Response Acceleration With Mirtazapine Augmentation of Citalopram in Obsessive-Compulsive Disorder Patients Without Comorbid Depression: A Pilot Study

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Background: Therapeutic action of selective serotonin reuptake inhibitors (SSRIs) is delayed from 8 to 12 weeks in patients with obsessive-compulsive disorder (OCD). Several different agents have been tested to reduce the SSRI therapeutic latency time. Mirtazapine, an antagonist at α_2-adrenoceptors, does not enhance serotonin (5-HT) neurotransmission directly but disinhibits the norepinephrine activation of 5-HT neurons and thereby increases 5-HT neurotransmission by a mechanism that may not require a time-dependent desensitization of receptors. The present study was undertaken to determine whether the mirtazapine-citalopram combination could induce an earlier and/or greater effect on the 5-HT system in OCD subjects than citalopram alone.

Method: Forty-nine patients with OCD (DSM-IV) without comorbid depression were randomly assigned to a 2-tailed, single-blind, 12-week clinical trial with citalopram (20–80 mg/day) plus placebo or citalopram plus mirtazapine (15–30 mg/day). Assessments were performed weekly with the Yale-Brown Obsessive Compulsive Scale (YBOCS), the Hamilton Rating Scale for Depression, and the Clinical Global Impressions scale. Data were collected from November 2001 to July 2003.

Results: The citalopram plus mirtazapine group achieved a reduction of at least 35% in YBOCS score and a "much improved" or "very much improved" rating on the Clinical Global Impressions-Improvement scale from the fourth week, while the citalopram plus placebo group obtained these results only from the eighth week. The number of responders was higher in the citalopram plus mirtazapine group at the fourth week of treatment, while no difference between groups in the response rate was noted at the eighth and twelfth weeks of treatment.

Conclusions: We found an earlier onset of response action in OCD symptoms and reduced undesired side effects when mirtazapine was added to citalopram. This augmentation strategy deserves clinical and research consideration through further double-blind, placebo-controlled studies.

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Although selective serotonin reuptake inhibitors (SSRIs) block serotonin (5-HT) reuptake rapidly, their therapeutic action is delayed for 8 to 12 weeks in subjects with obsessive-compulsive disorder (OCD). The increase in synaptic 5-HT activates feedback mechanisms mediated by 5-HT_{1A} (cell body) and 5-HT_{1B} (terminal) autoreceptors, which, respectively, reduce the firing in 5-HT neurons and decrease the amount of 5-HT released per action potential, resulting in attenuated 5-HT neurotransmission. Long-term treatment with SSRIs desensitizes the inhibitory 5-HT_1 autoreceptors, and 5-HT neurotransmission is enhanced. The time course of these events is similar to the delay of clinical action.[1]

Several different agents have been tested to reduce the SSRI therapeutic latency time. The addition of pindolol, which blocks 5-HT_{1A} receptors, to SSRI treatment decouples the feedback inhibition of 5-HT neuron firing and accelerates and enhances the therapeutic response in depression but not in OCD without depression.[2] Serotonin reuptake inhibitor (SRI) medications are effective in the treatment of both major depressive disorder and OCD, but with different neurobiological substrates for response. A recent report[3] has shown that elevated activity in the right caudate may be a marker of responsiveness to antiobsessional treatment, while lower right amygdala activity and higher midline prefrontal activity may be required for the response of depressive symptoms to treatment.

Mirtazapine is an antagonist of α_2-adrenoceptors and is also a 5-HT_2, 5-HT_3, and H_1 receptor antagonist, with low affinity for 5-HT_1 receptors. It is effective as an antidepressant, enhancing 5-HT neurotransmission via different mechanisms compared with the SSRIs. In fact, mirtazapine does not enhance 5-HT neurotransmission directly, but disinhibits the norepinephrine activation of 5-HT neu-

rons and thereby increases 5-HT neurotransmission by a mechanism that does not require a time-dependent desensitization of receptors. These neurobiological phenomena may underlie the apparently faster onset of action of mirtazapine in depression compared with the SSRIs.

A preclinical study[4] of the mirtazapine-paroxetine combination, using in vivo electrophysiologic paradigms, concluded that the combination shortened the delay in enhancing the tonic activation of postsynaptic 5-HT_{1A} receptors and produced a greater activation of the postsynaptic 5-HT_{1A} receptors than either drug given alone. These preliminary results suggested that the coadministration of mirtazapine with the SSRI may accelerate the clinical response as well as be more effective than administration of either drug alone.[5–7] Furthermore, mirtazapine's pharmacologic profile helps to provide several benefits over other antidepressants in terms of undesired side effects,[8] and it has been suggested that there is antagonism of SSRI-induced side effects when mirtazapine is used in combination with SSRI medication.[9,10]

Mirtazapine has also been recently reported as effective in some cases of OCD, without remarkable differences in terms of the length of latency time compared with SSRIs.[11]

We chose citalopram as an antiobsessive treatment for its demonstrated effectiveness in OCD[12,13] and its highly selective profile, which is suitable for combination treatments,[14] and because of our extensive experience with use of this drug in OCD subjects.[15–17] The present study was undertaken to determine whether the mirtazapine-citalopram combination could induce an earlier and/or a greater clinical effect than citalopram alone in OCD subjects. Furthermore, we expected a reduced prevalence of undesired side effects in subjects treated with the mirtazapine plus citalopram combination.

METHOD

Patients

Fifty-eight outpatients were eligible for the study, and 49 entered the trial after giving written informed consent to participate in this study, which had been approved by the institutional review board. Data were collected from November 2001 to July 2003. The diagnosis of OCD was made by means of the Structured Clinical Interview for DSM-IV Axis I[18] and Axis II[19] Disorders. Only patients with OCD symptoms of at least 1 year's duration and of at least moderate severity on the Clinical Global Impressions scale (CGI)[20] were included. Patients were included only if they were SRI-naive and if previous treatments included nothing other than behavior therapy, benzodiazepines, or antipsychotics.

Exclusion criteria were organic mental disorders, psychotic mental disorders (including OCD without insight), mental retardation or developmental disabilities, current depressive episode, substance or alcohol abuse or dependence within 6 months, a history of bipolar I or II disorder, personality disorders sufficiently severe to interfere with cooperation with the study, and women who were pregnant or nursing. The Schedule for Tourette and Other Behavioral Disorders (Adult Form, Version A1)[21] was also used to exclude subjects with current or past Tourette's disorder.

Patients were healthy, based on the results of a physical examination, electrocardiogram, and screening tests of blood and urine. Female subjects had negative results on serum human chorionic gonadotropin testing. Patients were free of psychotropic medications for at least 4 weeks before starting the study.

Study Design

Forty-nine patients with OCD (DSM-IV) without comorbid depression were randomly assigned to a 2-tailed single-blind clinical trial with citalopram (40–80 mg/day) plus placebo or citalopram plus mirtazapine (15–30 mg/day). Assessment of symptoms was performed weekly with the Yale-Brown Obsessive Compulsive Scale (YBOCS),[22] Hamilton Rating Scale for Depression (HAM-D),[23] and global CGI. Assignment to citalopram + placebo (CIT + PLC group) or citalopram + mirtazapine (CIT + MIR group) was performed randomly from a computer-generated list, with patients, treating staff (including prescribing physicians), and the rater blind to assignment.

Twenty-eight subjects entered the CIT + PLC trial, starting therapy at a dose of 20 mg/day (days 1 and 2) titrated up to 40 mg/day (days 3 and 4), 60 mg/day (from day 8, when tolerated), and 80 mg/day (from day 15, when tolerated). Twenty-one subjects entered the CIT + MIR trial. Citalopram was titrated in the same way as in the CIT + PLC group, while mirtazapine was started simultaneously at a dose of 15 mg/day (days 1–7) and titrated up to 30 mg/day from day 8 if tolerated. Drug dosage titration was stopped or lowered if not tolerated. Subjects who did not tolerate the entrance dosages (citalopram, 20 mg/day; mirtazapine, 15 mg/day) were considered as dropout cases. Subjects who did not complete the 12-week trial were considered statistically in the intent-to-treat analysis.

Ratings

Patients were assessed weekly by the same trained blinded rater (L.Q.). Obsessive-compulsive symptoms were measured with the YBOCS. Depression was rated with a 19-item version of the HAM-D, which excludes an item for rating OCD symptoms. A clinical rating of global improvement compared with the prerandomization baseline was made with the Clinical Global Impressions-Improvement scale (CGI-I) (7 = "very much worse," 4 = "no change," 1 = "very much improved").

Treatment Response

Criteria for response included (1) 35% or greater improvement on the YBOCS from the beginning of the trial

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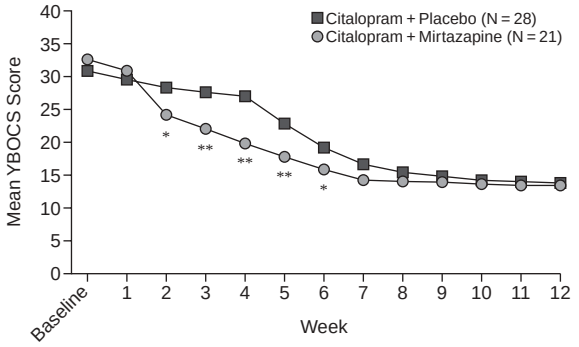
Table 1. Demographic and Clinical Characteristics at Baseline of Subjects With Obsessive-Compulsive Disorder Assigned to Citalopram Plus Placebo or Citalopram Plus Mirtazapine Treatment[a]

Characteristic	All Subjects (N = 49)	Citalopram + Placebo (N = 28)	Citalopram + Mirtazapine (N = 21)
Age, y	29.4 (5.5)	30.4 (5.8)	28.1 (4.8)
Gender, N, male/female	28/21	16/12	12/9
Age at onset, y	22.0 (5.3)	21.9 (5.4)	22.1 (5.3)
YBOCS score			
Obsessions	16.1 (3.1)	15.7 (3.1)	16.7 (2.8)
Compulsions	15.6 (3.0)	15.2 (2.8)	15.9 (3.3)
Total	31.7 (5.8)	30.9 (5.7)	32.6 (5.8)
HAM-D total score	8.7 (2.7)	9.0 (2.3)	8.9 (2.9)
CGI-S score	5.4 (1.1)	5.2 (1.1)	5.5 (1.1)

[a]Values shown as mean (SD) unless otherwise noted.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D = Hamilton Rating Scale for Depression, YBOCS = Yale-Brown Obsessive Compulsive Scale.

Figure 1. YBOCS Treatment Response in OCD Patients Treated With Citalopram Plus Placebo or Citalopram Plus Mirtazapine (intent-to-treat analysis)



*p < .05 (analysis of variance).
**p < .01 (analysis of variance).
Abbreviations: OCD = obsessive-compulsive disorder, YBOCS = Yale-Brown Obsessive-Compulsive Scale.

and a final YBOCS score of 16 or less, (2) a final CGI-I rating of "much improved" or "very much improved," and (3) consensus of the treating clinician and 2 of the investigators (S.P. and L.Q.) that the patient's condition was improved (based on a direct clinical interview and behavioral ratings). Patients who met all 3 criteria were classified as "marked" responders, those who met 2 of the criteria were "partial" responders, and those who met fewer than 2 of the criteria were nonresponders.

Physiologic Measures and Adverse Effects Assessment

Sitting and standing blood pressure and pulse, temperature, and respiratory rate were recorded at baseline and at the end of week 6 of the controlled trial. Each patient was examined for adverse effects using the Dosage Record and Treatment Emergent Symptom Scale (DOTES)[24] at baseline and at the end of each week of the trial. The Arizona Sexual Experience Scale (ASEX)[25] was used to detect the presence of at least moderate sexual dysfunction (total score ≥ 15).

Statistical Analysis

Descriptive statistics were computed and the analysis of variance F test was performed where appropriate to assess the significance of differences between and within groups, with alpha set at $p < .05$, 2-tailed. Intent-to-treat analysis was used for comparison procedures. Parametric tests were utilized for variables with an interval unit of measurement and for normally distributed data. Data were analyzed using an SPSS-PC package (SPSS, Inc; Chicago, Ill.).

RESULTS

Demographic and baseline clinical characteristics of the patients assigned to each treatment group are summarized in Table 1. There were no significant between-group differences in age, gender, age at onset, duration of the disorder, or YBOCS total score.

Two (7.1%) of the 28 subjects receiving citalopram plus placebo and 2 (9.5%) of the 21 subjects receiving citalopram plus mirtazapine dropped out of treatment. Three subjects were dropped from the study because of noncompliance. One subject in the CIT + PLC group dropped out due to intolerance to side effects after 1 week of treatment. A total of 26 subjects in the CIT + PLC group and 19 patients in the CIT + MIR group completed the 12-week protocol. The CIT + MIR group showed an early response, as rated with YBOCS mean score reduction, which reached significance from the second to the sixth week of treatment compared with the CIT + PLC group (Figure 1). No significant differences in response were observed between the 2 treatment groups from the seventh week to the end of the trial (Table 2).

The CIT + MIR group achieved at least a 35% reduction in YBOCS score and a "much improved" or "very much improved" CGI-I rating from week 4, while the CIT + PLC group obtained these results only from week 8. The number of responders was higher in the CIT + MIR group at 4 weeks of treatment, while no difference in response rate was observed between the 2 groups at the eighth and twelfth weeks of treatment (Table 3).

The prevalence of side effects that emerged during the trial as detected through the DOTES is summarized in Table 4. Baseline and end-of-study ASEX total scores in the 2 groups are shown in Figure 2. ASEX mean (SD) total scores were 10.3 (3.9) at baseline and 14.5 (4.3) at the end of the study in the CIT + PLC group and 9.6 (4.4) at baseline and 10.7 (3.8) at the end of the study in the

Table 2. YBOCS Total Scores From Baseline to the End of the Trial in OCD Patients Treated With Citalopram Plus Placebo (N = 28) or Citalopram Plus Mirtazapine (N = 21) (intent-to-treat analysis)

	Citalopram + Placebo		Citalopram + Mirtazapine			
Timepoint	Mean	SD	Mean	SD	ANOVA F	p[a]
Baseline	30.9	5.7	32.6	5.8	1.0	NS
Week						
1	29.6	5.6	31.1	5.4	0.39	NS
2	28.2	6.0	24.2	5.9	5.4	< .05
3	27.5	5.4	22.1	5.3	12.2	< .01
4	26.9	5.8	19.9	5.6	18.0	< .001
5	22.8	5.6	17.8	5.1	10.3	< .01
6	19.0	5.1	15.8	5.3	4.6	< .05
7	16.6	4.9	14.2	5.2	2.7	NS
8	15.3	5.4	13.9	5.5	0.8	NS
9	14.6	5.0	12.6	5.1	1.9	NS
10	14.1	5.2	13.5	5.4	0.2	NS
11	13.8	4.9	13.1	5.2	0.3	NS
12	13.6	4.7	12.9	5.0	0.3	NS

[a]df = 48.
Abbreviations: ANOVA = analysis of variance, NS = nonsignificant, OCD = obsessive-compulsive disorder, YBOCS = Yale-Brown Obsessive Compulsive Scale.

Table 3. OCD Responders According to ≥ 35% Reduction From Baseline in YBOCS Score and CGI-I Score of Much or Very Much Improved

Treatment	Week 4, N (%)	Week 8, N (%)	Week 12, N (%)
Citalopram + placebo (N = 28)	5 (17.8)	15 (53.5)	17 (60.7)
Citalopram + mirtazapine (N = 21)	10 (47.6)	12 (57.1)	13 (61.9)

Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, OCD = obsessive-compulsive disorder, YBOCS = Yale-Brown Obsessive Compulsive Scale.

CIT + MIR group (baseline: F = 0.35, df = 48, p = .56; end of study: F = 10.3, df = 48, p < .01).

DISCUSSION

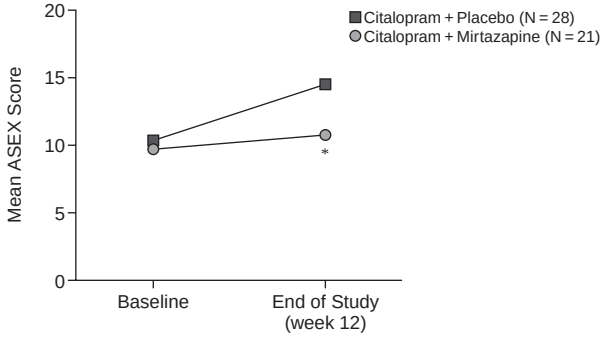
The results of the study suggest a faster onset of response in OCD patients treated with citalopram plus mirtazapine compared with subjects treated with citalopram plus placebo. From week 2 to week 6, the citalopram plus mirtazapine group demonstrated a significant superior response in terms of reduction of OCD symptoms compared with the citalopram plus placebo group at the same timepoints. The acceleration of response in this group did not predict a superior efficacy of the citalopram plus mirtazapine combination at the eighth and twelfth weeks of treatment. To date, there have been no published studies in which mirtazapine has been used to augment SSRI monotherapy in OCD patients. Our data do not seem to be in agreement with the observation of Koran et al.,[11] who found no significant efficacy of mirtazapine monotherapy in OCD during a 10-week course in 10 patients. Conversely, an open-label trial,[26] corroborated by a follow-up double-blind, placebo-controlled study,[27] reported significant improvement in depressed patients in whom mirtazapine was added to ongoing SSRI treatment. The blocking of α-adrenergic receptors by mirtazapine, in addition to SSRI activity, could be important in order to accelerate response in OCD.[28] Specifically, the mechanism could be related to mirtazapine's specific blocking of α-adrenergic heteroreceptors on serotonergic terminals in the prefrontal cortex. These terminals play a role in alterations of hippocampal 5-HT, in combination with SSRI activity. The faster onset of response in OCD found in our study resembles a similar observation from 4 large-scale, double-blind studies that found an earlier onset of action

Table 4. Frequency of Emergent Adverse Effects in OCD Patients Treated With Citalopram Plus Placebo (N = 28) or Citalopram Plus Mirtazapine (N = 21)

Adverse Effect	Citalopram + Placebo, N (%)	Citalopram + Mirtazapine, N (%)
Nausea	6 (21.4)[a]	3 (14.2)
Headache	4 (14.3)	3 (14.2)
Tremor	2 (7.1)	2 (9.5)
Insomnia	5 (17.9)	1 (4.8)
Somnolence	7 (25.0)	6 (28.6)
Anxiety	4 (14.3)	1 (4.8)
Asthenia	0 (0.0)	3 (14.2)
Dry mouth	8 (28.6)	7 (33.3)
Constipation	3 (10.7)	3 (14.2)
Delayed orgasm	7 (25.0)	4 (19.0)
Decreased libido	6 (21.4)	3 (14.2)
Blurred vision	1 (3.6)	1 (4.8)
Carbohydrate craving	5 (17.9)	8 (38.1)
Loss of appetite	3 (10.7)	0 (0.0)
Weight gain	7 (25.0)	10 (47.6)
Weight loss	2 (7.1)	0 (0.0)

[a]One patient dropped out due to nausea (the only dropout due to an adverse effect).
Abbreviation: OCD = obsessive-compulsive disorder.

Figure 2. ASEX Total Scores in OCD Patients Treated With Citalopram Plus Placebo or Citalopram Plus Mirtazapine (intent-to-treat analysis)



*p < .01 (analysis of variance).
Abbreviations: ASEX = Arizona Sexual Experience Scale, OCD = obsessive-compulsive disorder.

with mirtazapine than with the SSRIs fluoxetine, paroxetine, and citalopram in depression.[29]

The dropout rate was very low in this study, which may suggest the high tolerability of and compliance with these drugs in OCD patients. Evaluation of long-term tolerability and compliance should be undertaken and is a limitation of this study. The assessment of side effects in the 2 groups revealed that some undesired effects such as nausea, anxiety, insomnia, and sexual effects were less prevalent among subjects treated with the citalopram plus mirtazapine combination. Specifically, sexual dysfunction at the end of the trial was significantly more prevalent in the citalopram plus placebo group, suggesting that the combination with mirtazapine may reduce sexual effects induced by citalopram. This finding is in agreement with some previous observations on the relief of SSRI-induced nausea and sexual dysfunction by mirtazapine[9,10] and could be explained by mirtazapine's specific neurochemical properties. Its principal action is α_2 antagonism, while it blocks 5-HT_{2A}, 5-HT_{2C}, and 5-HT_3 receptors. When α_2 presynaptic heteroreceptors are blocked, 5-HT is released, but it is directed to 5-HT_{1A} receptors because the other 5-HT receptor subtypes are blocked. The result is that antidepressive and anxiolytic actions are preserved, but the side effects associated with the 5-HT_{2A}, 5-HT_{2C}, and 5-HT_3 receptors are blocked. Agitation, anxiety, insomnia, and sexual side effects are believed to be mediated through 5-HT_2 (5-HT_{2C} in the choroid plexus, 5-HT_{2A} in the cortex and basal ganglia) and 5-HT_3 (peripheral, autonomic, and central nervous system) stimulation. Possible relief of these symptoms elicited by an SSRI may result from blocking these specific receptors with mirtazapine.[30] Antagonism of 5-HT_3 is also associated with antiemetic effects.

No differences were found in reduction of depressive symptom scores between the citalopram plus mirtazapine and the citalopram plus placebo groups. Due to the absence of comorbid depression in this sample, the acceleration of the therapeutic response is not related to variations in depressive symptoms.

A first limitation of this study is its single-blind design and the absence of blinded rating of outcomes. Generally, a single-blind study allows for bias on the part of the investigators conducting the study. Investigators can in fact subtly convey confidence or a lack of it if they know who is receiving one therapy or the other, and they can also unconsciously bias their evaluation of the results. Another limitation of this study is the relatively short period of observation. Finally, we should not exclude that a higher level of response would be obtained with a higher dosage of mirtazapine. In fact, the maximum mirtazapine dosage of 30 mg/day could constitute a limitation of this study. This dosage protocol was decided upon after consideration of the fact that mirtazapine as monotherapy in OCD patients has been described in the literature only by Koran et al.[11] in a study of 10 subjects reaching a dosage of up to 45 mg/day. Furthermore, we found no literature studies of SSRI-treated subjects describing the use of mirtazapine as an augmentation strategy at a dosage higher than 30 mg/day.

However, the earlier onset of response observed in OCD symptoms with the use of mirtazapine added to citalopram, and the lack of a significant difference in response rate in comparison with citalopram alone after 8 weeks of treatment, suggests that this augmentation strategy deserves clinical and research consideration through further double-blind, placebo-controlled studies. In addition, the advantageous reduction in side effects that occurred when mirtazapine was added to citalopram warrants consideration in the light of possible enhanced tolerability and compliance of antiobsessive therapy.

Drug names: citalopram (Celexa), fluoxetine (Prozac and others), mirtazapine (Remeron and others), paroxetine (Paxil and others), pindolol (Visken and others).

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