

Combination of Fluoxetine and Nortriptyline in the Treatment of Obsessive Compulsive Disorders

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Abstract

Objective: There is growing interest in investigating noradrenergic functions in Obsessive Compulsive Disorder (OCD) because some antidepressants with strong effects of serotonin reuptake inhibition fail to relieve obsessive-compulsive symptoms. We undertook a trial to investigate whether the combination of fluoxetine with nortriptyline is more effective than fluoxetine alone.

Method: Thirty nine patients who met the DSM-IV criteria for OCD were included in the study. Patients were allocated in a random fashion, 19 patients to fluoxetine 40mg/day plus nortriptyline 40mg/day and 20 patients to fluoxetine 40mg/day plus placebo.

Results: Although both protocols significantly decreased the scores of the Yale-Brown obsessive-compulsive scale over the trial period, the combination of fluoxetine and nortriptyline showed a significant superiority over fluoxetine alone in the treatment of OCD.

Conclusion: As this study indicates, 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: fluoxetine, nortriptyline, OCD

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Introduction

Obsession, compulsion and rituals have been recognized as abnormal cognition 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} Obsession are intrusive, recurrent, 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 combination of medication and behavioural therapy, OCD patients tend to respond to medication with only a 30% to 60% reduction rate in symptoms, and patients tend to remain chronically symptomatic to some degree despite the best 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 More over, many studies using direct serotonergic agonists, such as chlorophenylpiperazine, and serotonergic antagonists, such as metergoline, suggest that brain serotonergic systems maybe intimately involved in the pathogenesis of OCD.^{4,5} It appears, however that not all serotonergic drugs are equally effective in treating patients with OCD. Sertraline, a highly specific serotonergic agent, has been shown to be not as effective as other serotonergic agents in the treatment of OCD.^{6,7}

Although there is a few data supporting a role for noradrenaline in OCD, there are some studies supporting further investigations of noradrenaline functions in OCD.^{8,11} Most antidepressants are more potent in uptake inhibition of noradrenaline than that of serotonin especially, desipramine, protriptyline and nortriptyline. Among them, nortriptyline has less orthostatic hypotension side-effects.^{12,13} the aim of this study was to investigate the serotonergic-noradrenergic hypothesis in the treatment of OCD.

Patients and Methods

After giving informed consent and discontinuing all psychotropic medications for 2 weeks, 45 cases (19 female and 26 male) between 18 and 35 years of age were enrolled in an 8-week, double-blind, placebo-controlled study. Six subjects dropped out after the first week of treatment due to non-compliance, leaving 39 cases who met the DSM-IV criteria for OCD and completed the trial.¹⁴ All subjects were outpatient and had experienced symptoms of OCD for at least 1 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 to the study.¹⁵

The Y-BOCS is a 10-item scale with five items assessing severity of obsession and five items for severity of compulsion. Each item is rated from 0 to 4. None of the patients met the DSM-IV criterias for major depression according to clinical interviews and each patient had a baseline 17- item Hamilton rating scale for depression score of less than 20, as well as score of two or less in item one (depressed mood) of this scale.¹⁶

Patients with history of other psychiatric disorders (schizophrenia, psychotic disorders, bipolar disorder, organic mental disorder, psychosurgery, personality disorders, panic disorders, agoraphobia, eating disorders, substance abuse or alcoholism) within 1 year prior to the study were excluded. Pregnant or lactating women were excluded. All patients did not have any unstable medical disorders, including cardiovascular, hepatic, renal, gastrointestinal, pulmonary, metabolic, endocrine or hematological illnesses. A complete medical and psychiatric history was taken from all patients and physical examination was performed before entry

into the study. Nineteen patients were then assigned in a random fashion to fluoxetine 40mg/day plus nortriptyline 50mg/day (group 1) and 20 patients to fluoxetine 40mg/day plus placebo (group 2) for an 8 week, double-blind placebo controlled-study. The dosage of fluoxetine were titrated up to 40mg/day over a week. Patients were not permitted to have behavior therapy. Eight out of 19 patients in group 1 and 14 out of 20 patients in group 2 were male. At each scheduled visit, patients were asked whether they had experienced any unusual or unwanted OCD symptoms. Patients were assessed by an experienced rater (two psychiatrists, A.A Nasehi and F. Raisi) at baseline and 2,4,6 and 8 weeks after medication was started. The principal measure of the outcome was the Y-BOCS. One rater assessed the patients throughout the course of the study. They used standardized instructions in the use of Y-BOCS. The mean decrease in Y-BOCS score from baseline was used to assess of the main outcome measure of response in treatment of obsessive-compulsive symptoms.

Statistical analysis

Using data of pitlot study and considering a five point difference in change of ADAS-cog 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 measure analysis of variance (time-treatment interaction) was used. The two groups as a between-subjects factor (group) and the five measurements during treatment as the within-subject factor (time) were considered. This was carried out for ADAS-cog and CDR-SB scores. In addition, a one-way repeated measure analysis of variance with a two-tailed post hoc Tukey mean comparison test were performed on the change in ADAS-cog and CDR-SB from baseline. To compare the reduction of score of ADAS-cog and CDR-SB scale at week 16 compared with baseline, an unpaired two-sided student's t-test had differences and were considered significant ($P < 0.05$) to compare the baseline data and frequency of side-effects between the protocols, Fisher's exact test was performed. A traditional 'observed case' (OC, the patients who completed the trial) analysis at 16 weeks was the primary efficacy analysis. In addition, Intention To Treat (ITT) analysis with Last Observation Carried Forward (LOCF) procedure was also performed. All results discussed are based on OC analysis unless otherwise stated.

Results

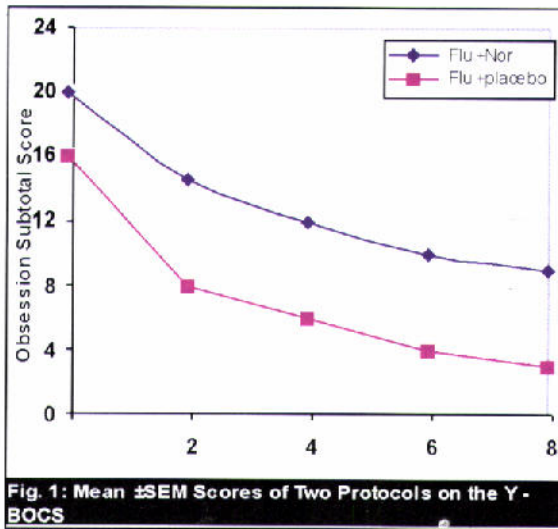
Patients were allocated in a random fashion, 19 to fluoxetine 40mg/day plus nortriptyline 50 mg/day and 20 patients to fluoxetine 40mg/day plus placebo.

Obsession

The mean \pm SEM of two groups of patients are shown in Fig. 1. There were no significant differences between two groups in week 0 in obsession subtotal score ($t=1.607$, $d.f=37$, $p=0.1166$). The difference between the two protocols was significant as indicated by the effect of group, the between-subjects factor ($F=6.289$, $df=1$, $P=0.017$).

The behavior of the two treatments was homogenous across the time (groups by time interaction, Green house-Geisser correction; $F=0.144$, $d.f=2.341$, $P=0.895$).

In addition, a one-way repeated measures analysis of variance showed a significant effect of both protocols in the obsession subtotal scores ($P<0.0001$). The difference between two protocols wasn't significant at the end point (week 8) ($t=1.895$, $d.f=43$, $P=0.1499$).

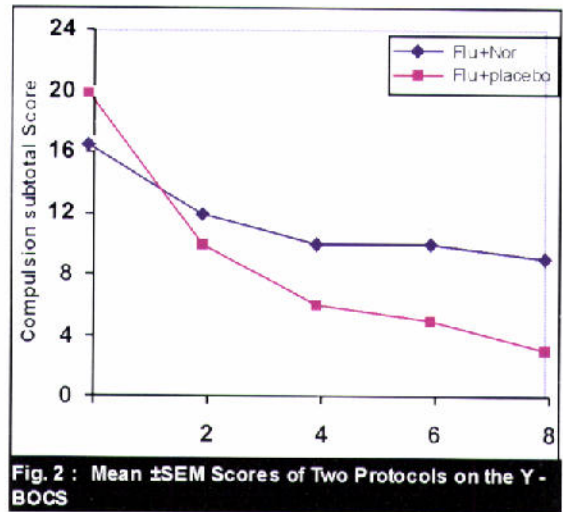


Compulsion

The mean \pm SEM of two groups of patients are shown in Fig.2. There were no significant differences between two groups in week 0 in compulsion subtotal score ($t=1.470$, $d.f=37$, $P=0.1499$). The difference between the two protocols was not significant as indicated by the effect of group, the between subjects factor ($F=1.412$, $d.f=1$, $P=0.242$). The behavior of the two treatments was homogenous

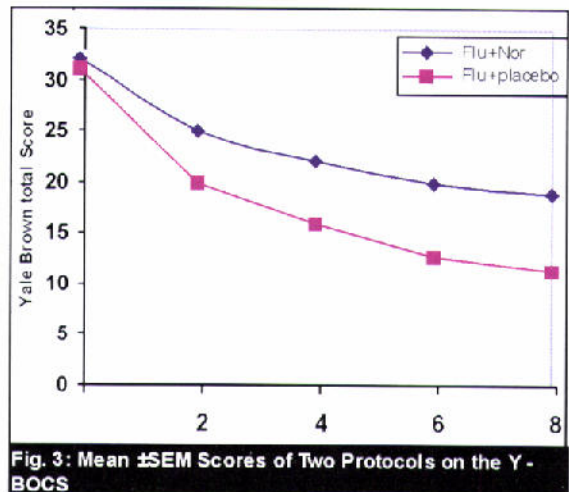
across the time (groups by time interaction, Green house Geisser correction; $F=6.728$, $d.f=2.706$, $P=0.001$).

In addition, a one-way repeated measures analysis of variance showed a significant effect of both protocols in the compulsion subtotal scores ($P<0.0001$). The difference between two protocols was significant at the end point (week 8) ($T=2.537$, $d.f=37$, $P=0.0155$).



Obsession and compulsion

The mean \pm SEM of two groups of patients are shown in Fig.3



There were no significant differences between two groups in week 0 in total score ($T=0.1931$, $d.f=37$, $P=0.8480$). The difference between the two protocols

was significant as indicated by the effect of group, the between-subjects factor ($F=5.713$, $d.f=1$, $P=0.022$).

The behavior of the two treatments was homogeneous across the time (groups by time interaction, green house-Geisser correction; $F=2.163$, $d.f=2.401$, $P=0.111$).

In addition, a one way repeated measures analysis on variance showed a significant effect of both protocols in the total scores ($P<0.0001$). The difference between two protocols was significant at the end point (week 8) ($T=2.317$, $d.f=37$, $P=0.0262$).

Adverse effects

To compare the adverse effects of two groups, a fisher's exact test with a two-sided P-value was used. Findings are shown in table1. No significant difference was observed in most adverse including: bradycardia, tachycardia, loss of Libido, urinary retention, visual disturbances, nausea, vomiting, tremor, weakness, weight gain, orthostatic hypotension, insomnia, confusion, fatigue, headache, constipation, impotence, anorexia and drowsiness.

Table 1: Adverse Effects in Two Groups

Adverse effects	Group 1	Group 2	PV
Tachycardia	7	3	0.1552
Loss of Libido	7	4	0.4756
Urinary retention	3	2	0.6614
Visual disturbance	4	1	0.1818
Vomiting	1	0	0.4872
Weakness	5	6	1.000
Weight gain	2	1	0.6050
Orthostatic hypotension	7	4	0.3008
Insomnia	4	7	0.4801
Tremor	7	4	0.4756
Nausea	3	5	0.6948
Confusion	2	3	0.6948
Fatigue	4	7	0.4801
Headache	3	2	0.6614
Impotence	2	0	0.2308
Anorexia	5	5	1.0000
Bradycardia	0	1	1.0000
Drowsiness	7	10	0.5231
Constipation	9	5	0.1908
Diarrhea	1	6	0.0915
Dry mouth	16	7	0.0031
Dizziness	8	1	0.0084

There was no quite significant difference between two groups in diarrhea, but incidence of diarrhea was

more frequent between patients who took fluoxetine and placebo. Significant difference was observed in a few adverse effects; dizziness ($P=0.0084$) and dry mouth ($P=0.0031$) that was more frequent between patients who took fluoxetine and nortriptyline.

Discussion

OCD is an intriguing and often debilitating syndrome characterized by the presence of two distinct phenomena, obsession and compulsion.¹ The hypothesis that describes OCD and abnormality in the serotonin neurotransmitter system has been called the serotonin hypothesis.^{17,19} Several evidences support this hypothesis. The first line of evidence is derived from treatments studies on treatment. It appears, however, that not all serotonergic drugs are equally effective in treating patients with OCD.^{20,21} In addition to this, the lack of a rapid onset of activity is one of the major problems with serotonin selective reuptake inhibitors (SSRIs). It seems both efficacy and probably the onset of activity in the treatment of major depression and obsessive-compulsive disorder with drugs (e.g venlafaxine) or combination of drugs (like fluoxetine and nortriptyline) which affects both norepinephrine and serotonin are more than drugs that only have effect on serotonin.^{11, 22, 23, 24}

Our goal of study was to investigate the serotonergic-noradrenergic hypothesis of OCD. Because nortriptyline induces less orthostatic hypotension¹, it was chosen to be added to fluoxetin, only 50mg/day of nortriptyline increased the efficacy of fluoxetin 40mg/day in the treatment of OCD. The combination of these drugs at these doses did not show any severe or moderate side-effects except dizziness and dry mouth. As this study indicates, one of the advantages of this combination is rapid onset of decreasing symptoms.

The results indicate that only a combination of fluoxetin and nortriptyline could induce a significant reduction in the scores of Y-BOCS as early as 2 weeks after the initial starting of medication, compared to fluoxetine alone. It should be emphasized that, in order to clarify the serotonergic-noradrenergic hypothesis, more studies (for example the combination of SSRIs and desipramine or reboxetin) should be carried out. Nevertheless, this, this study represents a basis for future trials.

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