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A Double-Blind Combination Study of Clonazepam with Sertraline in Obsessive-Compulsive Disorder

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This double blind, randomized, parallel, placebo-controlled study investigates whether clonazepam accelerates and/or increases the overall response in patients with obsessive compulsive disorder (OCD) who are treated with sertraline. Thirty-seven patients were randomized with 20 in the sertraline and clonazepam group and 17 in the sertraline and placebo groups. Male and female outpatients, age 18–65 years, met criteria for a primary diagnosis of obsessive compulsive disorder according to DSM-IV, as determined by the structured clinical MINI interview. Appropriate safety and efficacy parameters were measured throughout the study. The determination of efficacy was based primarily on changes from baseline to the last observation taken through week 12. Analysis revealed no significant difference between groups at endpoint on the main scale.

Keywords Obsessive-compulsive disorder; Combination therapy; Sertraline; Clonazepam.

INTRODUCTION

Obsessive compulsive disorder (OCD) is a serious and disabling disorder, in which onset of improvement with pharmacotherapy is often delayed many weeks (1). There is general agreement that an adequate drug trial consists of administering an effective daily dose for at least 10 to 12 weeks (2). Most patients with OCD receiving effective pharmacotherapy experience only partial symptom improvement, thus many adjuvant medications have been proposed to enhance or augment the response (3). If the debilitating symptoms of OCD could be relieved more quickly, then the risk of discontinuation and non-compliance might be reduced with an accompanying reduction in the morbidity of the illness. Thus the goal of combination therapy would be to reduce the response time, accelerate and/or enhance the response to treatment.

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The most commonly recommended combination or augmentation strategies have employed the addition of lithium, buspirone, clonazepam or haloperidol to ongoing SSRI treatment (4–7). Koran et al. (8) studied olanzapine augmentation in treatment-unresponsive OCD, but failed to demonstrate a significantly increased response rate. Iwata et al. (9) augmentated clomipramine with carbamazepine in a treatment-refractory OCD patient with some additional improvement being noted. Cora-Locatelli et al. (10) reported possible efficacy of gabapentin augmentation in OCD patients with incomplete response to fluoxetine in an open study. Inositol has been studied in a double-blind augmentation study by Fux et al. (11) with fluoxetine, fluvoxamine, and clomipramine in OCD patients with no significant benefits. Overall, the benefit from these various strategies has been modest, but perhaps still clinically useful.

There are published studies of benzodiazepines alone in the treatment of OCD. Hewlett et al. (12) reported an open label study of clomipramine, clonazepam and clonidine with no placebo control. Clonazepam was significantly more effective than the other medications during the first 3 weeks of treatment. There are several case reports of clonazepam as monotherapy in OCD by Hewlett et al. (13); Bacher (14); Bodkin et al. (15). These case reports of

clonazepam, as well as reports of Jenike et al. (16), further suggest its possible anti-obsessional action.

Results from controlled studies have been less encouraging (17). However, Pigott et al. (18) conducted a controlled comparison of adjunctive clonazepam versus placebo in clomipramine or fluoxetine-treated OCD patients. Eighteen partial responders were entered into a second double-blind crossover comparison of 4 weeks of clonazepam versus 4 weeks of placebo. The mean dose of clonazepam was 3.5 (+/−0.5) mg/day. Clonazepam was more effective than placebo for global anxiety and obsessive-compulsive scales, but not on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) or National Institute of Mental Health (NIMH) Obsessive-Compulsive Scale. These results thus suggested inconsistent benefit of clonazepam with either clomipramine or fluoxetine in reduction of anxiety and OCD symptoms. There are two published double-blind placebo controlled studies of benzodiazepines in OCD. The first study by Hollander et al. (19) included 27 patients with clonazepam or placebo as monotherapy and found no evidence for superiority of clonazepam. The authors did note that clonazepam as augmentation strategy added to an SSRI remained to be studied. A second study of alprazolam by Stein et al. (20) compared clomipramine, alprazolam, and placebo and reported lack of efficacy of alprazolam.

The mechanism by which benzodiazepine drugs could potentiate serotonergic drugs, if they do so, is not clear. Interestingly, within the benzodiazepine family, clonazepam may have unique effects on the serotonin system, by enhancing serotonergic neurotransmission (21). Pranzatelli suggests in rat models that certain benzodiazepine-related behaviors are 5HT2 receptor mediated (22). Thus, there may be a putative role for 5-HT in explaining the effects of benzodiazepines. The idea that early use of a benzodiazepine such as clonazepam can accelerate the response to an SSRI is not far fetched, as it has been demonstrated in panic disorder by Goddard et al. (23). Here we report on a study designed to assess whether the addition of clonazepam to sertraline hastened onset of improvemnent and/or lead to an overall greater response by the end of treatment.

METHODS

The study was a double-blind, randomized, parallel controlled comparison of clonazepam versus placebo in combination with sertraline in OCD. Inclusion criteria were the following: males and females, age 18–65, in good medical health, with women of childbearing potential to have a negative serum pregnancy test at baseline and to utilize appropriate contraception. Subjects must have had a primary diagnosis of OCD according to DSM-IV (24), as determined by the structured clinical MINI interview (25), with an NIMH Global OCD baseline Scale of 7 or more, and a Y-BOCS baseline score of 20 or above with CGI-Severity score of 4 or above. All patients had a washout period of 2 weeks (5 weeks if on fluoxetine) for prior psychotropic medications prior to entry into the study. Exclusion criteria were lifetime bipolar disorder, severe personality disorders, lifetime psychotic disorders, current drug/alcohol abuse or dependency and women who were pregnant or lactating. Subjects who were receiving current psychotherapy of any type were excluded.

Investigational Review Board approval was obtained. All subjects gave their informed consent in writing after the procedures and possible side effects were explained to them. All subjects received a screening physical exam, ECG, and baseline lab studies, including a urine drug screen and serum test for women of childbearing potential. Following the screening period, subjects were then treated for 12 weeks. Sertraline was administered orally at 50 mg/day for one week, to increase to 100 mg/day thereafter. The dose was reduced in the event of troublesome side effects. Clonazepam and placebo were initiated orally at 0.25 mg/day or equivalent for 3 days, increasing to a titration schedule for final maximum dosing of 4 mg/day by day 26, if tolerated. The clonazepam titration was dosed as 0.25 mg for 3 days, increasing to 0.5 mg for 2 days, and on day 6 to 1.0 mg. On day 8, the dose was increased to 1.5 mg, to 2 mg on day 14, 2.5 mg on day 16, then 3 mg on day 18, to 3.5 mg on day 22 and to 4 mg on day 26. The dose could be reduced to 1.0 mg in the event of side effects; all doses were given at bedtime.

Patients were then evaluated at weeks 1, 2, 4, 6, 8, and 12. The following scales were completed at baseline and at subsequent visits according to this schedule: NIMH Global Scale (26), Y-BOCS (27), Clinical Global Impression (CGI) (28), Hamilton Anxiety (HAM-A) (29) and Hamilton Depression Scales (HAM-D) (30). Efficacy was based primarily on changes from baseline to the last observation through week 12. Responders must have met the following criteria: Y-BOCS had decreased from baseline by 25% or more and CGI improvement rating was 1 or 2.

Outcome was measured categorically on the CGI-I and Y-BOCS by chi-square statistics. Continuous measures (total NIMH, Y-BOCS, HAM-A, HAM-D scale scores) were assessed by repeated measures analysis of variance with treatment as a grouping variable and time as a repeated measurement. The last observation carried forward technique was employed for missing data in these analyses.

Case Vignettes

The two cases presented here include one responder and one drop-out. Ms. A is a 24 year old SBF college student with onset of OCD symptoms five years ago. She became overly concerned with neatness and washing. She noted obsessions with her face and possible blemishes. She felt

that she must not touch her face, otherwise she would have the need to wash her hands. Her hair could not touch her face; she changed her pillow case daily, She checked the mirror constantly for blemishes and had to pick at her face. She calculated and felt compelled to run exactly five miles every day, and she also drank one bottle of water hourly. Premorbidly she was an achiever, with compulsive style and a perfectionist. The past history included honorable discharge from the Air Force for OCD and a trial of fluoxetine with dose to 40 mg with no benefit. The YBOCS score was 32 on entry. The patient did well in the study with a YBOCS score at end of 11. She completed the study and remained on sertraline 100 mg daily with successful weaning of clonazepam or placebo.She continued as an outpatient therapy in follow-up.

Ms. B is a 22 year old SWF recent college graduate with chronic obsessions dating back to the second grade. Recent counseling was of no benefit. The obsessions were aggressive in nature, with fears of abandonment and being isolated "forever." There were contamination, sexual, and religious obsessions, along with checking, repeating, ordering and touching compulsions, as well as a compulsion to complete all utterances. Past history included partial benefit of psychotherapy earlier in college, childhood anxiety with diarrhea, dyspepsia, poor sleep, frequent urination, worries and guilt about her sexual feelings. There was no history of substance abuse. Family history was positive for depression and alcoholism. There was no personal nor family history of bipolar illness. Patient experienced activation symptoms within 24 hours of entering the study which were disabling and included heightened sensation of taste and smell, restlessness, increased energy, and feeling of a "caffeine buzz." Patient was withdrawn from the study with a working diagnosis of treatment-induced hypomania. She was monitored by study staff for the mood swings and referred to clinic but failed to follow-up.

RESULTS

Thirty-seven patients who met DSM-IV criteria for OCD were entered into the study. These subjects were divided between the clonazepam (n = 20) and the placebo (n = 17) group. Univariate tests at baseline showed no difference in treatment groups. The study groups were comparable for age and baseline NIMH Global, Y-BOCS, HAM-A and HAM-D scores. Sample characteristics by group were as follows: 7 male and 13 female in the clonazepam group, 7 male and 10 female in the placebo group; mean (sd) age was 38.2 (11.1) in the clonazepam group and 32.5 (7.1) in the placebo group; severity of symptom scores at baseline were as follows (mean sd): NIMH Global Impression, 9.5 (1.1) for clonazepam and 9.8 (1.5) for placebo; Y-BOCS, 25.0 (5.3) for clonazepam and 26.3 (4.4) for placebo; HAM-A, 15.2 (9.6) for clonazepam and 11.3 (6.0) for placebo; HAM-D, 10.8 (7.9) for clonazepam and 8.7 (7.2) for placebo.

An intent to treat analysis showed that 37 subjects were randomized with n = 20 for clonazepam, n = 17 for placebo; 20 subjects completed week 12 of the study, but all randomized subjects were included in the analysis. Dropouts were related to the following events by study group: adverse events (n = 1 for clonazepam); ineffectiveness (n = 2 for placebo and n = 3 for clonazepam); loss to follow-up (n = 3 for placebo); withdrawal of consent (n = 3 for each group); and protocol violation (n = 1 for each group). Further description of dropouts by group and timing include: week 1(n = 1, placebo, n = 2, clonazepam); week 3 (n = 2, placebo); week 4 (n = 2, placebo; n = 1, for clonazepam); week 6 (n = 3 for each group); week 8 (n = 2, for clonazepam); week 10 (n = 1, for clonazepam). The six subjects who withdrew consent are here reviewed as to cause of withdrawal. Four subjects left with reason, 2 of whom experienced intolerable side effects (nausea, "hallucinations", nonspecific complaint of "medication effects"), 1 disliked medication, and 1 "felt depressed." Two more were lost to follow-up without reason being given for dropout.

Medication adherence was similar in both groups with a mean of 97% in the clonazepam group and 92% in the placebo group. The mean maximum dose was 2.7 mg (clonazepam group), 3.0 mg (placebo group) and 100 mg (sertraline). Maximum doses of clonazepam were as follows: 4 mg (n = 6), 3.5 mg (n = 1), 3 mg (n = 4), 2.5 mg (n = 1), 2 mg (n = 3), and less than 2 mg (n = 5). Subjects received maximum doses of sertraline as follows: 100 mg (n = 34), and 50 mg (n = 3). The mean dose of sertraline was 95.9 mg daily for subjects.

Measures of Efficacy (Table I)

On the NIMH Global mean score comparing baseline to endpoint, no significant difference between treatment groups was found. On theY-BOCS, comparing baseline to endpoint change, no significant difference between the treatment groups was noted. A comparison of mean HAM-A scores over 12 weeks indicated no significant differences between treatment groups. There was an effect of time in repeated measures ($F = 26.4$, $df = 1$, $p < 0.01$), but no effect of time x treatment ($F = 0.92$, $df = 1$, ns).

Table I Baseline and End of Trial Scores*

	Baseline		Final	
	Clonazepam (n = 20)	Placebo (n = 17)	Clonazepam (n = 20)	Placebo (n = 17)
NIMH Global (sd)	9.5 (1.1)	9.9 (1.5)	7.8 (2.5)	8.1 (2.6)
YBOC-S (sd)	25.1 (5.3)	26.2 (4.4)	19.4 (8.9)	18.3 (9.4)
HAM-A (sd)	15.2 (9.6)	11.3 (5.6)	10.8 (10.1)	7.8 (5.3)

sd = standard deviation.

*Intent-to-treat analysis, last observation carried forward. All comparisons between treatments were non-significant at all time points.

The percent rates of responders were compared between treatment groups for the CGI-I and Y-BOCS scales. On the Y-BOCS they were 54.5% for clonazepam and 45.5% for placebo (ns). CGI-I response rates for each treatment group were 54.1% for clonazepam and 45.9% for placebo (ns).

Adverse Events

Significant, or nearly significant differences in treatment emergent events occurred as follows: unsteadiness (55% for clonazepam group, 18% for placebo group) ($p = 0.02$); drowsiness (80% for clonazepam group, 52% for placebo group) ($p = 0.08$); increased appetite (20% for clonazepam group, 0% for placebo group) ($p = 0.05$) We also cited some cases of hypomania in both groups (12% for clonazepam and 7% for placebo, (ns)).

DISCUSSION

To our knowledge, this is the first placebo-controlled combination trial of an SSRI, (sertraline) with a benzodiazepine (clonazepam) in the treatment of OCD. Although such combination did not produce greater benefit on OCD symptoms, 48% failed to complete treatment, and the influence of this dropout rate remains unknown. Our results differ from those of Pigott et al. (18), and also those of Worthington et al. (31), who showed benefit of augmentation of paroxetine, with clonazepam in panic disorder. Lower dose clonazepam may be more effective as an augmentation agent to SRI agents, where low-dose clonazepam co-therapy with fluoxetine was safe and effective in patients with major depression (32), with early benefit for insomnia. In a similar double-blind study of early co-administration of clonazepam with sertraline in panic disorder by Goddard et al. (23), benefits were demonstrated with early and rapid stabilization of symptoms. However, a high dropout rate was also noted of 38% (placebo group) versus 25% (clonazepam group). It is possible that we would have found greater benefit for clonazepam at a lower dose.

Peripheral benzodiazepine receptors (PBR) have been studied in some anxiety disorders by Johnson et al. (33), who found abnormally low receptor density in all anxiety disorders with the exception of OCD. The absence of this abnormality in OCD may help explain the lack of efficacy of augmentation with clonazepam in OCD, but its benefit in panic disorder.

The use of clonazepam did not result in greater or faster anxiolytic effect: possibly the use of clonazepam in higher doses was poorly tolerated and contributed towards the comparatively high dropout rate, as well as limiting its benefits.

Although OCD is classified as an anxiety disorder, benzodiazepines do not appear to be effective, even though they are very widely used as anxiolytics. They have been reported as inferior to antidepressants in GAD (34,35,36). They are also ineffective, or even harmful for PTSD (37,38). The doses of clonazepam in this trial are higher than those used by Hollander et al . (14), who used 1–2 mg/day, and Goddard et al. (39) who dosed clonazepam to 1.5 mg/day. Pigott et al. (18) treated patients with 2–6 mg/day.

Of note was the 9% rate of treatment emergent hypomania. Three patients experienced this adverse event, of whom 2 received clonazepam. This reaction occurred in patients with no known risk factors for bipolar disorder. There may be a vulnerability in the OCD population for this risk, a topic worthy of further investigation. For example Diler et al. (40) reported paroxetine-induced mania in 3 children with OCD and Ackerman et al. (41) reported "increased excitement" or initial nervousness as a possible predictor of drug response in OCD.

Limitations

The limitations of this study include its small sample size. The high dropout rate is not explained by differences between the treatment groups and, although it may be attributed to the burden of illness with debilitation and lack of more immediate relief of symptoms of OCD, we cannot adequately explain this finding. While this is a high dropout rate, we note that 9/27 (33%) subjects also dropped early in the Hollander et al. study (19). Finally Hewlett et al. (13) reported the highest percentage of dropout in the clonazepam group, compared to other treatments, as a result of adverse psychiatric effects.

CONCLUSION

Serotonin reuptake inhibitors remain the most effective pharmacologic treatment for OCD but complete response is generally lacking. In this study we chose sertraline at a dose of 100 mg/day as an intermediate dose (in the range available) because we wanted to avoid under-dosing at 50 mg/day, and also avoid doses which could cause more side effects at 150–200 mg/day. Despite an earlier study by Greist et al. (42) which showed that 100 mg/day of sertraline was not better than placebo, that particular finding was seen as anomalous.

A possibly worthwhile next step would be to consider a double-blind trial of augmentation with clonazepam in SSRI non-responders or partial responders only.

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