European Neuropsychopharmacology (2008) **18**, 455–461

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Naltrexone augmentation in OCD: A double-blind placebo-controlled cross-over study

Revital Amiaz, Leah Fostick, Ari Gershon, Joseph Zohar *

Division of Psychiatry, Chaim Sheba Medical Center, Tel-Hashomer 52621 Israel

Received 3 January 2007; received in revised form 2 January 2008; accepted 22 January 2008

KEYWORDS
Obsessive–compulsive disorder;
Naltrexone;
Addiction;
Opioid antagonist;
Augmentation

Abstract

Current treatments for Obsessive Compulsive Disorder (OCD) rely primarily on serotonergic mechanisms. However, approximately 30% of patients do not respond to serotonin reuptake inhibitors and remain chronically ill. Given the behavioral similarities between some of the compulsive behaviors in OCD and addiction, we hypothesized that the opioid antagonist naltrexone might attenuate compulsions in OCD as well. The effect of naltrexone augmentation to SRI was compared to placebo in 10 OCD outpatients who had not responded to an adequate dose of SSRI or clomipramine for at least 2 months. Participants underwent 5 weeks of treatment with naltrexone or placebo (and 1 week of tapering) in a randomized, double-blind, cross-over design. Patients were evaluated weekly using the Y-BOCS, CGI, HAM-A, and MADRS scales. A two-way repeated measures MANOVA revealed no significant effect for Y-BOCS. However, while receiving naltrexone, patients had significantly higher scores on CGI, MADRS and HAM-A as compared to placebo. The lack of significant findings on OC symptoms could be due to either ceiling effect or alternatively, due to a non-specific exacerbation on anxiety and depression but not on OC symptoms.

1. Introduction

Obsessive Compulsive Disorder (OCD) affects approximately 2% of the population. It is characterized by repeated, uncontrolled obsessive thoughts and ritualistic behaviors — compulsions. OCD tends to be a chronic disorder, with significant social costs and increased suicidal behavior (Fineberg and Gale, 2005). The egodystonic nature of OCD contributes to the suffering which is commonly associated with it, and to the substantial comorbid depression.

Serotonin reuptake blockers have been proven effective against OCD and are the mainstay of anti-obsessive pharmacotherapy (Insel et al., 1985; Zohar and Insel, 1987; Zohar et al., 1987, 1988). The finding that these drugs are more effective than medications affecting other neurotransmitter systems (Hollander et al., 2000; Zohar and Insel, 1987; Zohar et al., 1992) has triggered the hypothesis that serotonin may be involved in the pathophysiology of OCD. However, since about 30% of patients do not respond to serotonergic pharmacotherapy it is becoming increasingly clear that the 5HT hypothesis provides only a partial explanation to our

* Corresponding author. Tel.: +972 3 530 3300; fax: +972 3 535 2788.
E-mail address: jzohar@post.tau.ac.il (J. Zohar).

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doi:10.1016/j.euroneuro.2008.01.006

understanding of the biology of this disorder (Pallanti et al., 2002). For these reasons, many investigators have looked beyond serotonin both for new treatments as well as new insights into OCD's mechanisms, such as dopamine blockers (Denys et al., 2004).

Several lines of evidence suggest that opioids may play a role in OCD. On a behavioral level, the pathological doubt or failure to reach certainty which characterizes OCD has been conceived to reflect a deficit in an opioid-mediated capacity to register reward (Pitman, 1987; Papageorgiou et al., 2003). In this model, a deficit in the reward signal of task completion or decision resolution leads to doubt, and to repetitive behavior such as checking. The signal is thought to be mediated at least in part by endogenous opioids (McDougle et al., 1999). This model is consistent with findings that opioids mediate stereotyped behavior in animals (Verebey et al., 1981; Numberg et al., 1997; Woods-Kettelberger et al., 1997) and that serotonin reuptake inhibition alters endogenous opioid signaling (McDougle et al., 1999). The presence of autoantibodies against the endogenous opioid precursor prodynorphin in OCD patients (Roy et al., 1994) as well as decreased levels of immunoreactive β-endorphin (Weizman et al., 1990) is consistent with the notion that opioid dysfunction may play a role in this disorder. Similarly, one study has raised the possibility of an association between a polymorphism in the μ opioid receptor gene and OCD with tics (Urraca et al., 2004).

Opioids also play an important role in the brain reward system which is thought to mediate motivation and pleasurable activities as well as addiction (Naranjo et al., 2001). Thus it is not surprising that several commonalities between OCD and substance related disorders have been identified, such as increased cerebellum volume and grey matter (Hill et al., 2007), and mutation in the epsilon sarcoglycan (SGCE) gene for myoclonus–dystonia (M–D) (Hess et al., 2007). Moreover, OCD prevalences of 10–12% (among psychoactive substance addicts) and 11.4% (in a sample of 71 opioid dependence patients) have been reported (Friedman et al., 2000) and higher prevalence of OCD was found among alcoholics as compared to non-alcoholic patients (Suzuki et al., 2002). Male relatives of alcoholics who show increased sensitivity to the opioid antagonist naloxone in an endocrinologic assay are also more likely to suffer from obsessive–compulsive symptoms (Mangold et al., 2000). This finding, which suggests that opioid system sensitivity might be a risk factor for both alcoholism and OCD, also links OCD with opioids. In addition, OCD symptom emergence resulting from methadone tapering has been reported (Ginsberg, 2005).

Functional neuroimaging has identified the orbitofrontal cortex as important both in OCD and in cocaine and alcohol cravings (Lubman et al., 2004; Ridley, 1994). This area receives input from mesolimbic areas which are part of the brain reward system (Pelchat, 2002). Phenomenological similarities between alcohol abuse and OCD have prompted some investigators to speculate that some of the thoughts and behaviors exhibited by alcoholics represent special cases of obsessive thought (about alcohol) (Anton, 2000, Moak et al., 1998) and compulsive (drinking) behavior (Modell et al., 1992). The level of compulsivity and obsessionality in opioid dependence was comparable to that found in OCD and alcohol addiction (Friedman et al., 2000). Moreover, both OCD and long-term abstinent heroin addicts share a common impairment of working memory and attentional deficits (Papageorgiou et al., 2003). Given these similarities, several groups have tried pharmacological agents useful in substance related disorders as a potential treatment for OCD (Koran et al., 2005; Papageorgiou et al., 2003).

Long acting opioid agonists are a widely used treatment for opiate addiction (Kreek, 2000). In a meta-analysis of randomized control trials of 2861 patients, the opioid antagonist naltrexone has been shown to be effective in short-term reduction relapses in alcohol-dependent patients (Srisurapanont and Jarusuraisin, 2005). It has been proposed that naltrexone attenuates the opioid contribution to the rewarding effects of alcohol in the mesolimbic dopamine pathway (Lee et al., 2005).

There have been several reports of opioid agonists as potential OCD treatments. Koran et al. reported that oral morphine caused transient relief of OCD symptoms in some patients in a double-blind trial (Koran et al., 2005). Shapira et al. reported improvement as measured by Y-BOCS score in an open trial of 7 patients treated with tramadol (Shapira et al., 1997). Warneke (1997) described two cases, one of trichotillomania and the other of OCD, which were treated first with naltrexone (with a moderate improvement) and later with oral morphine 20–40 mg every 5–8 days (with a major improvement of symptoms). Goldsmith et al. (1999) reported a case of OCD which responded to tramadol monotherapy.

Reports are mixed regarding to the effects of opioid receptor antagonists on OCD symptoms. Insel and Pickar (1983) reported that acute doses of naltrexone (0.03 mg/kg, i.v.) exacerbated chronic obsessive doubt in two OCD patients. However, Keuler et al. (1996) found no significant improvement or exacerbation in self- or patient-rated measures of OC and anxiety symptoms relative to placebo in a group of 13 adults with OCD given naloxone (175 μg/kg i.v.) in a double-blind, placebo-controlled design. However, three of the 13 patients did demonstrate an exacerbation of OC and anxiety symptoms, similar to that described by Insel and Pickar (1983). In contrast, Sandyk described two drug free Tourette patient cases with marked improvement in OCD symptoms, and some reduction in motor tics, after naloxone administration (Sandyk, 1987). Recent studies have shown naltrexone to be effective in improving symptoms of pathological gambling (Kim et al., 2001), kleptomania (Grant and Kim, 2001; 2002), compulsive sexual behavior (Grant and Kim, 2001), and in impulse control disorders (Kim, 1998).

In light of the similarity between OCD and substance abuse, especially alcohol abuse, we hypothesized that naltrexone might help a subset of OCD patients, namely resistant cases. Our rationale was that in this subset of patients, compulsive behavior might represent an addiction reinforced by an opioid-mediated reward signal. If the reward was blocked, we surmised, the compulsive behavior would attenuate with time. We therefore speculated that augmentation of serotonin reuptake inhibitors (SRIs) with naltrexone would improve obsessive–compulsive symptoms in OCD patients who had not responded or not fully responded to SRI treatment alone.

2. Subjects and methods

2.1. Patients

Twelve patients from our OCD clinic aged 18 to 65 were recruited to the study. Out of the 12 recruits, one participant took medication only 1 day, and one did not take study medication at all. Both participants