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Research Article

POST-TREATMENT EFFECTS OF EXPOSURE THERAPY AND CLOMIPRAMINE IN OBSESSIVE–COMPULSIVE DISORDER

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We sought to determine whether adults with obsessive–compulsive disorder (OCD) who respond to intensive exposure and response (ritual) prevention (EX/RP) with or without clomipramine (CMI) fare better 12 weeks after treatment discontinuation than responders receiving CMI alone. After receiving 12 weeks of treatment (EX/RP, CMI, EX/RP+CMI, or pill placebo [PBO] in a randomized clinical trial conducted at three outpatient research centers), 46 adults with OCD who responded to treatment (18 EX/RP, 11 CMI, 15 EX/RP+CMI, 2 PBO) were followed after treatment discontinuation for 12 weeks. Patients were assessed every 4 weeks with the Yale–Brown Obsessive–Compulsive Scale, the National Institutes of Health Global Obsessive–Compulsive Scale, and the Clinical Global Impressions scale by an evaluator who was blind to original treatment assignment. The primary hypothesis was that EX/RP and EX/RP+CMI responders would be less likely to relapse 12 weeks after treatment discontinuation than responders to CMI alone. Twelve weeks after treatment discontinuation, EX/RP and EX/RP+CMI responders, compared to CMI responders, had a significantly lower relapse rate (4/33 = 12% versus 5/11 = 45%) and a significantly longer time to relapse. The CMI relapse rate was lower than previously reported. Nonetheless, responders receiving intensive EX/RP with or without CMI fared significantly better 12 weeks after treatment discontinuation than responders receiving CMI alone. Depression and Anxiety 19:225–233, 2004. © *2004 Wiley-Liss, Inc.*

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INTRODUCTION

Obsessive–compulsive disorder (OCD), with a lifetime prevalence as high as 2–3% [Robins et al., 1984] and a typically chronic course [Skoog and Skoog, 1999], was identified by the World Health Organization as one of the world's leading causes of illness-related disability [Murray and Lopez, 1996]. Two treatments have been proven efficacious in randomized controlled trials for adults with OCD: cognitive-behavioral therapy consisting of exposure and response (or ritual) prevention (EX/RP) and pharmacotherapy using serotonin reuptake inhibitors (SRIs, i.e., clomipramine [CMI] and the selective serotonin reuptake inhibitors [SSRIs] such as fluoxetine, fluvoxamine, paroxetine, sertraline, and citalopram). Although these treatments' acute efficacy has been established, it is unclear how long gains last once EX/RP or SRI treatment is discontinued, whether one treatment maintains its effects longer than the other, and whether combining EX/RP and SRIs leads to better maintenance of gains than monotherapy.

Foa and Kozak [1996] reviewed 16 studies that examined the long-term outcome of adult OCD patients after EX/RP treatment. Of 376 patients, 76% were treatment responders at follow-up (individual study range = 50–100%; mean follow-up = 29 months). Although suggestive, these findings are inconclusive because of: 1) design limitations in some of the studies (e.g., uncontrolled studies with naturalistic follow-up); 2) methodological limitations in others (e.g., use of imprecise assessment procedures); and 3) inconsistencies in whether additional treatment during follow-up was permitted (and reported). No published randomized controlled trial has examined the post-treatment effects of intensive EX/RP after sustained treatment discontinuation using evaluators blind to original treatment assignment.

Data on the outcome of adult OCD patients after SRI discontinuation are also limited. Although SRI responders have been followed naturalistically after SRI discontinuation [Fontaine and Chouinard, 1989; Maina et al., 2001; Pato et al., 1991; Thoren et al., 1980], there are only three published double-blind SRI discontinuation studies in adults with OCD. Each uses a different SRI and comes to a different conclusion. Pato et al. [1988] found that 16 of 18 (89%) CMI responders had "substantial recurrence" of OCD 7 weeks after patients were blindly switched to placebo (PBO). Romano et al. [2001] found no significant difference in relapse rates between 36 fluoxetine (FLX) responders maintained on FLX (Kaplan-Meier 1-year relapse rate = 21%) and 35 FLX responders switched to PBO (Kaplan-Meier 1-year relapse rate = 32%). Koran et al. [2002] found that sertraline (SER) responders who were switched to PBO were significantly more likely to leave the study within 28 weeks because of relapse or insufficient clinical response than SER responders maintained on SER (i.e., 27 of 114 [24%] versus 10 of 109 [9%]), but the relapse rates for both groups were relatively low. Given the paucity of blind studies and the methodological differences among them (e.g., SRI examined, procedure for PBO substitution, length of follow-up, relapse definition), these discrepant results are difficult to resolve, and the post-treatment effects of SRIs in OCD remain unclear.

Data comparing the relative durability of EX/RP and SRI treatment are the most limited. Of six studies that compared outcome in adult OCD patients after treatment discontinuation [Cottraux et al., 1990; Cottraux et al., 1993; de Haan et al., 1997; Marks et al., 1980; Marks et al., 1988; van Balkom et al., 1998], all used designs that confounded the different treatments' effects (e.g., crossing over CMI nonresponders to EX/RP or providing patients additional treatment after treatment discontinuation). None compared the effects of EX/RP, SRIs, and their combination after sustained treatment discontinuation using evaluators blind to original treatment assignment.

We report results from the Discontinuation Phase of a multi-site randomized controlled trial in adults with OCD that compared intensive EX/RP and CMI, two of the most efficacious treatments for OCD [Franklin et al., 2000; Kobak et al., 1998]. During the Acute Phase [Foa et al., in press], patients received 12 weeks of EX/RP, CMI, their combination (EX/RP+CMI), or pill placebo (PBO). During the Discontinuation Phase, responders were followed for 12 weeks after stopping treatment to compare these treatments' short-term durability using a design that mimics clinical practice (i.e., without placebo substitution). Because the literature [Foa and Kozak, 1996; Pato et al., 1988] suggested that EX/RP responders (either on or off medication) have a lower relapse rate than CMI responders, the primary hypothesis was that EX/RP and EX/RP+CMI responders would be less likely to relapse 12 weeks after treatment discontinuation than responders to CMI alone.

MATERIALS

SAMPLE

Between 1990 and 2000, 122 patients were recruited and treated at the Anxiety Disorders Clinic (New York State Psychiatric Institute, New York; $n = 52$), the Center for the Treatment and Study of Anxiety (Philadelphia; $n = 56$), and the Anxiety Disorders Research Program (St. Boniface General Hospital, Winnipeg; $n = 14$). Institutional review boards at each site approved the study. Participants gave written consent after full description of study procedures.

Eligible patients were between the ages of 18–70, had DSM-III-R or DSM-IV OCD for at least 1 year as their primary psychiatric diagnosis, and had a Yale–Brown Obsessive–Compulsive Scale (Y-BOCS) [Goodman et al., 1989a,b] total score of at least 16. Patients were excluded for current major depressive episode

plus a Hamilton Depression Rating Scale (HAM-D; 17 items) [Hamilton, 1960] score of greater than 18, substance abuse or dependence within the past 6 months, current schizotypal or borderline personality disorder, previous CMI treatment of 150 mg/day or more for more than 4 weeks, previous intensive EX/RP (i.e., at least 3 times per week for 2 or more weeks), or any significant medical problem (e.g., cardiac conduction system disease). Eligibility was determined by a psychiatric evaluation carried out by senior clinicians, a structured clinical interview for DSM [First et al., 1996; Spitzer et al., 1990] administered by trained raters to confirm psychiatric diagnoses, and a comprehensive medical exam.

ACUTE PHASE (WEEKS 0–12)

Details are given in Foa et al. [in press]. After random assignment to EX/RP, CMI, EX/RP+CMI, or PBO, patients were treated as follows. Patients receiving CMI or PBO were seen weekly by a psychopharmacologist. Dosing was fixed for the first 5 weeks, starting at 25 mg (or half a pill)/day and increasing to 200 mg (or 4 pills)/day, with an optional increase thereafter to 250 mg (or 5 pills)/day if tolerated and indicated. Dosage increases could be delayed or lowered if clinically indicated. EX/RP [Kozak and Foa, 1997] was delivered intensively during the first 4 weeks (i.e., two information gathering sessions, 15 2-hr exposure sessions over 3 weeks, and two home visits); for the remaining 8 weeks, patients met weekly with their therapists for 45 min to review OCD problems and EX/RP procedures, but no exposure exercises were conducted in session. Patients receiving EX/RP+CMI met individually with both a therapist and psychopharmacologist. Responders were those judged by an independent evaluator (IE) blind to randomization to be much or very much improved relative to Week 0, as measured by the Clinical Global Impression-Improvement (CGI-I) scale [Guy, 1976]. Responders who completed the Acute Phase were eligible to enter the Discontinuation Phase. Non-responders were removed from the study and offered open treatment.

DISCONTINUATION PHASE (WEEKS 12–24)

During the Discontinuation Phase, EX/RP was stopped, and medication was tapered and stopped, but patients still met with their psychopharmacologist or therapist for general support and monitoring of clinical status. Patients on CMI (or PBO) were seen weekly for the first 4 weeks while tapering off their medication (decreasing by 50 mg (or 1 pill)/week), and every 2 weeks thereafter. EX/RP patients were seen every 2 weeks, and EX/RP+CMI patients met with both their psychopharmacologist and therapist. In all cases, sessions lasted 20 min or less.

During the Discontinuation Phase, patients who relapsed were removed from the study and offered open treatment. There is no standard definition of relapse in OCD. Because our goal was to estimate how many responders had poor clinical outcome after treatment discontinuation, relapse was defined a priori as: 1) a return to pretreatment (i.e., Week 0) severity or worse in the past week on the CGI-Severity (CGI-S) scale (Guy 1976); or 2) a clinical state that made further study participation (i.e., ongoing assessment without any OCD treatment) unsafe based on the clinical judgment of the treating clinician. If their OCD worsened between regular visits, patients were instructed to contact their clinician to schedule an additional assessment to ascertain whether they met criteria for relapse.

ASSESSMENTS

Patients were assessed (at Weeks 0, 12, 16, 20, 24) by IEs blind to original treatment assignment. Patients were instructed not to disclose their treatment assignment to the IE. IE measures for OCD included the Y-BOCS, the National Institutes of Mental Health Global Obsessive Compulsive Severity Scale (NIMH-OC) [Insel et al., 1983], and the CGI-I (1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; 7, very much worse) and CGI-S (1, normal/not at all ill; 2, borderline mentally ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; 7, among the most extremely ill patients) scales; the HAM-D scale was used to assess depression. IEs received training and ongoing supervision (from faculty from the Center for the Treatment and Study of Anxiety) and carried out practice ratings of taped interviews. Throughout the study, IEs from different sites met to discuss assessment issues and to practice using specific measures to promote inter-rater reliability

STATISTICAL METHODS

As is typical of discontinuation studies, patients entering the Discontinuation Phase were not a random sample because only responders (as defined above) who completed the Acute Phase were eligible. Thus, demographic and clinical characteristics of entrants to the Discontinuation Phase were compared by treatment group using χ^2 tests for categorical variables and one-way analysis of variance (ANOVA) or two-sample *t*-tests (depending on the number of groups) for continuous variables. If the overall ANOVA tests were significant, post hoc pairwise comparisons were conducted, correcting for multiple comparisons using the Tukey method. Missing Week 12 ratings (one Y-BOCS, three NIMH-OC, one CGI-S, three HAM-D) were imputed using last observation carried forward (LOCF).

To test the primary hypothesis that EX/RP and EX/RP+CMI responders would be less likely to relapse after treatment discontinuation than responders to CMI alone, proportions of relapsers (defined above)

were compared (EX/RP or EX/RP+CMI versus CMI) using the Fisher's exact test, and Kaplan-Meier estimates of the time to relapse were compared (EX/RP or EX/RP+CMI versus CMI) using the log-rank test [Osmer and Lemeshow, 1999]. To explore the effect of Week 12 OCD severity on time to relapse, Cox proportional hazards models examined time to relapse as a function of treatment (EX/RP or EX/RP+CMI vs. CMI), Week 12 Y-BOCS scores, and their interaction; Cox proportional hazards models also examined time to relapse as a function of treatment, percent Y-BOCS improvement at Week 12, and their interaction. To explore the effect of site, Cox proportional hazards models examined time to relapse as a function of treatment (EX/RP or EX/RP+CMI versus CMI), site (NY versus PA), and their interaction. Site analyses excluded the Canada site because it contributed only five patients to the Discontinuation Phase. All statistical tests were two-tailed with level of significance $\alpha = .05$.

RESULTS

SAMPLE DESCRIPTION

As shown in Table 1, 122 patients entered the Acute Phase, 87 patients completed it, and 48 patients responded to 12 weeks of treatment and thus were eligible to enter the Discontinuation Phase. Of these 48 patients, 46 entered the Discontinuation Phase. Two CMI responders refused to enter: one, for fear her symptoms would return after CMI discontinuation; the other, for unknown reasons. Of the 46 entrants to the Discontinuation Phase, 18 had received EX/RP, 11 had received CMI, 15 had received EX/RP+CMI, and two had received PBO during the Acute Phase. Because inferences from a sample of two are unreliable, the placebo responders are described below but were not included in the statistical analyses.

Demographic and clinical characteristics of all 46 entrants to the Discontinuation Phase are shown in Table 2. There were no significant differences in age, gender, ethnic origin, marital status, age of OCD onset, duration of OCD, or HAM-D scores (at Week 0 or 12) between the three active treatment groups or between responders to EX/RP and EX/RP+CMI versus responders to CMI alone. The Week 12 CMI dose was significantly lower for the EX/RP+CMI than for the CMI group (t [22] = 3.79, $P = .001$).

For all 46 entrants to the Discontinuation Phase, OCD severity at entry to the Acute Phase (Week 0), entry to the Discontinuation Phase (Week 12), and completion of the Discontinuation Phase (Week 24) is shown in Table 3 by treatment group. At entry to the Discontinuation Phase (Week 12), the three active treatment groups differed significantly in mean scores on the NIMH-OC (F[2,41] = 5.73, $P = .006$) but not on the Y-BOCS (F[2,41] = 2.86, $P = .069$) or CGI-S (F[2,41] = 2.98 $P = .062$); on all measures, the CMI group had higher mean scores than either the EX/RP or EX/RP+CMI groups. When the groups receiving EX/RP were combined, EX/RP and EX/RP+CMI responders had significantly lower mean scores (*sd*) on all Week 12 OCD measures than responders to CMI alone (Y-BOCS: 8.06 [5.00] versus 12.00 [4.54], F[1,42] = 5.68, $P = .022$; NIMH-OC: 3.48 [1.81] versus 5.73 [2.10], F[1,42] = 11.27, $P = .002$; CGI-S: 2.44 [1.01] versus 3.27 [1.19], F[1,42] = 5.57, $P = .023$).

Descriptively, all entrants to the Discontinuation Phase had a Week 0 CGI-S score of 4, 5, or 6, which translated into a mean Week 0 Y-BOCS score (*sd*) of 20.69 (3.43), 24.90 (3.71), and 29.50 (2.65), respectively. They responded to 12 weeks of Acute Phase treatment with a mean percent Y-BOCS decrease (range) at Week 12 of 63% (22–100%) for the EX/

TABLE 1. Study sample and descriptive outcome

Treatment group[a]	Entrants to the acute phase[b] (Week 0)	Acute phase completers who responded[c]	Entrants to the discontinuation phase[d] (Week 12)	Completers to Week 24 without relapse[e]	Entrants to the discontinuation phase who relapsed[f]	Entrants to the discontinuation phase who dropped[g]
EX/RP	29	18	18	16	2	0
CMI	36	13	11	6	5	0
EX/RP+CMI	31	15	15	12	2	1
PBO	26	2	2	1	0	1
Total	122	48	46	35	9	2

[a]EX/RP, exposure and response (ritual) prevention; CMI, clomipramine; PBO, placebo.
[b]Randomized patients who had at least one treatment session.
[c]Patients who received 12 weeks of treatment and responded (i.e., were much or very much improved relative to Week 0).
[d]Patients who completed and responded to 12 weeks of treatment during the Acute Phase and agreed to enter the Discontinuation Phase.
[e]Relapse: A return to Week 0 severity (or worse) on the Clinical Global Impression-Severity scale for at least one week or a clinical state that made further study participation unsafe.
[f]Relapse week: EX/RP at Weeks 16 and 16; CMI at Weeks 16, 16, 20, 20, and 24; EX/RP+CMI at Weeks 20 and 24.
[g]Drop week: EX/RP+CMI at Week 20; PBO at Week 20.

TABLE 2. Demographic and clinical characteristics of entrants to the Discontinuation Phase

	EX/RP ($n=18$)	CMI ($n=11$)	EX/RP + CMI ($n=15$)	PBO ($n=2$)	Total ($n=46$)
Mean age, years (*sd*)	33.1 (10.5)	32.8 (12.3)	34.1 (11.8)	33.5 (12.0)	33.4 (11.0)
Gender					
Female	9	4	8	2	26 (56.5%)
Male	9	7	7	0	20 (43.5%)
Ethnicity					
African American	0	1	1	0	2 (4.3%)
Asian	1	0	0	1	2 (4.3%)
Caucasian	16	9	10	1	36 (78.3%)
Hispanic	0	1	2	0	3 (6.5%)
N/A	1	0	2	0	3 (6.5%)
Marital status					
Single	9	5	8	1	23 (50.0%)
Married	7	5	5	0	17 (37.0%)
Divorced or separated	1	1	0	0	2 (4.3%)
Living with family	0	0	1	0	1 (2.2%)
Unknown	1	0	1	1	3 (6.5%)
Mean age of OCD onset, years (*sd*)	20.3 (11.2) N/A 2	16.9 (7.8)	17.4 (6.4)	14.0 (0.0)	18.4 (8.8)
Duration of OCD, years (*sd*)	13.6 (12.2) N/A 2	15.9 (11.4)	16.3 (13.4)	11.0 (0.0)	15.0 (12.0)
Mean HAM-D (*sd*)					
Week 0	8.9 (5.2)	9.9 (6.3)	9.2 (4.7)	10.5 (6.4)	9.3 (5.2)
Week 12	5.1 (4.7)	6.2 (3.2)	5.9 (3.9)	5.5 (7.8)	5.7 (4.1)
Mean medication dose at Week 12 (*sd*)	None	236 (23)	186 (44)	(5 pills)[a]	211 (35)

[a]Both placebo patients were on the maximum number of pills (which would have equaled 250 mg had it been CMI).
CMI, clomipramine; EX/RP, exposure and response (ritual) prevention; HAM-D, Hamilton Rating Scale for Depression (17 item); PBO, placebo.

TABLE 3. OCD symptom severity at Week 0, 12, and 24 for the 46 entrants to the Discontinuation Phase

OCD Measures	EX/RP ($n=18$)	CMI ($n=11$)	EX/RP + CMI ($n=15$)	PBO ($n=2$)
Y-BOCS				
Week 0	23.06 (3.52)	24.55 (5.32)	24.87 (4.56)	25.50 (3.50)
Week 12	8.28 (5.34)	12.00 (4.54)	7.60 (4.60)	15.00 (2.80)
Week 24	9.33 (6.62)	17.00 (8.54)	10.40 (7.00)	14.50 (4.95)
NIMH-OC				
Week 0	8.89 (1.18)	8.82 (1.17)	9.53 (1.46)	9.00 (1.40)
Week 12	3.33 (1.81)	5.73 (2.10)	3.73 (1.87)	6.50 (0.71)
Week 24	3.78 (2.34)	6.73 (2.72)	4.73 (2.76)	6.50 (0.71)
CGI-S				
Week 0	4.50 (0.51)	4.91 (0.70)	5.07 (0.46)	5.00 (0)
Week 12	2.28 (1.07)	3.27 (1.19)	2.53 (0.99)	3.50 (0.71)
Week 24	2.33 (1.19)	3.82 (1.33)	2.80 (1.26)	3.50 (0.71)

Mean scores (*sd*) on the Y-BOCS (Yale-Brown Obsessive Compulsive Scale), NIMH-OC (National Institutes of Mental Health Global Obsessive Compulsive Severity Scale), and CGI-S (Clinical Global Impression-Severity scale) are presented for each treatment group. Missing values (e.g., due to dropout or relapse) were imputed using last observation carried forward.
EX/RP, exposure and response (ritual) prevention; CMI, clomipramine; PBO, placebo.

RP group, 50% (18–76%) for the CMI group, 69% (38–97%) for the EX/RP+CMI group, and 41% for the PBO group (39–43%).

OUTCOME

Of all 46 entrants to the Discontinuation Phase, 35 completed it without relapsing. Nine relapsed, one was withdrawn for a protocol violation (i.e., took alprazolam), and one was lost to follow-up. The week these 11 patients relapsed or dropped from the study is shown in Table 1. Of the nine relapsers, all had received active treatment during the Acute Phase (2 EX/RP, 5 CMI, 2 EX/RP+CMI); eight relapsed with a return to Week 0 CGI-S, and one was terminated by the treating clinician because of a rapidly deteriorating clinical state.

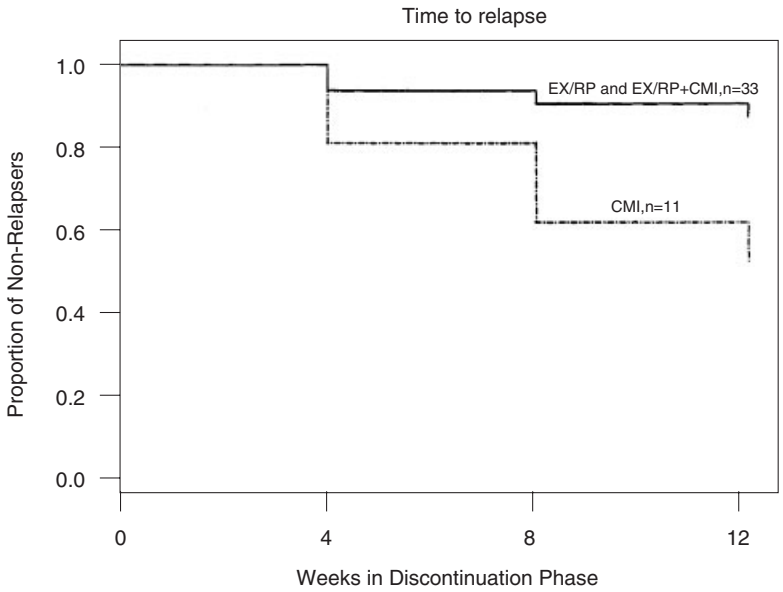

Fig. 1. Time to relapse. Kaplan-Meier estimates for the time to relapse after treatment discontinuation. Responders to clomipramine (CMI) had a significantly shorter time to relapse than responders to exposure and response (ritual) prevention (EX/RP) or EX/RP+CMI (log-rank test χ^2 [1] = 5.80, $P = .017$).

Significantly fewer EX/RP and EX/RP+CMI responders relapsed after treatment discontinuation than responders to CMI alone (4/33 = 12% versus 5/11 = 45%; Fisher's exact test, $P = 0.031$). Exploratory comparisons found that the relapse rates for the EX/RP (2/18 = 11%) and EX/RP+CMI (2/15 = 13%) groups were each lower than for the CMI group (5/11 = 45%), but these differences did not reach significance (Fisher's exact test, $P = .074$); however, the power for detecting them was only .40.

Survival curves for the time to relapse are presented in Figure 1. CMI responders had a significantly shorter time to relapse after treatment discontinuation than the combined group of EX/RP and EX/RP+CMI responders (log-rank test χ^2 [1] = 5.80, $P = .017$). Exploratory comparisons of the three groups found that EX/RP and EX/RP+CMI responders did not significantly differ from each other (log-rank test χ^2 [1] = 0, $P = .872$), but CMI responders had a significantly shorter time to relapse than EX/RP responders (log-rank test χ^2 [1] = 4, $p = .044$) and a nonsignificant shorter time to relapse than EX/RP+CMI responders (log-rank test χ^2 [1] = 3.50, $P = .061$); the power for detecting the latter difference was only .46.

OCD severity at entry to the Discontinuation Phase had a significant effect on the time to relapse (likelihood ratio test: treatment × Week 12 Y-BOCS, χ^2 [1] = 4.61, $P = .031$). Specifically, among EX/RP and EX/RP+CMI responders, those with higher Week 12 Y-BOCS scores were more likely to relapse. In contrast, among CMI responders, those with lower Week 12 Y-BOCS scores were more likely to relapse. Percent Y-BOCS improvement at Week 12 showed a consistent pattern of results, even though the interaction term was not significant at the $P < .05$ level (likelihood ratio tests: treatment × percent Y-BOCS improvement at Week 12: χ^2 [1] = 2.82 , $P = .093$; percent Y-BOCS improvement at Week 12, χ^2 [1] = .27, $P = .604$). Among EX/RP and EX/RP+CMI CMI responders, those with greater percent Y-BOCS improvement were less likely to relapse; in contrast, among CMI responders, those with greater Y-BOCS percent improvement were more likely to relapse. Site had no significant effect on the time to relapse (likelihood ratio tests: treatment × site, χ^2 [1] = 0.56, $P = .454$); site, χ^2 [1] = 1.92, $P = .166$).

DISCUSSION

This is the first study to compare the post-treatment effects of intensive EX/RP and CMI in OCD by following treatment responders after sustained treatment discontinuation and assessing relapse blind to the original treatment. In this study, responders to intensive EX/RP or EX/RP+CMI fared better than responders to CMI alone: they had less severe OCD at the start of the Discontinuation Phase, they were less likely to relapse during the Discontinuation Phase, and they had a significantly longer time to relapse if they did relapse.

The low relapse rate (12%) of EX/RP and EX/RP+CMI responders is consistent with prior findings [Foa and Kozak, 1996] showing that EX/RP effects (with and without medication) persist after treatment

discontinuation. In contrast, the CMI relapse rate (45%) is substantially lower than the 89% relapse rate reported by Pato et al. [1988], the only double-blind CMI discontinuation study in adults. Differences in method of discontinuation (CMI was discontinued over 4 days in Pato et al. [1988] versus 4 weeks in this study), in CMI duration before discontinuation (the mean CMI duration was 10.7 (5.5) months in Pato et al. [1988] versus 12 weeks in this study), and in relapse definition (relapse was defined as a "substantial recurrence" of OCD symptoms after CMI was substituted with PBO in Pato et al. [1988] versus a return to pretreatment OCD severity in this study) could all account for the discrepancy. In an open-label study of 13 CMI responders whose CMI was discontinued after 6 months and where relapse was defined as a 25% Y-BOCS increase plus a rating of much or very much worse relative to being on CMI, Ravizza et al. [1996] also found a substantially lower 3-month relapse rate (30.8%) after CMI discontinuation than Pato et al. [1988].

Our findings, together with those of Ravizza et al. [1996], suggest that the short-term relapse rate after CMI discontinuation (whether defined as a return to pretreatment severity as in our study or as an increase in symptoms relative to being on CMI as in Ravizza et al., 1996) may be substantially lower than previously thought, and thereby more similar to SSRI relapse rates [Koran et al., 2002; Romano et al., 2001]. Methodological differences (e.g., length on medication before discontinuation, length of follow-up, use of placebo substitution, relapse definition) make direct comparisons with these SSRI studies difficult. In their open-label study, Ravizza et al. [1996] found no significant differences between CMI, FLX, and fluvoxamine in the cumulative proportion of relapsers 2 years after SRI discontinuation. After 2 years, however, the relapse rates were all $>76\%$ (and significantly greater than the relapse rates of those who continued on SRIs), suggesting that most OCD patients who discontinue their SRI (regardless of which one) will eventually suffer a worsening of OCD.

OCD severity at entry to the Discontinuation Phase had different effects on the likelihood of relapse depending on the treatment received. Amongst EX/RP and EX/RP+CMI responders, those with greater OCD severity after treatment were at higher risk of relapsing, confirming prior findings [Foa et al., 1983]. In contrast, CMI responders with less severe OCD after treatment were at greater risk of relapsing. Two scenarios could account for this difference: 1) EX/RP and EX/RP+CMI patients with relatively less severe OCD at Week 12 learned well how to do EX/RP and did not relapse during the Discontinuation Phase because they correctly applied EX/RP techniques on their own; and 2) CMI patients with relatively less severe OCD at Week 12 had a true medication (versus a placebo) response, which was lost once CMI was discontinued.

This study has a number of limitations. First, the sample size was small because recruitment was limited to responders who completed the first 12 weeks of active treatment. For this reason, the study was originally designed (and only had sufficient power) to compare EX/RP and CMI relapse rates when the two groups receiving EX/RP were combined. Despite the small sample, however, significant differences in relapse rates were observed. Second, patients received only 12 weeks of treatment before treatment was discontinued. Longer treatment may have led to less relapse. In the only double-blind CMI discontinuation study in adults [Pato et al., 1988], the CMI relapse rate was higher despite longer treatment (although other factors could explain the higher rate, as discussed above). Third, patients were followed after treatment discontinuation for only 12 weeks. During these 12 weeks, they met briefly with their treating clinicians every 2 weeks for general support and monitoring of clinical status. With longer follow-up (or less clinical contact), the relapse rates could be substantially higher, as found by Ravizza et al. [1996] for CMI. Fourth, our results are based on an a priori and conservative definition of relapse (i.e., a return to pretreatment severity) and on one OCD measure (i.e., the CGI-S). However, exploratory analyses using the CGI-I or Y-BOCS scale produced comparable results. A complete post hoc analysis of relapse using various definitions of relapse (e.g., definitions based on a return to pretreatment severity versus a worsening relative to treatment completion and constructed using different OCD measures) will be presented elsewhere. Fifth, we can not exclude the possibility that the extra clinician time received during the Acute Phase by the groups receiving EX/RP versus the group receiving CMI alone contributed nonspecifically to their lower relapse rates during the Discontinuation Phase. Sixth, although the IEs who determined relapse were blind to randomization, IEs and patients knew treatment was being discontinued, introducing possible expectancy bias (but also a situation closer to clinical practice). Moreover, even though IEs met regularly to maintain reliability, formal data on inter-rater reliability were not collected. Seventh, the study was not designed (and did not have the power) to detect small differences between EX/RP and EX/RP+CMI. Our data, however, did not show a trend toward combined therapy and medication losing its effects after treatment discontinuation as found by Barlow et al. [2000] in patients with panic disorder.

Our results are applicable to intensive EX/RP and CMI, currently two of the most efficacious treatments for OCD; similar data are needed for less intensive versions of EX/RP and for the SSRIs, which are used more commonly in clinical practice. Whether EX/RP, if diluted, would retain its superiority over medication is unknown. Abramowitz et al. [2003] recently demonstrated that a twice-weekly EX/RP protocol produced

as good results at 3 months follow-up as the intensive EX/RP protocol used here, suggesting that a twice-weekly EX/RP treatment may produce better outcome than SRI treatment as well.

CONCLUSION

In this sample of OCD outpatients seeking care at specialty research centers, responders to intensive EX/RP or EX/RP+CMI had lower relapse rates and longer times to relapse 12 weeks after treatment discontinuation than responders to CMI alone. EX/RP should be adapted for wider use in the treatment of OCD, given the magnitude [Foa et al., in press] and durability of improvement it can produce.

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