts, impulses or images that produce anxiety, and by repetitive behaviors or rituals aimed at reducing anxiety (Diagnostic and Statistical Manual of Mental Disorders, 2000, 4th edition). The quality of life of patients with OCD (Eisen et al., 2006; Rapaport et al., 2005), as well as the quality of life of relatives of patients with OCD (Stengler-Wenzke et al., 2006), is severely affected. Selective serotonin reuptake inhibitors (SSRIs) are considered as first-line intervention March et al., 1997). Despite the existence of effective treatments for OCD (Koran et al., 2007), it is known that 40% of patients do not respond to treatment, and that less than 30% of patients experienced substantial symptom improvement (Hollander and Pallanti, 2002). Several augmentation strategies have been proposed for the treatment of refractory and resistant OCD (Koran et al., 2007; Bloch et al., 2006). Among the most replicated strategies, antipsychotic augmentation has been reported to improve the rate of response, blocking the effects of striatal dopamine release, resulting in improvement of repetitive thoughts and behaviors (Bloch et al., 2006). However, given the side-effect profile of antipsychotics, and since only one third of treatment refractory OCD patients show a meaningful treatment response to antipsychotic augmentation (Bloch et al., 2006), the search for other pharmacological strategies has generated considerable interest. A potential augmentation strategy is based on the co-localization of serotonin-3 (5-HT3) receptors with gamma-amino-butyric acid interneurons in the ventral tegmental area, and therefore on their indirect inhibitory action on cortico-mesolimbic dopaminergic release (Bloom and Morales, 1998). A low dose of ondansetron, the first selective 5-HT3 serotonin blocking agent to be marketed, modulates dopamine (DA) turnover in the nucleus accumbens (NAc) in the mesolimbic reward pathway (Koob, 1992). A net result is reduction in striatal dopamine-induced repetitive behavior (Pallanti et al., 2009). Ondansetron is also a weak antagonist of the 5-HT4 receptor (Hasler et al., 2008) and may bind to other serotonin receptors as well (Tonini, 2005). Previously, in an 8-week, open-label pilot trial (n=8), three out of six OCD patients treated with ondansetron monotherapy (1 mg TID) who completed the study, achieved a clinically significant response (Hewlett et al., 2003). Noteworthy, five patients referred to constipation during this trial. Ondansetron showed efficacy also in a 12-week, single-blind study (n=14), when used as low-dose (0.25–0.5 mg BID) augmentation in OCD patients who had not responded adequately to both SRIs and antipsychotic agents (Pallanti et al., 2009). More recently, in an 8-week, double-blind, randomized combination clinical trial (n=42) in OCD outpatients randomly assigned to receive either ondansetron (4 mg QD) plus fluoxetine, or fluoxetine (20 mg QD) plus placebo, there was a significantly higher efficacy of ondansetron augmentation strategy than with the placebo arm (Soltani et al., 2010). However, since in this last study fluoxetine and ondansetron were initiated simultaneously, the response rate was not purely attributable to the efficacy of ondansetron augmentation strategy, and literature about ondansetron efficacy in the treatment of OCD remains limited by a low level of evidence, lack of safety data and by the short duration of previous trials (Pallanti et al., 2009; Hewlett et al., 2003; Soltani et al., 2010). The objective of the current study was to investigate whether low-dose ondansetron is effective as an augmentation strategy added to SRI monotherapy for OCD patients who had not responded adequately to treatment with SRIs, and if effective, whether symptoms would recur after the drug was discontinued. Moreover this study has the merit compare to the others to administer ondansetron with a slow initiation and low dosing to avoid the severe side effects and to analyses possible relapses during the discontinuation phase, which was lacking in any other study. Demonstration of effectiveness during the treatment period, and relapse of symptoms after discontinuation, would both signal a potential therapeutic efficacy of low-dose ondansetron for this OCD subpopulation. Eventually, if proven safe and effective in larger scale placebo-controlled trials, low-dose ondansetron might replace antipsychotic augmentation use in resistant OCD, thereby eliminating the safety and tolerability issues of antipsychotic augmentation therapy. Moreover this study has the aim compare to the previous ones to administer ondansetron with a slow initiation and low dosing tom avoid severe side effects and to analyses possible relapses during the discontinuation phase, which was lacking in any other study on ondansetron.

2. Experimental procedures

2.1. Participants

All participants were recruited between January and December 2009 at the Institute of Neuroscience, Florence, Italy. Inclusion criteria were: (1) a diagnosis of OCD established by clinical interview with a licensed psychiatrist; (2) inadequacy of treatment response in OCD, defined as a Yale–Brown Obsessive Compulsive Scale (YBOCS) (Goodman et al., 1989) severity score of $\geq$24 and a Clinical Global Inventory (CGI) (Guy, 1976) severity score $\geq$4 after having completed an adequate trial of an SRI at a moderate to high dose for at least 12 weeks; and (3) an age between 18 and 60 years old. Exclusion criteria included a DSM-IV diagnosis of schizophrenia, schizoaffective disorder, organic mental disorder, bipolar disorder, current substance dependence or abuse, and current major depressive episode preceding the onset of OCD. Individuals requiring treatment with psychotropic drugs other than their SRI or undergoing concomitant behavior therapy, or having significant cardiovascular, hepatic, renal or pulmonary diseases, were also excluded. Eligible candidates were invited to undergo further screening including the Structured Clinical Interview for DSM-IV Axis I Disorder (SCID-I) (First et al., 1996) to exclude psychiatric comorbidities, as well as a medical history and a physical examination. All patients

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