

Naltrexone in Obsessive-Compulsive Disorder: an Open- Label Trial

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Objective: In spite of introduction of novel drugs, Obsessive-Compulsive Disorder (OCD) has still found no suitable treatment. On the other hand, high rates of co-morbidity of OCD with bipolar spectrum disorders are increasingly recognized. Mood switching and development of rapid cycling with antidepressants are significant problems in these patients. From this viewpoint, introducing a non-antidepressant anti-OCD drug has great theoretical and clinical importance. In this open-label clinical trial we evaluated the effects of naltrexone on OCD symptoms.

Method: In this study, 23 OCD outpatients treated with a fixed dose of clomipramine, fluoxetine, or both, for at least 3 months before trial underwent treatment with naltrexone, 25 to 100 milligrams a day as adjunctive treatment. Change in symptoms was evaluated by Yale-Brown Obsessive-Compulsive Scale (YBOCS), Persian version, administered at baseline and at the end of the 2 months trial.

Results: Seven patients dropped out of the study before the end of the 2 months: 4 patients for non-response and 3 patients for intolerable side effects. Sixteen patients, 9 females and 7 males, completed the study. The most frequent co-morbid disorders found in these patients were bipolar spectrum disorders (68.7%). Non-parametric (Wilcoxon Signed Ranks Test) and parametric (paired t-test) analyses both showed significant reductions in YBOCS ratings after naltrexone treatment ($P < 0.001$). Two patients remained symptom free over 6 months after discontinuation of all medications.

Conclusion: Although small sample size and open design of the trial make the results tentative, it appears that naltrexone may be effective on at least certain subgroups of OCD patients, especially those with both OCD and bipolar spectrum disorders. Long-term effects of the drug after discontinuation should be addressed in future double-blind studies.

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Introduction

In spite of introduction of novel drugs, especially medications working on the serotonergic system, obsessive-compulsive disorder (OCD), has still not found a suitable treatment. All Meta-analyses have shown efficacy of serotonergic drugs, especially clomipramine, in the treatment of OCD (1-5), but results have not been dramatic. Piccinelli et al. for example reported 61 and 22 to 28 percent cure rates for clomipramine and other serotonergic drugs respectively (3).

On the other hand, there are an increasing number of reports about co-morbidity of OCD

with bipolar spectrum disorders. Such cases are characterized by more frequent aggressive, impulsive, sexual, religious, hoarding, and repetition compulsions (6), more episodic course (6-8), higher rates of suicide attempts (6), and less favorable response to antidepressant anti-OCD drugs (6). The prevalence of this type of co-morbidity in OCD patients is not low, and it may be more common than the co-morbidity of OCD and unipolar depression (9). A clinically important issue in this regard is the risk of switching and induction of manic or hypomanic episodes after antidepressant treatment (6, 7, 10-13). It is suggested that, "when bipolar and obsessive-compulsive disorder co-exist, bipolarity should take precedence in diagnosis, course, and treatment considerations" (11). From this point of view, introduction of a non-

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antidepressant anti-OCD medication is clearly important.

There are several reports about the effectiveness of naltrexone in treating OCD-related disorders, e.g. pathological gambling (14-21), self-injurious behaviors (22-26), adult stereotypic movements (27), trichothillomania (28), compulsive sexual behavior (29,30), and kleptomania (30-32), in addition to the better studied indications of the drug in opioid addiction (33), and alcoholism (34-36). However, we are aware of only one report on the effectiveness of naltrexone in treatment of OCD by Lorne Warneke who reported successful treatment of six patients with OCD, trichotillomania, and pathological gambling with naltrexone and morphine (37).

Our experience in the use of naltrexone in the treatment of OCD began with the treatment of a 27 years old single female with a ten-year history of social phobia, severe aggressive behavior, and washing compulsions. Years of treatment with various antidepressants, benzodiazepines, and antipsychotics produced no significant improvement. Therefore, assuming that the observed effects of naltrexone on impulsive disorders could be extended to OCD cases as well, we began treatment with 25 milligrams per day of naltrexone. Surprisingly, two weeks later the patient reported almost complete remission of washing compulsions. This incidental finding urged us to evaluate effects of naltrexone on OCD in this open-label clinical trial.

Materials and Methods

23 consecutive OCD outpatients without mental retardation or history of psychosis whose disorder was diagnosed clinically by a psychiatrist based on DSM-IV diagnostic criteria participated in this open-label clinical trial after the study was fully described to them and informed consent was obtained. Only patients were included who had been maintained on a fixed dose of clomipramine, fluoxetine, or both, for at least 3 months before beginning of the trial. This inclusion criterion was adopted especially with respect

to ethical considerations. For the same reason, the dose of standard anti-OCD medications remained fixed throughout the trial.

A two-month trial period began after administering baseline Yale-Brown Obsessive-Compulsive Scale (YBOCS), Persian version, by a psychometrician. YBOCS is a valid and reliable instrument for assessing the severity of OCD symptoms and their response to treatment (38-41). During the trial, 25 to 100 mg per day of naltrexone was prescribed based on tolerability and response to medication.

Seven out of the 23 patients dropped out trial; three for intolerable side effects (predominantly headache), and four for experiencing no effects of the medication. Sixteen patients completed the trial.

At the end of the two-month trial, YBOCS was readministered and data analyzed parametrically (t-test), and non-parametrically (Wilcoxon Signed Ranks Test).

Results

Nine out of 16 patients were female (56.3%). Half of the patients were single and half were married. The average age of participants was 29 years (SD = 6.7 years). The age of onset of OCD in average was 19.1 years (range=10-28 years), and patients suffered from the disorder for an average of 8.1 years (range=2-23 years).

At the beginning of the trial, 4 patients were treated only with clomipramine (110 mg/day on average), 4 patients were treated only with fluoxetine (27.5 mg/day on average), 4 patients were treated with both fluoxetine (range=10-80 mg/day) and clomipramine (range=25-250 mg/day), and 1 patient only with antipsychotics (fluphenazine and chlorpromazine).

The most frequent co-morbidities found in diagnostic interviews were bipolar spectrum disorders in 11 patients (68.7%): 10 patients were cyclothymic (with or without bipolar II disorder), and one patient who was treated with antipsychotic drugs was diagnosed as bipolar I disorder. Other co-morbid disorders were social and specific phobias, trichothillomania, bulimic behaviors, nail

biting and other stereotypic movement disorders, and impulsivity.

Patients were treated with an average daily dose of 59.4 milligrams of naltrexone (range=25-100 mg/day). Nine patients (56%) reported mild adverse effects of naltrexone, most commonly headache, which lasted for one week after beginning of trial.

Table 1 presents severity of OCD symptoms before and after treatment with naltrexone based on ratings on YBOCS. Analysis of these data with Wilcoxon Signed Ranks Test showed statistically significant reduction in "Obsessions" ratings ($p < 0.001$) in all patients. It also showed significant reduction in "Compulsions" ratings in 15 patients ($p < 0.001$), and in the total ratings in all patients ($p < 0.001$).

Table 1: Means and standard deviations of YBOCS ratings before and after treatment with naltrexone, analyzed by Wilcoxon Signed Ranks Test (n=16)

	Before Treatment	After Treatment	Change score	P
Obsessions	14.7 ± 3.4	7.6 ± 2.7	7.1 ± 3.9	<0.001
Compulsions	13.6 ± 4.0	7.7 ± 3.8	5.9 ± 3.1	<0.001
Total	28.3 ± 6.4	14.8 ± 5.4	13.5 ± 6.2	<0.001

Table 2 presents changes of ratings on YBOCS before and after treatment based on sex. It appears that men reported more reduction in symptom severity, but in statistical testing using the Man-Whitney test, this difference was not statistically significant.

On both obsessions and compulsions, the magnitude of change was mostly between 5 to 9 points (56.2%). A one-Sample Kolmogorov-Smirnov test showed that data obtained from YBOCS were normally distributed, so a set of paired t-tests were also conducted which supported the results of Wilcoxon Signed Ranks Tests.

Table 2: Means and standard deviations of change scores on YBOCS after treatment with naltrexone based on patient sex

	Females (n=9)	Males (n=7)
Obsessions	6.1±3.2	8.4±4.5
Compulsions	6.2±2.9	5.6±3.7
Total	13.1±5.5	14.0±7.8

Clinically, all patients who responded to naltrexone did so during the first two weeks of trial, although the time course of response was not evaluated quantitatively.

Discussion

Parametric and nonparametric analyses showed that naltrexone may be effective in OCD as an adjunctive treatment. Small sample size and open-label design of the trial make the results tentative. A high rate of drop out due to no response may have shifted the results towards very significant p values. It is also possible that our sample was not representative of the population of patients with OCD as 11 out of 16 patients suffered from both OCD and bipolar spectrum disorders. This comorbidity might have biased our results. Whether or not comorbid bipolar spectrum disorders moderate the response to naltrexone in OCD patients needs to be investigated in future studies.

An interesting finding of the study is that nearly all patients who responded to medication did so during the first two weeks of the trial. If corroborated by future studies, this and other findings from this study raise new questions about the mechanism of action of naltrexone in treatment of OCD specifically, and the role of opiate system in OCD psychopathology in general. One distinct possibility is that the effect of naltrexone on OCD symptoms is similar to its effect on addictive disorders, i.e., up-regulation of opioid receptors (42-44). Other possible mechanisms of action need to be explored in future studies.

Effectiveness of naltrexone in OCD should be evaluated in large double-blind clinical trials. However, the results of this pilot study are promising as they present the prospect of developing more specific treatment strategies for OCD in which non-antidepressant anti-OCD medications with a low risk of switching in mood and development of rapid cycling would have a cardinal role (6-11). From a theoretical standpoint, if the role of naltrexone in OCD is confirmed by other studies, it is possible to postulate that a wide range of impulsive and compulsive disorders

and behaviors besides addictive disorders share a biological vulnerability, although they manifest differently (45-50).

Two patients in our sample stayed symptom-free more than six months after discontinuation of naltrexone and other medications. This finding is similar to the case reported by Crews and coworkers (51) of a young female with self-injurious behaviors who stayed symptom-free over one year after discontinuing naltrexone. Better understanding of the long-term response to naltrexone would require studies with longer follow up.

Conclusions

This study suggests that some OCD patients may benefit from naltrexone, a non-antidepressant medication with a unique time of onset of action and, possibly, enduring effects after discontinuation. Future double-blind clinical trials should investigate more fully the possible role of naltrexone in treatment of OCD.

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