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

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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 two months. Participants underwent 5 weeks of treatment with naltrexone or placebo (and one 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; Zohar et al., 1988). The finding that these drugs are more effective than medications affecting other neurotransmitter systems (Zohar and Insel, 1987; Hollander et al., 2000; 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 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 have 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 was 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 and colleagues 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 20-40mg 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 (0.03mg/Kg, i.v.) exacerbated chronic obsessive doubt in two OCD patients. However, Keuler (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 (175µg/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 (Insel and Pickar, 1983). In contrast, Sandyk described two drug free Tourette patients cases with marked improvement in OCD symptoms, and some reduction in motor tics, after naloxone administration (Sandyk, 1987). Recent studies have showed naltraxon 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

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 one day, and one did not take study medication at all. Both participants were dropped out before any evaluation was done, leaving 10 patients, five men and five women, with a mean (SD) age of 34.6(10.5), who participated and completed the study. Using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1996), patients were diagnosed by a senior psychiatrist (JZ, RA) as suffering from OCD as their primary disorder for at least 3 years, according to DSM IV criteria, eight of them had a past diagnosis of major depressive disorder (MDD). All patients had failed 2 or more adequate SRI trials. Concurrent benzodiazepine, where in use, was continued with dose unchanged. Dosages of SRI (SSRI, clomipramine) and benzodiazepine at study entry were all stable for at least 2 months prior to study inclusion. Excluded were subjects with unstable medical illness and relative contraindication to naltrexone administration such as liver disease. Eligible subjects also had no history of substance abuse, psychosis, or mania. Concurrent OCD-focused behavioral therapy was an exclusion criterion. After the study was fully explained, all patients signed an informed consent.

Study Design

After the screening visit subjects were enrolled for 11 weeks. A cross-over double-blind design was employed in the study. Each patient was randomized to either naltrexone or placebo for five weeks, and then following one week of tapering off, the alternative treatment (placebo/naltrexone) was given.

Study Medication

Naltrexone 50 mg/placebo tablets were used. Dosage was increased to two tablets (naltrexone 100mg) after one week of treatment. This dosage was used, based on
previous studies that showed improvement of OCD symptoms among alcohol abuse patients who were treated with naltrexone 50-100mg (Garbutt et al., 1999; Glazara et al., 1997; Volpicelli et al., 1992) On the sixth week (tapering off week) patients were given one tablet for three days and four days of no-treatment.

Assessments

The screening visit included administration of the SCID, medical and psychiatric history and drawing blood for liver function and standard laboratory tests. Yale-Brown OCD Scale (Y-BOCS) (Goodman et al., 1989), Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), Hamilton Anxiety (HAM-A) (Hamilton, 1959), and Clinical Global Impression – Improvement (CGI-I) (Guy, 1976) were administered at baseline and every week for 11 weeks. Liver function was closely monitored before and after each phase of treatment.

Statistical analysis

To compare the effects of naltrexone versus placebo, four different two-way repeated measures ANOVA were carried out for each scale, with treatment type (naltrexone/placebo) and week of treatment (0,2,3,4,5) as within variables and the order of medications (placebo-naltrexone versus naltrexone-placebo) as a between variable. Post-hoc paired t-tests were performed when significant effects and interactions were found.

3. Results

Table 1 details the characteristics of the 10 patients that completed the study. All subjects had failed at least 3 adequate SRI trials for OCD. Six of the patients had at least one adequate augmentation with atypical antipsychotic drug, four had adequate lithium augmentation. Concurrent medications included SSRIs (N=9), clomipramine
(N=1), and benzodiazepines (N=8). Naltrexone was generally well tolerated. Mild headaches and drowsiness were reported in five of the patients.

Patients' scores on YBOCS, CGI, MADRS and HAM-A are described in Table 2. Repeated measures analysis revealed no differences in YBOCS between naltrexone and placebo, or between weeks of treatment (figure 1). However, a significant effect was found in CGI for both treatment type ($F_{(1,8)}=14.39, p<.01$), week of treatment ($F_{(4,32)}=4.52, p<.01$), and for the interaction of treatment type X week of treatment ($F_{(4,32)}=6.42, p<.005$, figure 2). As demonstrated in figure 2, CGI was lower for patients receiving naltrexone at week 0 ($t_{(9)}=2.71, p<.05$), but significantly higher at week 2, 3, and 4 ($t_{(9)}=-2.45, p<.05; t_{(9)}=-2.38, p<.05; and t_{(9)}=-4.99, p<.01$, respectively). No difference was found between groups in week 5.

Treatment type was also found to differ in MADRS ($F_{(1,8)}=5.63, p<.05$, figure 3). Mean MADRS score was found to be higher among patient receiving naltrexone than in patients receiving placebo ($t_{(9)}=2.27, p<.05$). A significant interaction between treatment type X week of treatment was found for HAM-A ($F_{(4,32)}=2.86, p<.05$, figure 4). However, no significant difference was found between naltrexone and placebo in any of the treatment weeks.

The effect of the order of medications given to the subjects was not found to be significant in either of the scales measured.

4. Discussion

This double-blind, cross-over study show that naltrexone was associated with higher scores on MADRS and CGI in OCD patients as compared to treatment with placebo. These findings suggest that opioid antagonists are associated with a non-specific increase in depression and anxiety in OCD patients.
This study has several limitations. First, it has a relatively small sample size (10 patients). We sought to reduce this limitation by using a cross-over design. Inherent in this design is the possibility for an order of treatment effect. However, this effect was not found, despite being looked for specifically. In spite of the small sample studied, significant results were obtained, as for the worsening of symptoms among patients receiving naltrexon, as compared to placebo. Secondly, we included in the study only partial- or non- responders to previous treatment, hence limiting the generalizability of the data to this subset of patients. This could also be the reason for the lack of significant findings in the YCOCS, as including non responders with already very high Y-BOCS score might cause a ceiling effect in the scores of this scale. In the other scales, however, which did not have as higher scores, the exacerbation is evident.

Another limitation of this study is the concomitant SRIs that the patients were receiving. For this reason, the study does not provide us with information regarding the role of naltrexone per se, but about the effect of naltrexone augmentation in resistant OCD patients. Also, the heterogeneity of the anti-obsessive medications (clomipramine, fluvoxemine, fluoxetine, or paroxetine) might obscure specific interactions between a particular anti-obsessive drug and naltrexone. The main conclusion is therefore limited to the detrimental effects of naltrexone and serotonergic antiobsessive medications as a class.

Lastly, Chappell et al. (1992) suggested that naltrexone might have a therapeutic window, meaning that different doses can cause different responses. While a dose of 0.3 mg/Kg did not affect OCD patients (Keuler et al., 1996) or cause symptoms
exacerbation (Insel and Pickar, 1983), use of a lower dosage has brought relief in OCD symptoms (Sandyk, 1987). In the current study we used 50mg-100mg of naltrexone which increased symptoms related depression and anxiety, but not to OC. Only testing different dosages of naltrexone could further examine this "therapeutic window".

Despite the above mentioned limitations, there was a significant signal (exacerbation) that is worth noting. Higher resolution on symptomatology done in the current study, differentiated between general effect of naltrexone on the patients’ depression and anxiety and between specific effect on OC symptoms. The lack of a specific effect of naloxone on OC symptoms is in line with the study of Keuler et al. (1996) which also failed to detect specific changes after naltrexone administration.

Recent studies have showed naltraxon 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). The differences in outcome between these studies and the current might represent a difference in treatment outcome between OCD and OC spectrum disorders.

Several potential explanations can be entertained from this study. Firstly, that compulsive behavior does indeed produce a reward signal. However, by attenuating the reward signal with naltrexone, patients needed to engage in more compulsive behavior in order to achieve the desired reward. Despite this, naltrexone might still have a role in the treatment of OCD in the context of behavior therapies which are
based on extinction of the reward from compulsive behavior. An alternative model which considers that it is not only the opioid-mediated reward system, but also its processing or interaction with other neural pathways that is deficient, would be in line with our results as well as those of the opioid agonist studies.

The findings of an increase in CGI, MADRS and HAM-A are in line with previous studies in which naltrexone augmentation was associated with increase in symptomatology (Insel, and Pickar, 1983) . The modest effect of morphine (Koran et al., 2005) and tramadol (Shapira et al., 1997; Warneke, 1997; Goldsmith et al., 1999) might also be explained by the relatively weak and indirect effect of naltrexone observed in this study. However, the findings are in contrast to the beneficial effect of naltrexone in other types of compulsive spectrum behaviors, such as pathological gambling, kleptomania, and compulsive sexual behavior. As all of these behaviors are related more to the impulse end of the compulsive-impulsive spectrum, naltrexone challenge might be considered as a potential tool for mapping the compulsive-impulsive dimension; if it is associated with an exacerbation, then it might be reflecting the compulsive end (which benefits from opioid agonist), and if it is associated with beneficial effect, than it might point out more toward the impulsive end, an end in which the ritualistic behavior might be considered as more impulsive than compulsive.
References


Montgomery SA, and Asberg M. A new depression scale designed to be sensitive to change. British Journal of Psychiatry 1979, 134: 382-38


Roy BF, Benkelfat C, Hill JL, Pierce PF, Dauphin MM, Kelly TM, Sunderland T, Weinberger DR, Breslin N. Serum antibody for somatostatin-14 and


Table 1. Characteristics of patients included in the study

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Table 2. Patients' scores on YBOCS, CGI, MADRS, and HAM-A pre and post Naltrexone phase

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Figure 1. Mean YBOCS score for patients receiving naltrexone and Placebo in each week of treatment
Figure 2. Mean CGI score for patients receiving naltrexone and placebo in each week of treatment

a CGI for placebo is significantly higher than for naltrexone
b CGI for naltrexone is significantly higher than for placebo

Figure 3. Mean MADRS score for patients receiving naltrexone and placebo in each week of treatment. MADRS total score was significantly higher for naltrexone than placebo.
Figure 4. Mean HAM-A score for patients receiving naltrexone and placebo in each week of treatment. A significant interaction between treatment group and week of treatment was found.