Addition of Desipramine to Serotonin Reuptake Inhibitors in Treatment-Resistant Obsessive-Compulsive Disorder

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Objective: *The purpose of this study was to determine whether combined treatment with a selective serotonin reuptake inhibitor (SSRI) and a norepinephrine reuptake inhibitor, desipramine, effectively reduces obsessive-compulsive symptoms in patients who do not respond to SSRIs.* *Method:* *In a double-blind study, desipramine or placebo was added for 6 or 10 weeks to the treatment of 30 patients with obsessive-compulsive disorder whose symptoms were refractory to SSRI treatment (fluvoxamine, fluoxetine, or sertraline) alone.* *Results:* *There were no significant differences between the adjunctive desipramine and placebo groups in obsessive-compulsive or depressive symptoms.* *Conclusions:* *These data suggest that clomipramine's possibly superior efficacy in the treatment of obsessive-compulsive symptoms may not stem from its capacity to inhibit reuptake of norepinephrine.*

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Meta-analytic studies (1, 2) have suggested that clomipramine may be more effective in reducing obsessive-compulsive symptoms than agents that more selectively inhibit serotonin reuptake. 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 (1). Relapse in patients whose treatment is changed from clomipramine to fluoxetine suggests that these two selective serotonin reuptake inhibitors (SSRIs) may induce remission of obsessive-compulsive symptoms through different mechanisms (3).

Of importance, then, is the question of whether the addition of an agent active on the norepinephrine system might prove effective in the management of those patients with obsessive-compulsive disorder (OCD) whose symptoms are resistant to monotherapy with an SSRI. The purpose of this study was to determine whether combined treatment with an SSRI and a norepinephrine reuptake inhibitor, desipramine, effectively reduces obsessive-compulsive symptoms in patients who do not respond to SSRIs. Of the available norepinephrine reuptake inhibitors, desipramine was chosen for its relatively specific inhibition of norepinephrine reuptake and its lack of efficacy in reducing obsessive-compulsive symptoms when administered as a single agent.

METHOD

Thirty-three medically healthy subjects who met DSM-III-R criteria for OCD for at least 2 years participated. Subjects were consecutively admitted clinic patients who met enrollment criteria. Patients had received fluvoxamine (N=25), fluoxetine (N=5), or sertraline (N=3) for at least 10 weeks before random assignment to treatment group. Patients were considered refractory to SSRI treatment if they met the following criteria: 1) total duration of SSRI treatment of more than 10 weeks (with minimum daily doses for at least 4 weeks of that time of fluvoxamine, 250 mg; fluoxetine, 80 mg; or sertraline, 200 mg) and 2) Yale-Brown Obsessive Compulsive Disorder Scale (4) total score of 16 or more and Clinical Global Impression rating of minimally improved, unchanged, or worse after SSRI treatment. All patients gave written informed consent to participate.

Low-dose benzodiazepines were permitted if patients had been stabilized with them before random assignment to treatment group

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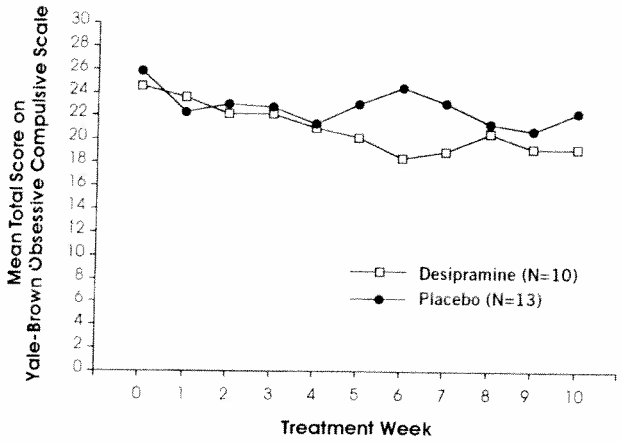
FIGURE 1. Yale-Brown Obsessive Compulsive Scale Scores for SSRI-Treated Patients Receiving 10 weeks of Desipramine or Placebo Treatment[a]



[a]No significant drug-by-time interaction at week 6 (F=3.46, df=1, 27, p=0.07) or week 10 (F=0.57, df=1, 20, p=0.45).

(N=3). Participants were allowed to continue behavior therapy (N=3) if it had begun before randomization and patients were deemed to have made no improvement in the month before the study.

The study consisted of a 6- or 10-week double-blind trial of desipramine or placebo addition to ongoing SSRI treatment. The study as originally designed included a 6-week trial of the combination treatment. However, our interim clinical impression was that some patients who continued to take desipramine after completion of the study improved. The formal trial period of combination treatment was therefore extended to 10 weeks for those patients subsequently enrolled. Patients were randomly assigned to treatment with either desipramine or placebo. The daily dose of desipramine was adjusted weekly in order to obtain a plasma desipramine level greater than 125 ng/ml. The dose of desipramine was limited if a subject experienced clinically significant side effects. Plasma levels were obtained approximately 12 hours after the last desipramine dose during both the initial titration phase (through week 6) and on completion of the study. Levels were reviewed by a psychiatrist who did not participate in the clinical assessment of the patient. Behavioral ratings included the Yale-Brown Obsessive Compulsive Scale, the 25-item Hamilton Depression Rating Scale (5), and the Beck Depression Inventory (6). Behavioral ratings were obtained by research clinicians at baseline and weekly during combination treatment. Desipramine plasma levels were determined by National Health Laboratory, Cranford, N.J.

Data were subjected to analysis of covariance (ANCOVA) by using the baseline rating score as the covariate; p values of less than 0.05 were considered significant.

RESULTS

Thirty-three patients were randomly assigned to treatment with desipramine or placebo. Three patients dropped out of the protocol within the first 3 weeks of treatment secondary to physical symptoms associated with desipramine administration. Thirty patients completed 6 weeks of treatment with either desipramine or placebo (17 women, 13 men; mean age=37.9 years, SD=9.3). A subgroup of these patients (N=25) were enrolled in the 10-week trial of combination treatment; 23 completed treatment. Four patients who completed the study were considered to have low plasma desipramine levels (less than 125 ng/ml); these patients were omitted from portions of the analysis when indicated.

There were no differences between the groups in mean age, sex, Beck Depression Inventory score, initial SSRI, baseline score on the Yale-Brown Obsessive Compulsive Scale, or mean baseline score on the Hamilton depression scale (desipramine-treated group: mean=20.8, SD=9.4; placebo-treated group: mean=19.1, SD=7.0). The mean final desipramine dose was 150.9 mg/day (SD=69.7); the mean final plasma desipramine level was 148.3 ng/ml (SD=82.0).

No significant effect of treatment was present when desipramine and placebo were compared for the groups that completed 6 or 10 weeks of treatment (figure 1). Exclusion of those subjects (N=4) with final plasma desipramine levels less than 125 ng/ml also failed to demonstrate effects of desipramine for the groups that completed 6 weeks (F=2.38, df=1, 23, p=0.13) or 10 weeks (F=1.06, df=1, 16, p=0.32) of treatment.

ANCOVA demonstrated no effect of desipramine treatment on severity of depression as reflected in Hamilton depression scores at week 6 (F=1.10, df=1, 27, p=0.30) or week 10 (F=0.02, df=1, 20, p=0.90). Similarly, Beck depression ratings did not demonstrate significant effects of desipramine treatment at week 6 (F=0.18, df=1, 27, p=0.67) or week 10 (F=0.02, df=1, 20, p=0.88). Exclusion of those patients with final plasma desipramine levels less than 125 ng/ml did not alter these findings.

DISCUSSION

Results of this double-blind trial suggest that the addition of desipramine to ongoing SSRI administration does not substantially reduce obsessive-compulsive or depressive symptoms in patients with SSRI-refractory OCD. Power analysis indicates that this study had the capacity to detect an effect size of 0.70 (alpha=0.80, beta=0.20). This effect size corresponds to a change of 4 points or more in Yale-Brown Obsessive Compulsive Scale score. Thus, a smaller change in Yale-Brown scale scores induced by desipramine may not be excluded. These data suggest that clomipramine's possibly superior efficacy in the treatment of obsessive-compulsive symptoms may not stem from its capacity to inhibit reuptake of norepinephrine.

On entry into this trial, most of the participating patients (as is generally true of patients with OCD who present for treatment) had depressive symptoms that fulfilled criteria for major depression. While subjects tended to report fewer depressive symptoms through the course of the study, desipramine was not more effective than placebo in reducing depressive symptoms.

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