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Comparison of Clomipramine, Alprazolam and Placebo in the Treatment of Obsessive–Compulsive Disorder

D. J. STEIN*, E. HOLLANDER†, L. S. MULLEN†, C. M. DeCARIA‡ and M. R. LIEBOWITZ†

†*Department of Psychiatry, College of Physicians and Surgeons, Columbia University, and the New York State Psychiatric Institute, 722 W 168 St, New York, NY, 10032, USA*

‡*Department of Psychiatry, Hillside Hospital Division of the Long Island Jewish Medical Center, Glen Oaks, NY, 11004, USA*

Forty-four patients with obsessive–compulsive disorder (OCD) were entered into a double-blind randomly assigned treatment protocol with clomipramine (CMI) or placebo. In addition, alprazolam was administered to 14 OCD patients in a separate open-treatment study. The response rate of patients completing treatment was 50 per cent with CMI, 19 per cent with placebo, and 18 per cent with alprazolam. Self-ratings of obsessive–compulsive symptoms in intent to treat and completer samples demonstrated a significantly greater benefit with CMI than with alprazolam. Ratings of depression and clinician ratings of obsessionality in both intent-to-treat and completer samples did not, however, indicate differences between the treatment groups.

KEY WORDS—Obsessive compulsive disorder, pharmacotherapy, clomipramine, alprazolam.

INTRODUCTION

Obsessive–compulsive disorder is a chronic debilitating disorder with a high prevalence (Rasmussen and Eisen, 1985). Although patients with the disorder have been thought refractory to treatment, in recent years specific pharmacological interventions have been found promising (Zohar and Insel, 1987; DeVaugh-Geiss *et al.*, 1990).

Several double-blind trials have indicated that clomipramine, a partially selective serotonin reuptake blocker, is effective in the treatment of OCD (Zohar and Insel, 1987; DeVaugh-Geiss *et al.*, 1990). Studies of serotonin metabolites in cerebrospinal fluid (Thoren *et al.*, 1980; Insel *et al.*, 1985), serotonergic pharmacological challenges (Zohar *et al.*, 1987; Hollander *et al.*, 1988; Hollander *et al.*, 1992), and favourable response to other serotonin reuptake blockers (Jenike *et al.*, 1990) have further suggested involvement of serotonin in this disorder, and provided support for the use of these medications.

Nevertheless, side-effects of serotonin reuptake blockers may interfere with adequate treatment, and OCD symptoms may remain refractory to treatment. Furthermore, investigations of neurotransmitters other than serotonin (Siever *et al.*, 1983; Hollander *et al.*, 1991) indicate that OCD cannot be understood as simply a disorder of the serotonin system.

Alprazolam, a triazolobenzodiazepine, has been reported to be of value in a few OCD patients treated in open trails (Tesar and Jenike, 1984; Tollefson, 1985). OCD has phenomenological and biological links to both anxiety and mood disorders (Insel *et al.*, 1982a,b; Stein and Hollander, 1993), and alprazolam, which has anxiolytic and antidepressant properties (Cohn, 1981; Fawcett and Kravitz, 1982; Feighner *et al.*, 1983), may provide an alternative pharmacotherapeutic approach to the disorder.

Given the limited experience with alprazolam for OCD, we decided to begin our investigation of this medication in OCD patients using an open-trial format. We later participated in a randomly assigned double-blind multicentre study of clomipramine (CMI) and placebo in OCD, using the same inclusion and exclusion criteria, as well as the same rating scales. In this report we compare the efficacy of CMI, alprazolam, and placebo in the treatment of OCD.

METHODOLOGY

Subjects

All patients met DSM-III criteria for obsessive–compulsive disorder and were aged 18–65. Inclu-

* Author to whom correspondence should be addressed.

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sion criteria for both the CMI/placebo and the alprazolam protocols included minimal severity, defined by a score of at least 56 on the Self-Rating Obsessional Neurotic Scale (SRON) and on the Self-Rating Obsessive–Compulsive Personality Inventory (SROC). Patients with depressive symptoms were included in both protocols if OCD dominated the clinical picture, if the depressive symptoms did not precede OCD in onset, and if the depressive symptoms were secondary to the OCD. All patients gave their consent after procedures and possible side-effects were explained to them.

CMI/placebo

The CMI/placebo protocol was carried out as part of a multicentre trial. Forty-four patients at two sites (New York State Psychiatric Institute and Hillside Hospital) received a 2-week single-blind placebo washout, and then were randomized to either CMI or placebo for 10 weeks.

Patients were seen weekly after randomization, with dosage titration done on a double-blind basis following a fixed-flexible schedule. Medication was initiated at 25 mg/day, and increased by 25 mg/day every 3–4 days to 100 mg/day by day 10. Dosage was raised as clinically indicated to 150 mg at day 14, 200 mg at day 21, 250 mg at day 28, and 300 mg after 7 weeks. Medication was given t.i.d., but could be altered to b.i.d. or h.s. to reduce side-effects.

Patients were evaluated at all visits using the Clinician Global Impression (CGI) scale, Obsessive–Compulsive Rating Scale (OCS), the Self-Rating Obsessional Neurotic (SRON) scale and the Self-Rating Obsessive–Compulsive Personality Inventory (SROC). The Hamilton Depression Scale (Ham-D) was completed at baseline, and at visits 4, 7, and 9. This study was initiated prior to the development of scales such as the Y-BOCS (Goodman *et al.*, 1989), that are now more widely used to assess OCD symptoms.

Alprazolam

Fourteen patients at the New York State Psychiatric Institute received a 1-week single-blind placebo washout before beginning a 12-week open trial with alprazolam.

Patients were seen weekly for 8 weeks after the placebo washout, then biweekly for the remaining 4 weeks of the trial. Alprazolam was initiated at 1·5 mg/day, and increased to 2 mg/day at day 3, 2·5 mg/day at day 7, and 3·0 mg/day at day 10. Dosage was raised as clinically indicated after day 14 by 1 mg/day every 3 days up to 10 mg/day by day 35. Medication was given t.i.d.

Patients were evaluated at all visits using the CGI, OCS, SRON, and SROC. The Ham-D was completed at baseline, and at visits 4, 7, and 9.

Data analysis

In the CMI/placebo protocol, completers were prospectively defined as patients who received 10 weeks of medication, took at least 150 mg of CMI or placebo per day for at least 4 consecutive weeks, missed less than three psychiatrist visits, and failed to take medication for a total of fewer than 10 days. In the alprazolam protocol, completers were prospectively defined as patients who received 12 weeks of medication, took at least 3 mg of alprazolam per day for at least 2 consecutive weeks, missed less than three psychiatrist visits, and failed to take medication for a total of fewer than 10 days. Responders in both trials were defined as patients who rated much improved (2) or very much improved (1) on the CGI change scale at the endpoint (week 10 or week 12).

Age, baseline depression, and baseline obsessional severity at the two sites were compared using independent *t*-tests. Age, baseline depression, and baseline obsessional severity were compared in patients randomized to treatment with CMI or placebo, or assigned to alprazolam, and in patients completing these treatments, using analysis of variance (ANOVA). Sex distribution at the two sites, in patients assigned to the three treatments, and in patients completing these treatments, were compared using chi-square analysis.

Drop-out rates in the CMI and placebo groups at each site, and response rates in each group for assigned and completing patients at each site, were calculated as a percentage, and compared using chi-square analysis. Drop-out rates in the three treatment groups, and response rates in each group for assigned and completing patients, were also calculated as a percentage and again compared using chi-square analysis.

Comparisons of outcome between treatment groups were made using multivariate analysis of variance (MANOVA). Analyses were performed for both assigned patients, using endpoint analysis (i.e. carrying the results of the last evaluation forward), and for study completers. If significant

Table 1. Baseline demographic and clinical features of patients randomized to the CMI/placebo trial at two sites

	Site 1 ($n = 20$)	Site 2 ($n = 24$)	Significance
Age	36·8 + 11·1	33·6 + 11·9	n.s.
Sex			
male	12	11	
female	8	13	n.s.
OCS	14·6 + 3·2	15·7 + 4·1	n.s.
SROC	67·6 + 10·0	70·0 + 9·4	n.s.
SRON	73·6 + 12·5	71·6 + 12·9	n.s.
Ham-D	11·6 + 6·2	11·8 + 5·3	n.s.

Table 2. Baseline demographic and clinical features of patients assigned to CMI, placebo, and alprazolam

	CMI ($n = 21$)	Placebo ($n = 24$)	Alprazolam ($n = 14$)	Significance
Age	32·7 + 11·6	37·2 + 11·2	38·7 + 13·4	n.s.
Sex				
male	10	13	7	n.s.
female	11	10	4	n.s.
OCS	15·7 + 3·4	14·8 + 4·0	15·4 + 2·9	n.s.
SROC	65·6 + 8·9	72·0 + 9·4	67·5 + 9·8	n.s.
SRON	71·8 + 12·4	73·2 + 13·0	67·6 + 15·4	n.s.
Ham-D	12·7 + 6·9	10·8 + 4·1	13·3 + 5·4	n.s.

Table 3. Baseline demographic and clinical features of patients completing CMI, placebo, and alprazolam

	CMI ($n = 14$)	Placebo ($n = 21$)	Alprazolam ($n = 11$)	Significance
Age	30·4 + 11·9	38·0 + 11·4	38·7 + 10·9	n.s.
Sex				
male	8	12	7	n.s.
female	6	9	4	n.s.
OCS	15·6 + 3·6	15·0 + 4·1	15·5 + 2·9	n.s.
SROC	65·6 + 9·4	72·4 + 9·8	67·5 + 9·8	n.s.
SRON	73·1 + 13·3	74·4 + 12·9	67·6 + 15·4	n.s.
Ham-D	12·8 + 8·2	11·2 + 3·9	13·3 + 5·5	n.s.

effects were found, paired t-tests were employed to compare initial and endpoint scores of depression and obsessionality in completers, and ANOVA was employed to compare endpoint scores of completers in different treatment groups.

RESULTS

Baseline demographic and clinical features such as age, sex, severity of obsessive-compulsive symptoms, and level of depression were tabulated for patients at each of the two sites (Table 1), for patients assigned to each of the three treatment groups (Table 2), and for patients completing trials of CMI, placebo or alprazolam (Table 3).

Baseline demographic and clinical features did not differ significantly in patients at the two sites, or in patients assigned to the three treatment groups, or in patients completing trials of CMI, placebo and alprazolam.

Drop-out rates, and response rates for randomized and completing patients in the CMI and pla-

Table 4. Frequency of completion and non-completion with CMI, placebo, and alprazolam

	CMI	Placebo	Alprazolam
	n (%)	*n* (%)	*n* (%)
Completers	14 (67)	21 (87)	11 (79)
Non-completers	7 (33)	2 (13)	3 (21)

Significance: CMI vs placebo $X^2 = 4{\cdot}09$, $p = 0{\cdot}04$
CMI vs alprazolam $X^2 = 0{\cdot}58$, $p = 0{\cdot}44$
Placebo vs alprazolam $X^2 = 1{\cdot}20$, $p = 0{\cdot}27$

Table 5. Frequency of response and non-response to CMI, placebo, and alprazolam in completers

	CMI	Placebo	Alprazolam
	n (%)	*n* (%)	*n* (%)
Responders	7 (50)	4 (19)	2 (18)
Non-responders	7 (50)	17 (81)	9 (82)

Significance: CMI vs placebo $X^2 = 3{\cdot}73$, $p = 0{\cdot}05$
CMI vs alprazolam $X^2 = 2{\cdot}70$, $p = 0{\cdot}10$
Placebo vs alprazolam $X^2 = 0{\cdot}004$, $p = 0{\cdot}95$

cebo groups, were compared at the two sites. There were no significant differences between the sites. Seven of the 21 patients on CMI, two of the 23 patients on placebo, and three of 14 patients on alprazolam failed to complete the study (Table 4). Thus the drop-out rates were 33 per cent with CMI, 13 per cent with placebo, and 21 per cent with alprazolam. Three-way chi-square analysis did not show significant differences. Two-way chi-square analysis demonstrated a significant difference between CMI and placebo ($X^2 = 4{\cdot}09$, $p = 0{\cdot}04$) only.

Seven of the 21 patients who began a CMI trial were responders, two of the 23 who began a placebo trial were responders, and two of the 14 who began an alprazolam trial were responders. Thus response rates in patients initiating treatment were 33 per cent with CMI, 17 per cent with placebo, and 14 per cent with alprazolam. Three-way chi-square analysis and two-way chi-square analysis did not demonstrate significant differences between treatment groups for patients initiating treatment.

Seven of the 14 CMI completers were responders, four of the 21 placebo completers were responders, and two of the 11 alprazolam completers were responders (Table 5). Thus response rates in completers were 50 per cent with CMI, 19 per cent with placebo, and 18 per cent with alprazolam. Three-way chi-square analyses showed a trend toward significance ($X^2 = 4{\cdot}69$, $p = 0{\cdot}09$). Two-way chi-square analysis demonstrated a significant difference between patients completing CMI and placebo ($X^2 = 3{\cdot}73$, $p = 0{\cdot}05$), and a trend towards significant differences between patients completing CMI and alprazolam ($X^2 = 2{\cdot}70$, $p = 0{\cdot}10$).

Scores of depression and obsessional severity were plotted for completers in each treatment group (Figures 1–4). Analyses were as follows.

OCS (Figure 1): In assigned patients there was a significant time effect ($F = 8{\cdot}110$, d.f. $= 3{\cdot}43$, $p = 0{\cdot}001$), but drug and drugtime effects were non-significant. In completing patients there was also a significant time effect ($F = 7{\cdot}969$, d.f. $= 3{\cdot}28$, $p = 0{\cdot}001$), but again drug and drug × time effects were non-significant. Initial and final scores for all completers differed significantly ($t = 3{\cdot}965$, d.f. $= 40$, $p = 0{\cdot}0001$), but ANOVA showed no significant differences between treatment groups in endpoint score.

SROC (Figure 2): In assigned patients there were significant time effects ($F = 47{\cdot}561$, d.f. $= 3{\cdot}43$, $p = 0{\cdot}0001$), drug effects ($F = 3{\cdot}470$, d.f. $= 2$, $p = 0{\cdot}03$), and drug × time effects ($F = 3{\cdot}435$, d.f. $= 6{\cdot}86$, $p = 0{\cdot}004$). In completing patients there were also significant time effects ($F = 44{\cdot}498$, d.f. $= 3{\cdot}41$, $p = 0{\cdot}001$), drug effects ($F = 3{\cdot}821$, d.f. $= 2$, $p = 0{\cdot}03$), and drug × time effects

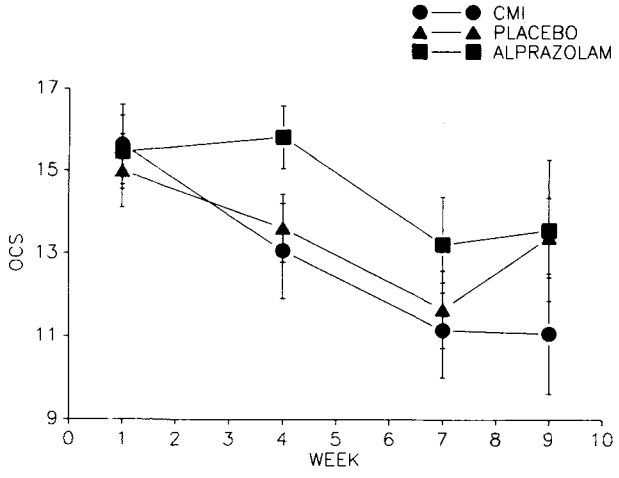

Figure 1. Obsessive–compulsive Rating Scale (OCS) scores over time (weeks) in patients treated with clomipramine (CMI) (circle), placebo (triangle), and alprazolam (square)

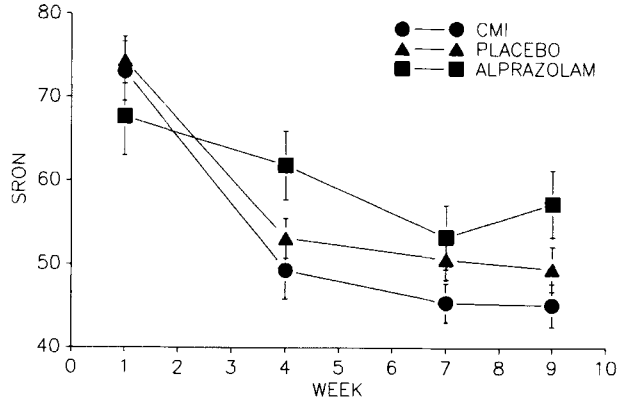

Figure 2. Obsessive-Compulsive Personality Inventory (SROC) scores over time (weeks) in patients treated with clomipramine (CMI) (circle), placebo (triangle), and alprazolam (square)

($F = 3{\cdot}373$, d.f. $= 6{\cdot}82$, $p = 0{\cdot}005$). Initial and final scores for all completers differed significantly ($t = 10{\cdot}533$, d.f. $= 46$, $p = 0{\cdot}0001$). ANOVA showed a significant difference between CMI and alprazolam groups at visits 9 ($F = 4{\cdot}570$, d.f. $= 2$, $p = 0{\cdot}02$), but not between CMI and placebo, or between alprazolam and placebo. At this visit, mean scores for CMI patients were significantly lower than in alprazolam patients ($t = 2{\cdot}876$, $p = 0{\cdot}008$).

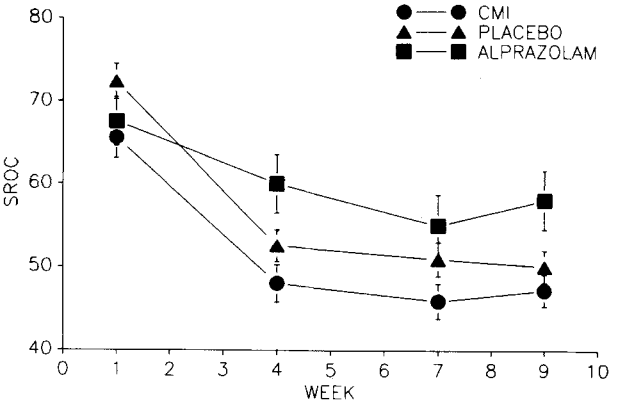

Figure 3. Self-Rating Obsessional Neurotic Scale (SRON) scores over time (weeks) in patients treated with clomipramine (CMI) (circle), placebo (triangle), and alprazolam (square)

SRON (Figure 3): In assigned patients there were significant time effects ($F = 38{\cdot}919$, d.f. $= 3{\cdot}43$, $p = 0{\cdot}0001$), and drug × time effects ($F = 4{\cdot}387$, d.f. $= 6{\cdot}86$, $p = 0{\cdot}001$). In completing patients there were also significant time effects ($F = 37{\cdot}224$, d.f. $= 3{\cdot}41$, $p = 0{\cdot}0001$), and drug × time effects ($F = 4{\cdot}256$, d.f. $= 6{\cdot}82$, $p = 0{\cdot}001$). Initial and final scores for all completers differed ($t = 9{\cdot}863$, d.f. $= 47$, $p = 0{\cdot}0001$). ANOVA showed a significant difference between CMI and alprazolam groups at visit 9 ($F = 3{\cdot}128$, d.f. $= 2$, $p = 0{\cdot}0537$), but not between CMI and placebo, or between alprazolam and placebo. At this visit mean scores for CMI patients were significantly lower than in alprazolam patients ($t = 2{\cdot}574$, $p = 0{\cdot}017$).

Ham-D (Figure 4): In assigned patients there were no main effects for time, drug, or drug × time. In completing patients there were significant time effects ($F = 3{\cdot}044$, d.f. $= 3{\cdot}29$, $p = 0{\cdot}045$), but drug × time effects were non-significant. Initial and final scores in all completers differed significantly ($t = 2{\cdot}662$, d.f. $= 45$, $p = 0{\cdot}01$), but ANOVA showed no significant differences between treatment groups at visit 9.

DISCUSSION

The drop-out rate in the CMI group was significantly higher than the drop-out rate in the placebo group, but did not differ significantly from the drop-out rate in the alprazolam group. These

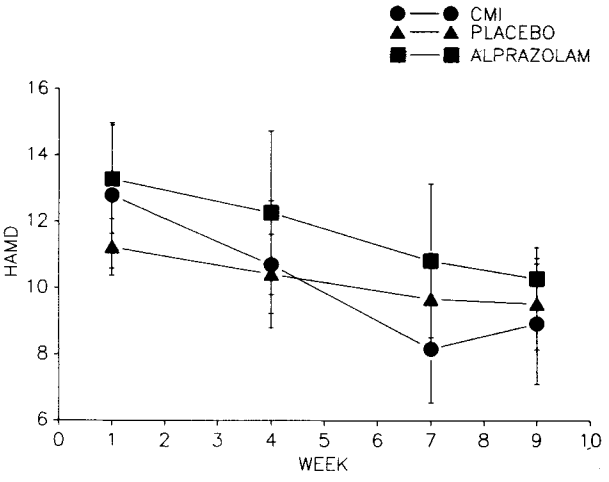

Figure 4. Hamilton Depression Scale (Ham-D) scores over time (weeks) in patients treated with clomipramine (CMI) (circle), placebo (triangle), and alprazolam (square)

results may reflect the side-effects of CMI and alprazolam.

Response rates in patients assigned to the three treatment groups did not significantly differ. However, in patients completing the treatments, response rate to CMI was significantly higher than for placebo and tended to be higher than for alprazolam. In clinical practice, gradual adjustment of medication regimes and symptomatic treatment of side-effects may result in higher response rates in patients beginning psychoactive medication.

In both assigned patients and treatment completers there were significant drug × time effects. Furthermore, self-ratings of obsessive–compulsive symptoms in both assigned patients and treatment completers demonstrated a clear benefit of CMI over alprazolam.

Clinician ratings of obsessionality in both assigned patients and treatment completers did not, however, indicate differences between treatment groups. The clinician scale used here may not be as sensitive to change as newer scales such as the Y-BOCS (Goodman *et al.*, 1989).

Scores of depression (Ham-D) did not show drug × time differences. The existence of antiobsessional effects apart from antidepressant effects with clomipramine treatment is consistent with previous findings (DeVaugh-Geiss *et al.*, 1990).

The CMI/placebo and alprazolam studies did not comprise randomly assigned, concurrently studied comparison groups. Nevertheless, the entrance criteria, duration of treatment, baseline demographic and clinical characteristics were similar in both groups. Furthermore, placebo effect in OCD has consistently been found low (Montgomery, 1980; DeVaugh-Geiss *et al.*, 1990).

Therefore this study does suggest that OCD patients respond better to CMI than to alprazolam. This finding is consistent with the hypothesis that serotonergic dysfunction in OCD is corrected by serotonin reuptake blockers.

Although differences between completing patients treated with alprazolam and placebo did not reach significance, our data also raise the question of whether benzodiazepines exacerbate OCD symptoms. However, a small subset of patients did respond to alprazolam. Furthermore, it has been suggested that some anxiolytics may be useful in augmenting serotonin reuptake blockers in OCD (Markovitz *et al.*, 1990). Further research is necessary to clarify the effect of these medications on OCD symptoms.

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