Mirtazapine for Obsessive-Compulsive Disorder: An Open Trial Followed by Double-Blind Discontinuation

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Background: Many patients with obsessive-compulsive disorder (OCD) experience little response to standard treatment with serotonin reuptake inhibitors. Mirtazapine enhances serotonergic function by a mechanism distinct from reuptake inhibition. Because a pilot study suggested effectiveness of mirtazapine in OCD, we conducted a controlled trial.

Method: We recruited 30 subjects, 15 treatment-naive and 15 treatment-experienced, with DSM-IV OCD of ≥ 1 year's duration and a Yale-Brown Obsessive Compulsive Scale (YBOCS) score of ≥ 20. In the 12-week, open-label phase, subjects received mirtazapine starting at 30 mg/day and titrated over 2 weeks as tolerated to 60 mg/day. At week 12, responders (YBOCS score decrease > 25%) were randomly assigned, double-blind, to continue mirtazapine or switch to placebo for 8 weeks, including a 1-week, double-blind taper week for placebo subjects.

Results: In the open-label phase, the mean ± SD YBOCS score fell from 28.3 ± 3.7 to 20.3 ± 8.5 (paired samples $t = 4.81$, $p < .0001$). Four subjects (13.3%) discontinued for side effects. Sixteen subjects (53.3%) (8 treatment-naive, 8 treatment-experienced) were responders and 15 agreed to randomization. Response was independent of comorbid mood disorders. In the 8-week, double-blind, placebo-controlled discontinuation phase, the mirtazapine group's mean YBOCS score fell a mean ± SD of 2.6 ± 8.7 points while the placebo group's mean score rose a mean ± SD of 9.1 ± 7.5 points (Mann Whitney $U = 6.5$, $p = .005$, 1-tailed). All other outcome measures were consistent with mirtazapine's superiority versus placebo.

Conclusion: Mirtazapine may be an effective pharmacotherapy for OCD. If our results are replicated, larger double-blind studies would be indicated.

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Serotonin reuptake inhibitors (SRIs) are the only drugs approved by the U.S. Food and Drug Administration for the treatment of obsessive-compulsive disorder (OCD). A substantial proportion of OCD patients, however, are unresponsive to SRIs, as defined by the International Treatment Refractory OCD Consortium (ITROC).[1] ITROC defined "unresponsive" as experiencing a < 25% decrease in Yale-Brown Obsessive Compulsive Scale (YBOCS) score and a Clinical Global Impressions-Improvement (CGI-I) score of ≥ 4 (unchanged). Rates of unresponsiveness for treatment-experienced OCD patients range from 20%[2] to 40%–60%,[3–7] with most studies reporting rates in the higher range. Even treatment-naive patients have been reported to have rates of unresponsiveness to SRI treatment approaching 60%.[8] These unresponsive patients suffer substantial impairment in functioning and a diminished quality of life.[9]

The high rate of inadequate response to SRI treatment indicates a need for alternative pharmacotherapies. Yet, the frequent therapeutic response of OCD to SRIs suggests that its pathophysiology often involves deficient serotonergic neurotransmission.[10] The antidepressant drug mirtazapine increases both serotonin and norepinephrine release.[11] Mirtazapine increases norepinephrine release by blocking presynaptic adrenergic α_2 autoreceptors[12] and increases serotonin (5-HT) release both by blocking serotonergic neurons' presynaptic α_2 heteroceptors and by increasing noradrenergic stimulation of these neurons. Because mirtazapine promotes serotonergic neurotransmission, we hypothesized that it would be effective in the treatment of OCD.

In a 10-week, open-label pilot study, we treated 10 OCD subjects with mirtazapine.[13] Six had failed from 1 to 5 prior adequate trials of SRIs, and 4 were treatment-naive. Of the 6 study completers, 2 were responders (YBOCS score decrease > 25%), both of whom were treatment-naive. Both treatment-experienced completers were nonresponders. The 2 responders had no significant depressive symptoms at any time during the trial, suggesting that mirtazapine's effect was independent of effects on mood symptoms. Because treatment-naive OCD patients have an SRI response rate of 40%–50%,[6,14] our pilot result supported the hypothesis that mirtazapine is effective in such patients. In that only 2 treatment-experienced subjects completed the trial, the drug's effectiveness in such subjects remained undetermined. To investigate further the utility of mirtazapine in treating OCD in treatment-naive and treatment-experienced patients, we conducted a larger, controlled trial.

METHOD

We conducted a 2-phase study, utilizing a "population-enrichment" design. In phase 1, subjects received open-label mirtazapine for 12 weeks to identify responders. In phase 2, the subjects within this responder population were randomly assigned to a double-blind, placebo-controlled, 7-week mirtazapine discontinuation trial to investigate whether the open-label mirtazapine response represented a placebo effect or a true drug effect. We chose a 7-week double-blind treatment period because in the only double-blind discontinuation study available when we designed our trial, 16 of 18 patients relapsed within 7 weeks after placebo was substituted for clomipramine.[15] Moreover, case series and anecdotal reports indicated that significant worsening of OCD symptoms occurred within a few weeks of discontinuing this medication.[16] Our study design carries some risks. If, in the double-blind phase, the placebo group continues to benefit from a true drug effect achieved in the open-label phase and therefore exhibits no greater relapse rate than the active drug group, one will erroneously conclude that no true drug effect existed in the open-label phase. If an open-label phase placebo effect persists in both treatment groups, one will conclude correctly that the open-label response was a placebo response. Only if the placebo group exhibits a significantly greater relapse rate than the active drug group in the double-blind phase will one have an indication that the open-label response rate contained a true drug effect.

Eligible subjects were adult outpatients who had had DSM-IV OCD for ≥ 1 year, as established by a Mini-International Neuropsychiatric Interview[17,18] and confirmed by the senior investigator (L.M.K.), and a YBOCS score of ≥ 20 at screening. Comorbid conditions were similarly established and confirmed. We planned to enroll 15 treatment-naive OCD subjects and 15 who had failed exactly 1 adequate SRI trial (treatment-resistant). We limited treatment failure to exactly 1 adequate SRI trial in order to gather preliminary data on mirtazapine's effectiveness in a somewhat, but not severely, treatment-resistant group.

An adequate SRI trial was defined as ≥ 10 weeks at an adequate dose. Because there are no reports of dose-finding studies for clomipramine and fluvoxamine, the minimum adequate dose for these drugs was defined as 100 mg/day (the minimal effective dose indicated by the Expert Consensus Guideline for the Treatment of OCD[19]). For other SRIs, the minimum adequate dose was defined as the minimum effective dose established in fixed-dose, double-blind trials: citalopram 20 mg/day[20]; fluoxetine 20 mg/day, sertraline 50 mg/day, and paroxetine 40 mg/day (all reviewed elsewhere[21]); and venlafaxine 150 mg/day.[22] Treatment "failure" was defined as "failure to benefit substantially" from the trial as established by the senior investigator's (L.M.K.'s) interview of the patient and, when available, examination of clinical records. Eligible subjects had no serious medical condition, no principal Axis I diagnosis other than OCD, and no Tourette's disorder, severe personality disorder, or substance abuse within the past 6 months. They had taken no depot neuroleptics within 6 months, fluoxetine within 5 weeks, monoamine oxidase inhibitor (MAOI) within 2 weeks, or regular psychotropic medication within 1 week of starting study medication. Concurrent behavior therapy was not allowed. After the study was fully explained, all subjects signed an informed consent form approved by the Stanford University institutional review board.

Subjects were seen at a screening visit, baseline, and at the end of weeks 1, 2, 3, 4, 6, 8, and 12 in the open-label phase and at the end of weeks 13, 14, 16, and 20 in the double-blind phase. Severity of OCD was rated with the YBOCS[23] and the Clinical Global Impressions-Severity of Illness scale (CGI-S).[24] Depressive symptoms were rated with the Montgomery-Asberg Depression Rating Scale (MADRS).[25] Vital signs and weight were monitored at each visit, and spontaneously reported adverse events were recorded. The primary outcome measure was absolute change in YBOCS score. Secondary outcome measures were percent change in YBOCS score, proportion of responders, change in CGI-S score, absolute CGI-I score, and change in MADRS score. Responder status was defined prospectively as a decrease from baseline of > 25% in YBOCS score.

Mirtazapine was begun at 30 mg/day for 1 week, increased to 45 mg/day for 1 week, and then continued at 60 mg/day for the remaining 10 weeks of the 12-week, open-label phase of the study. Patients who could not tolerate 60 mg/day were allowed to continue in the open-label phase at 45 mg/day or, if need be, at 30 mg/day. In

Table 1. Comparison of Treatment-Naive Versus Treatment-Resistant Subjects With DSM-IV Obsessive-Compulsive Disorder

Variable	Naive	Resistant	Combined Groups
Age, mean (SD), y	36.6 (11.2)	32.3 (9.0)	34.5 (10.24)
Sex, N			
Male	8	7	15
Female	7	8	15
YBOCS score, mean (SD)			
Baseline	27.8 (3.2)	28.9 (4.1)	28.3 (3.7)
End of week 12	21.0 (7.7)	19.3 (9.0)	20.3* (8.5)
CGI-S score, mean (SD)			
Baseline	5.0 (0.65)	5.1 (0.74)	5.1 (0.69)
End of week 12	2.8 (1.4)	3.8 (1.6)	3.3 (1.5)
MADRS score, mean (SD)			
Baseline	10.3 (8.9)	13.2 (10.5)	11.7 (9.7)
End of week 12	6.7 (8.1)	7.3 (8.9)	7.0 (8.3)
Mirtazapine dose at randomization, mean (SD), mg/d	52.5 (11.3)[a]	60 (0)	56.9 (8.4)
Responders, N	8	8	16

[a]At randomization in the naive group, 1 subject was taking 30 mg, 2 subjects were taking 45 mg, and 5 were taking 60 mg.
*Paired t test, $t = 4.81$, $p < .0001$ versus mean baseline YBOCS score.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness, MADRS = Montgomery-Asberg Depression Rating Scale, YBOCS = Yale-Brown Obsessive Compulsive Scale.

the double-blind phase, responders at the end of 12 weeks of open-label treatment were randomly continued on their final open-label mirtazapine dose or tapered double-blind to placebo over 1 week. The taper schedule for those at 60 mg/day (N = 12) was 45 mg/day for 4 days, 30 mg/day for 3 days, then placebo. The schedule within the 45-mg/day group (N = 2) was 30 mg/day for 4 days, 15 mg/day for 3 days, then placebo. Within the 30-mg/day group (N = 1), the schedule was to continue this dose for the taper week and then switch to placebo. In order to protect the blind, each subject continued to take the same number of capsules daily that he or she was taking at the end of the open-label phase. The placebo and mirtazapine capsules were identical in appearance.

In the open-label phase, continuous variables were examined for statistical significance with the Student t test and $p \leq .05$. Categorical variables were examined with Fisher exact test utilizing the same p value. Relationships among variables were examined with Pearson product moment correlations at $p \leq .05$. Results were analyzed utilizing the last observation carried forward (LOCF). Because of the small number of subjects in each treatment group in the double-blind phase, continuous outcome variables in this phase were not normally distributed. We examined statistical significance, therefore, with the nonparametric Mann Whitney U test and $p \leq .05$, using the LOCF method.

We hypothesized that mirtazapine would be effective for both treatment-naive and treatment-resistant subjects. We did not hypothesize a differential effectiveness between these 2 groups because the effect size is unknown and possibly small, and as a result our sample size precluded meaningful power to test such a hypothesis.

RESULTS

By means of advertising and referrals from our OCD clinic and from colleagues, we recruited the planned 15 treatment-naive and 15 treatment-resistant OCD subjects between September 2000 and September 2003. At baseline, the naive and resistant groups did not differ significantly in mean age, gender distribution, or mean YBOCS, CGI-S, or MADRS scores (Table 1). Four treatment-naive subjects each had 1 comorbid condition at baseline: generalized anxiety disorder (N = 2), major depressive disorder (N = 1), and social phobia (N = 1). Five treatment-resistant subjects had comorbid conditions at baseline: major depressive disorder (N = 3), dysthymic disorder (N = 2), agoraphobia without history of panic disorder (N = 3), social phobia (N = 2), and bulimia nervosa (N = 1). Two subjects had 4 comorbid conditions; 3 subjects each had 1 such condition.

Five treatment-naive subjects (33%) discontinued the open-label phase: 3 because of side effects (1 for severe fatigue, 1 for sexual side effects, 1 for weight gain and lack of efficacy [week 8]), 1 because of abnormal liver function tests, and 1 because of lack of efficacy (week 10). Two treatment-resistant subjects (13%) withdrew, 1 for side effects (edema, dizziness, sedation, and feeling short of breath [week 1]) and 1 for increased depression (week 3).

Results of the Open-Label, 12-Week Treatment Phase

Because there were no statistically significant differences at baseline between the treatment-naive and treatment-resistant subjects in OCD severity or other clinical characteristics (other than treatment history), results are presented for the combined group. Results of clinical interest for the separate groups are reported to inform future research. The subjects' (N = 30) mean YBOCS score decreased significantly from baseline to open-label endpoint (Table 1). The mean percent decrease in YBOCS scores (LOCF) was 26.2% (range, 41% increase to 87% decrease). The naive and resistant groups did not differ significantly on these outcome variables. Despite similar baseline mean CGI-S scores in the 2 groups, the naive group experienced a larger mean decrease in CGI-S score than the treatment-resistant group (2.2 points vs. 1.3 points). Baseline and open-label endpoint YBOCS scores were not significantly correlated, but MADRS scores were ($r = 0.6$, $p \leq .01$). Percent changes in YBOCS and MADRS scores were also significantly correlated ($r = 0.55$, $p \leq .01$). Of the 5 subjects with mood disorders who completed more than 1 week of treatment, 2 were OCD responders and experienced remission of mood symptoms, 1 was an OCD responder with little change in mood symptoms, and 2 experienced neither OCD nor mood response (and withdrew at weeks 3 and 10).

Table 2. Side Effects[a] in the Open-Label Mirtazapine Phase (N = 30)

Side Effect	Subjects, N	% (% Severe[b])
Sedation	18	60 (10)
Fatigue	14	47 (17)
Increased appetite with weight gain	9	30 (0)
Feeling "spacey"	6	20 (7)
Headaches	6	20 (3)
Hypersomnia	5	17 (7)
Dizziness	5	17 (0)
Decreased coordination	4	13 (0)
Vivid dreams	3	10 (0)
Dry mouth	3	10 (0)
Decreased erection/delayed orgasm/ anorgasmia	3	10 (7)

[a]Affecting 3 or more subjects.
[b]Severe = side effects affecting functioning.

At the end of open-label treatment, there were 16 responders (53.3%) (8 treatment-naive and 8 treatment-resistant). The mean ± SD baseline YBOCS scores of the responders and nonresponders did not differ significantly (responders, 29.1 ± 3.7; nonresponders, 27.5 ± 3.7; t = 1.7, p = .13), nor did the mean maximum dose of mirtazapine received (responders, 56.3 mg/day; nonresponders, 57.7 mg/day). In terms of ITROC response categories,[1] there were 4 (13%) "partial responders" (YBOCS decrease > 25% but < 35%), 4 (13%) full responders (YBOCS decrease ≥ 35% but score ≥ 16), and 8 (27%) remitters (YBOCS score < 16). (The ITROC definitions were published after this study was well underway.) More treatment-resistant than treatment-naive subjects experienced ITROC "remission" (5/15 vs. 3/15), but the numbers of subjects are too small to have confidence in this difference.

As noted, medication side effects led 17% (5/30 subjects) to discontinue the study. Most side effects, however, were experienced as mild to moderate (Table 2). Of the 28 subjects taking mirtazapine for at least 4 weeks, 9 (32%) gained ≥ 7% of starting weight.

Fifteen responders entered the 7-week, randomized double-blind discontinuation phase of the study. One responder declined to enter because of weight already gained.

Results of the Double-Blind Discontinuation Phase

At the start of double-blind treatment (week 12), the YBOCS scores of the 2 treatment groups did not differ significantly. Three subjects withdrew, all from the placebo group and all due to lack of efficacy (at end of week 14). At discontinuation endpoint, the absolute and percent changes in YBOCS scores of the 2 treatment groups differed significantly, both for the intent-to-treat group and in a completers analysis (Table 3).

Categorical analyses, although supportive of the superior outcome in the mirtazapine group, were not statistically significant. These analyses, however, have less statistical power than the Mann Whitney U (rank order) analyses. For example, 5 (71%) of 7 subjects assigned to double-blind mirtazapine remained responders compared with only 3 (38%) of 8 assigned to double-blind placebo (Fisher exact test p = .21). Four of the 5 open-label mirtazapine ITROC remitters assigned to double-blind placebo lost their remission compared with neither of the 2 ITROC remitters assigned to mirtazapine continuation; moreover, 3 additional subjects assigned to double-blind mirtazapine continuation achieved ITROC remission by week 20.

Table 3. Outcomes for 12-Week Open-Label Mirtazapine Responders Randomly Assigned to Double-Blind Mirtazapine Versus Placebo

	YBOCS Score			% Change
Patient ID#	Baseline	EOW12	EOW20	Weeks 12–20
Mirtazapine				
303	24	16	9	–43.8
311	31	18	1	–94.4
312	26	18	20	+11.1
313	24	7	4	–42.9
316	32	16	27	+68.8
325	30	20	15	–25.0
330	34	11	12	+9.1
Mean	28.7	15.1	12.6[a]	–16.7[b]
SD	4.0	4.6	9.0	52.1
Placebo				
305	29	14	16	+14.3
306	32	12	20	+66.7
310	23	17	31	+82.4
321	31	20	25	+25.0
323[c]	34	22	26	+18.2
326	32	10	15	+50.0
329[c]	26	4	29	+625.0
332[c]	26	12	22	+83.3
Mean	29.1	13.9	22.7	+120.6
SD	3.8	5.8	5.8	205.7

[a]Mean (SD) YBOCS score change, weeks 12 to 20: mirtazapine, –2.6 (8.7); placebo, +9.1 (7.5); Mann Whitney U = 6.5, p = .005, 1-tailed (LOCF); for completers, U = 4.5, p = .015.
[b]Mirtazapine versus placebo, Mann Whitney U = 5.0, p = .005, 1-tailed (LOCF); for completers, U = 4.00, p = .015.
[c]Did not complete double-blind phase.
Abbreviations: EOW = end of week, LOCF = last observation carried forward, YBOCS = Yale-Brown Obsessive Compulsive Scale.

DISCUSSION

This first study of a modest number of OCD subjects treated with mirtazapine suggests that mirtazapine may be as effective as SRIs. The mean decrease in YBOCS score (8.0 points) after 12 weeks of open-label treatment was nearly identical to that observed in similarly designed, 12-week, open-label trials of fluoxetine (8.3,[26] 8.4[27]) and in a 12-week single-blind trial of clomipramine (8.4 points) versus venlafaxine (6.6 points).[28] The mean YBOCS decrease was larger than that in an open-label venlafaxine case series (5.2)[29] and slightly smaller than that in a 12-week, single-blind comparison of paroxetine (8.9 points), fluoxetine (9.2 points), and citalopram (9.5 points).[30] The

mean percent decrease (26%) in YBOCS score in the 12-week, open-label phase was of the same magnitude as that reported in large, 12-week, double-blind trials of fluoxetine, sertraline, and paroxetine.[7] Given the larger mean symptom severity change often seen in open-label as contrasted with double-blind studies, our open-label results could, however, have been expected to be larger. The mean percent decrease in YBOCS score in our open-label phase fell between those observed for treatment-experienced (22%) and treatment-naive (34%) subjects in a meta-analysis of 4 double-blind, 12-week sertraline OCD trials.[31]

The results of the 7-week, double-blind discontinuation phase suggest that the clinical response in the open-label phase was not a placebo response. The severity of OCD in the placebo group markedly increased in the discontinuation phase, while that in the mirtazapine group significantly lessened, as reflected in YBOCS scores, percent change in YBOCS scores, responder status, and ITROC remitter status. The absolute increase in mean YBOCS score in the placebo group was slightly more than that observed in the only other trial with a 7-week, double-blind, placebo substitution design (8.8 vs. about 7 points[15]). Unfortunately, we cannot compare the relapse rates in our study with those of other studies. Although the ITROC has proposed a definition of relapse (CGI-I of ≥ 6 [much worse] or a ≥ 25% increase in YBOCS from remission score), this definition has not yet been adopted. All of the published relapse studies utilize idiosyncratic relapse definitions and report 28-week,[32] 6-month,[33,34] or 1-year[35,36] rates rather than rates after 7 weeks or week by week. The ITROC relapse rates in our study were 80% (4/5) in the placebo group and 0% (0/2) in the mirtazapine group (Table 3).

Of course, changes in side effects during the double-blind phase may have compromised the blind. Of the 6 placebo subjects with side effects at entry to the double-blind phase, 2 had all side effects disappear, 1 had some disappear, and 3 had some disappear while new ones appeared. Of the 5 mirtazapine subjects with side effects at double-blind entry, 1 had all side effects disappear, 3 had some disappear, and 1 had new side effects appear. Still, the particular side effect changes may have given either the patients or the clinicians clues about treatment status. Not evaluating the intactness of the blind was a methodological shortcoming, but one that is widely shared.[37]

Although there was a significant correlation between percent change in YBOCS and MADRS scores in the open-label phase, the therapeutic effect of mirtazapine was independent of mood disorder status. Thirteen of the 16 responders to mirtazapine did not have a comorbid mood disorder.

The profile of serotonergic receptor action of mirtazapine differs from that of the SRIs. While the increased synaptic serotonin levels induced by SRIs produce stimulation of all 5-HT receptor types, those induced by mirtazapine affect only the subtypes 5-$HT_{1A/1B/1D/5/7}$ because mirtazapine is a potent antagonist of 5-HT_2 and 5-HT_3 receptors. Thus, the therapeutic effect of mirtazapine that we observed is consistent with the hypothesis of deficient serotonergic function in OCD[38] but argues against the hypothesis that OCD pathophysiology involves 5-HT_2 receptor stimulation.[39]

Mirtazapine was as well tolerated as are the SRIs in OCD trials. Dropouts attributed solely to side effects (13%) were similar to those reported in a meta-analysis of such trials (9%–13%).[40] As in depression treatment trials, however, a significant minority of patients treated with mirtazapine experienced a weight gain of ≥ 7% of starting weight. In clinical practice, weight gain could be approached with a trial of adding either topiramate[41,42] or zonisamide.[43]

If our results are replicated, then a large, parallel-group, double-blind, placebo-controlled trial of mirtazapine treatment of OCD would be worthwhile. If such a study confirms our results, this new pharmacotherapeutic treatment approach would be a boon to OCD sufferers. Future studies should include OCD subjects with even greater degrees of treatment resistance, and the results should be examined for a relationship of these degrees to the likelihood of benefit from mirtazapine. Whether mirtazapine might be utilized as an augmentation strategy in OCD patients partially responsive to an SRI also deserves study. Mirtazapine, like risperidone, is a potent antagonist at 5-HT_{2A} receptors, and risperidone is an effective augmenter of SSRIs in treatment-resistant OCD.[44] A case report of serotonin syndrome from combined mirtazapine and fluoxetine treatment suggests that special care should be taken in designing such a study.[45] Mirtazapine has, however, been successfully and safely combined with SSRIs in treating treatment-resistant depression.[46]

Drug names: citalopram (Celexa), clomipramine (Anafranil and others), fluoxetine (Prozac and others), mirtazapine (Remeron and others), paroxetine (Paxil and others), risperidone (Risperdal), sertraline (Zoloft), topiramate (Topamax), venlafaxine (Effexor), zonisamide (Zonegran).

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