Combination of Citalopram and Nortriptyline in the Treatment of Obsessive-Compulsive Disorder: A Double – Blind, Placebo-Controlled Trial

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Objective: The fact that some antidepressants with strong effects on serotonin reuptake blockade fail to relieve obsessive-compulsive symptoms has caused growing interest in investigating noradrenergic function in obsessive-compulsive disorder (OCD) . In light of the above, we undertook a trial to investigate whether the combination of citalopram with nortriptyline is more effective in treating obsessive-compulsive symptoms than citalopram alone.
Method: 40 patients who met the DSM-IV criteria for OCD were included in the study. Patients were allocated in a random fashion: 20 patients to citalopram 40mg /day plus nortriptyline 50mg /day, and 20 patients to citalopram 40mg /day plus placebo.
Results: Both protocols significantly decreased the scores of the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) over the trial period, but the combination of citalopram and nortriptyline showed a significant superiority over citalopram alone in the treatment of OCD.
Conclusion: As this study indicates, nortriptyline improves the efficacy of citalopram. In addition, a rapid onset of action is one of the advantages of this combination. This study supports further investigation of the noradrenergic– serotonergic hypothesis in OCD.
Key Words:
Citalopram, Combination, Drug therapy, Nortriptyline, Obsessive-compulsive disorder

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Obsessions, compulsions and rituals have been recognized as abnormal cognitions and behaviors for several centuries. These symptoms and signs, which have been variously referred to in different cultures and ages, are encompassed under the present diagnosis of obsessive-compulsive disorder (OCD) (1,2). Obsessions are intrusive, recurrent, and unwanted ideas, thoughts or impulses that are difficult to dismiss despite their disturbing nature. Compulsions are repetitive behaviors, either observable or mental that are intended to reduce the anxiety engendered by obsessions.

Although we can effectively treat many patients with OCD by combinations of medication and behavior therapy, OCD patients tend to respond to medication with only a 30–60% reduction in symptoms, and patients tend to remain chronically symptomatic to some degree despite the best of pharmacological interventions(3). Although some patients respond to a variety of drugs, the mainstay of pharmacological treatment for OCD is antidepressant drugs, especially those with prominent serotonergic reuptake blocking properties(2). Moreover, many studies using direct serotonergic agonists, such as m-chlorophenylpiperazine, and serotonergic antagonist, such as metergoline, suggest that brain serotonergic systems may be intimately involved in the pathogenesis of OCD (4,5) Therefore, in this study citalopram was chosen because it is a selective serotonin reupake inhibitor (SSRI).

Meta-analytic studies (6,7) have suggested that clomipramine may be more effective in reducing obsessive-compulsive symptoms than agents that inhibit serotonin reuptake more selectively. This observation has led to the proposal that clomipramine's action as a norepinephrine reuptake inhibitor may contribute to its efficacy as an antiobsessional agent (6). Although there is less data supporting a role for noradrenaline in OCD, there are some studies to support further investigations into the role of noradrenaline in OCD(7-10). Tricyclic antidepressants act on both serotonin and noradrenaline reuptake ; e.g. nortriptyline, desipramine and protriptyline. Among them nortriptyline causes less orthostatic hypotension (11,12).

The aim of this study was to investigate the serotonergic – noradrenergic hypothesis in the treatment of OCD.

Materials and Methods

After obtaining informed consent and discontinuing all psychotropic medications for 2 weeks, 42 subjects (19 male and 23 female) between 18 and 65 years of age were enrolled in an 8-week, double–blind , placebo-controlled study. Two subjects dropped out after the first week of treatment due to non-compliance (both from group 2), leaving 40 subjects who met the DSM

IV criteria for OCD who completed the trial. All subjects were outpatients and had experienced symptoms of OCD for at least one year.

To ensure that patients had substantial OCD symptoms, a minimum score of 18 on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) was required for entry into the study. The Y-BOCS is a 10-item clinician-administered scale, which is perhaps the most widely used rating scale for OCD. This scale is designed to rate symptom severity and provides five rating dimensions for obsession and compulsion: time spent or occupied, interference with functioning or relationships, degree of distress, resistance and control (success in resistance). The 10 items of Y-BOCS are each scored on a four-point scale from 0 (no symptoms) to 4 (extreme symptoms). This scale has been translated into Persian and its reliability, validity and sensitivity to change are well-established (13) .

None of the patients met the DSM-IV criteria for major depression according to clinical interviews, and all patients had a baseline 17-item Hamilton Rating Scale for Depression (HAM-D) score of less than 18, as well as a score of two or less on item one (depressed mood) in the same rating scale. Patients with a history of other psychiatric disorders (schizophrenia, psychotic symptoms, bipolar disorder, organic mental disorder, psychosurgery, personality disorder, panic disorder, agoraphobia, eating disorder, substance abuse or alcoholism) within one year prior to the study were excluded. Pregnant or lactating women were also excluded. All patients were free of unstable medical disorders including cardiovascular, hepatic, renal, gastrointestinal, pulmonary, metabolic, endocrine and hematological illnesses. All patients gave a complete medical and psychiatric history and were given a physical examination before entry into the study.

20 subjects were then assigned in a random fashion to citalopram 40 mg/day plus nortriptyline 50mg/day (group 1), and 20 patients to citalopram 20mg/day plus placebo (group2) in an 8-week, double–blind, placebo-controlled study. The dosages of citalopram were titrated up to 40mg/day over a one-week period in both groups, and the dosages of nortriptyline were titrated up to 50 mg/day over the same duration in group 1. Patients did not receive other psychopharmacological drugs during the trial and were not permitted to receive behavior therapy. Nine of 20 patients in group 1 and nine of 20 patients in group 2 were male. Patients were assessed by an experienced rater (a third-year resident in psychiatry) at baseline and 2, 4, 6 and 8 weeks after the beginning of medications. The principal measure of the outcome was the Y-BOCS. One rater assessed the patients throughout the course of the study. The rater used standardized instructions in the use of Y-BOCS. The mean decrease in Y-BOCS scores from baseline was used as the main outcome measure of response of obsessive-compulsive symptoms to treatment. Side effects were systematically recorded throughout the study and were assessed using a checklist administered by a resident in psychiatry on weeks 2, 4, 6 and 8.

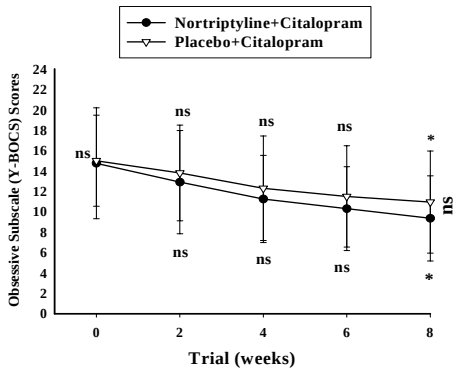

Figure 1. Mean ± SEM scores of the two protocols on the obsessive subscale scores on Yale-Brown Obsessive-Compulsive Scale(Y-BOCS)
*** p< 0.05, ns = non – significant.**

Statistical analysis

Using data from a pilot study and considering a five-point difference in the change of Y- BOCS score between patients who were treated in group 1 and 2, we calculated that at least 15 patients were needed in each arm. A two-way repeated measures analysis of variance (ANOVA) (time–treatment interaction) was used.

The two groups were considered as a between–subjects factor (group), and the five measurements during treatment as the within–subjects factor (time). This was carried out for Y-BOCS scores. In addition, a one-way repeated measure analysis of variance (ANOVA) with a two-tailed post hoc Tukey mean comparison test were performed on the change in Y-BOCS from baseline. An unpaired two-sided Student's t-test was used to compare the reduction of score of Y-BOCS at week 8 compared with the baseline. Results are presented as mean±SEM differences and are considered significant at $P \leq 0.05$. Fisher's exact test was performed in order to compare the baseline data and the frequency of side effects between the protocols.

Results

No significant difference was identified between patients randomly assigned to the two groups with regard to basic demographic data including age, gender, duration of illness and baseline HAM-D score.

Table 1. Demographic charactristics of two groups of patient with obsessive-compulsive disorder receiving citalopram+ nortriptyline or citalopram+ placebo

Variable	Nortriptyline Group	Placebo Group	P
Gender	Male:9 Female :11	Male: 9 Female:11	1.24
Age (Mean ± SD)	8.42 (year) ± 27.95	11.07 (year) ± 30	0.51
Length of illness	49.60(month) ± 93.90	109.37 ± 107.30	0.62

Obsession

The means±SEM of the two groups of patients are shown in Figure 1.

There was no significant difference in obsession subtotal score between the two groups at week 0 (t = 0. 58, df=38, p=0.56).

The difference between the two protocols was not significant, as indicated by the effect of group and the between-subject factor (f=0.51, df=1, P=0.47).

The effects of the two treatments were homogeneous overtime (group by time interaction Greenhouse-Geisser correction; F=0.65, df=1.55, P=0.48). Inaddition, a one-way repeated measures analysis of variance (ANOVA) showed a significant effect of both protocols in the obsession subtotal scores (P< 0.01).In both groups post hoc comparsions showed a significant change from week 8, on the obsession subtotal score. The difference between two protocols was notsignificant at the end point (week 8) (t=1.09, df=38, P=0.27).

The changes at the endpoint, compared with the baseline, were –5.4±4.61 (mean±SD) and –4.1±3.33 for nortriptyline and placebo, respectively. No significant difference was observed on the change of obsession subtotal score at week 8, as compared to the baseline, in the two groups (t=1.02, df=38, P=0.31).

Compulsion

The means±SEM of the two groups of patients are shown in Figure2. There was no significant difference between the two groups at week 0, regarding the compulsion subtotal scores (t= 0.25, df= 38, P=0.8).

The difference between the two protocols was not significant, as indicated by the effect of group and the between subject factor.

The effect of the two treatments were not homogeneous across time (group by the time intraction

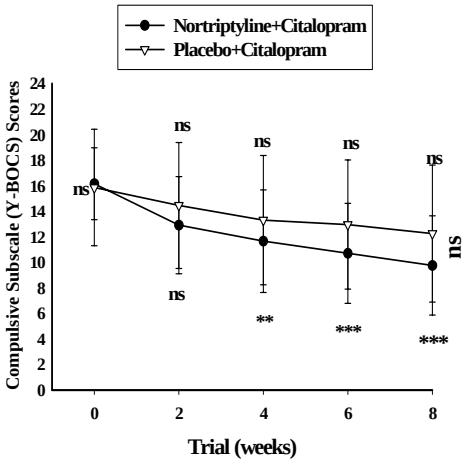

Figure 2. Mean ± SEM scores of the two protocols on the compulsive subscale scores on Yale-Brown Obsessive-Compulsive Scale(Y-BOCS)

*** p<0.05, ** p<0.01, *** p<0.001, ns = non – significant.**

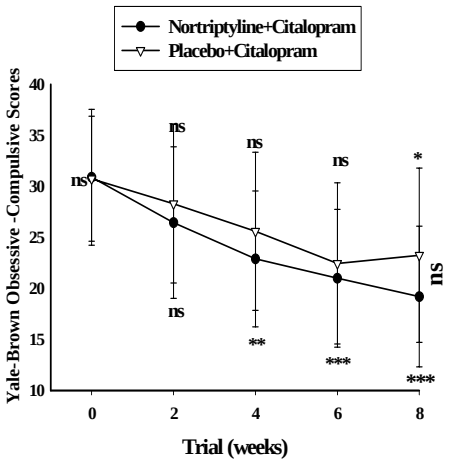

Figure 3. Mean ± SEM scores of the two protocols on the total scores on Yale-Brown Obsessive-Compulsive Scale(Y-BOCS)

*** p<0.05, ** p<0.01, *** p<0.001, ns = non – significant.**

Greenhouse-Geisser correction; F=4.12, d=2, p=0.02). (t=1.69, df=38, P =0.09).

In addition, a one-way repeated measures analysis of variance (ANOVA) showed a significant effect of nortriptyline protocol in the compulsion subtotal score (P<0.0001), but did not show a significant effect of placebo protocol in the compulsion subtotal score nortriptyline group, post hoc comparsions showed a signficant change from week 4, on the compulsion subtotal score. The difference between two protocols was not significant at the end point (week 8) (P=0.18).

The changes at the end point compared with baseline were –6.4±3.40 (Mean±SD) and –3.55±3.63 for nortriptyline and placebo, respectively. A significant difference was observed on the change of compulsion subtotal score at week 8 compared to the baseline, in the two groups (t=2.5, p=0.01).

Obsession and compulsion

The means±SEM of the two groups of patients are shown in Figure 3.

There was no significant difference between the two groups in the week 0 total score (t=0.07, df=38, P=0.94). The difference between the two protocols was not significant, as indicated by the effect of group and the between-subjects factor (F=1.27, df=1, P=0.26).

The effect of the two treatments was homogeneous over time (group by time interaction, Greenhouse–Geisser correction; F=2.43, df=1.67, P=0.1). In addition, a one-way repeated measures analysis of variance (ANOVA) showed a significant effect of both protocols in the total scores (P<0.0001 in nortriptyline group) (P<0.01 in the placebo group). In nortriptyline group, post hoc comparsions showed a significant change in total score from week 4, but the placebo group post hoc comparison showed a significant change from week 8.

The difference between two protocols was not significant in the end, at week 8 (t=1.65, df=38, P=0.1). The changes at the end point compared with baseline were–11.2±6.99 (Mean±SD) and -7±5.15 nortriptyline and placebo, respectively .A significant difference was observed on the change of the total score at week 8 compared to the baseline in the two groups (t=2.17, df =38, P=0.03).
To obtain at least 35% reduction on the total Y-BOCS scores, the difference between two protocols was significant for the total score according to Fisher's exact test (P=0.04).

Adverse effects
To compare the adverse effects of two medication protocols, a Fisher's exact test with a two-sided P value was used. Findings are shown in Table 2. No significant difference was observed with regard to the adverse effects including sedation, confusion, diarrhea, constipation, nausea, dizziness, weakness, fatigue, and urinary retention.

Discussion

The hypothesis that describes OCD an abnormality in the serotonin neurotransmitter system has been called the serotonin hypothesis (14-16). Several pieces of evidence support this hypothesis. The first line of evidence is derived from treatment studies. It appears, however, that not all serotonergic drugs are equally effective in treating patients with OCD (17,18).
In addition, the lack of a rapid onset of activity is one of the major problems with serotonin-selective reuptake inhibitors (SSRIs). It seems that drugs (e.g. venlafaxine) or drug combinations (e.g. citalopram and nortriptyline) that affect both norepinephrine and serotonin, show a faster onset of activity and a higher efficacy in the treatment of major depression and obsessive-compulsive disorder (17-24). Of course, some studies have indicated that these drugs (serotonin and norepinephrine reuptake inhibitors) might be as efficacious as SSRIs in the acute treatment of OCD, with fewer side effects (25) also, some other studies have indicated that these drugs may be a useful therapy for OCD patients, but are not superior to SSRIs (26, 27). Our goal in this study was to investigate the serotonergic–noradrenergic hypothesis of OCD. Therefore, nortriptyline was chosen to be added to citalopram. In this study, only a dosage of 50mg/day of nortriptyline increased the efficacy of citalopram (40 mg/day) in the treatment of OCD. The combination of these drugs at these doses did not show any severe or moderate side effects.
As this study indicates, one of the advantages of this combination is a rapid onset of symptom improvement. The results indicate that compared to citalopram alone, the combination of citalopram and nortriptyline could induce a significant reduction in the compulsion subtotal score and total scores of Y-BOCS as early as 4 weeks after starting medication.

Table 2. Adverse effects in two groups of patients with obsessive-compulsive disorder receiving citalopram+ nortriptyline or citalopram+ placebo

Adverse effects	Group I (Nortriptyline)	Group 2 (Placebo)	p-value
Sedation	10	8	0.75
Insomnia	2	5	0.4
Headache	4	5	1
Dry mouth	1	2	1
Sexual dysfunction	3	2	1
Confusion	4	5	1
Constipation	10	8	0.75
Nausea	1	4	0.34
Dizziness	4	4	1
Weakness	4	6	0.71
Fatigue	6	6	1
Diarrhea	3	3	1
Urinary retention	5	4	1

However, this conclusion should be tempered by the small sample size and the short duration of this study.
To conclude, we would like to point out that in order to clarify the serotonergic–noradrenergic hypothesis, more studies (e.g. the combination of SSRIs and desipramine or reboxetine) should be carried out; and this study could represent a basis for future trials.

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