Cognitive Therapy versus Fluvoxamine as a Second-Step Treatment in Obsessive-Compulsive Disorder Nonresponsive to First-Step Behavior Therapy

Anton J.L.M. van Balkom^a Paul M.G. Emmelkamp^b Merijn Eikelenboom^a
Adriaan W. Hoogendoorn^a Johannes H. Smit^a Patricia van Oppen^a

^aDepartment of Psychiatry and EMGO⁺ Institute, VU University Medical Center, Academic Outpatient Clinic for Anxiety Disorders, GGZinGeest, and ^bRoyal Netherlands Academy of Arts and Sciences and Department of Clinical Psychology, University of Amsterdam, Amsterdam, The Netherlands

Key Words

Obsessive-compulsive disorder • Treatment resistance • Selective serotonin reuptake inhibitor • Randomized controlled trial • Cognitive behavior therapy • Algorithm

Abstract

Background: To compare the effectiveness of second-step treatment with cognitive therapy (CT) versus fluvoxamine in patients with obsessive-compulsive disorder (OCD) who are nonresponsive to exposure in vivo with response prevention (ERP). **Methods:** A 12-week randomized controlled trial at an outpatient clinic in the Netherlands comparing CT with fluvoxamine in OCD. Of 118 subjects with OCD treated with 12 weeks of ERP, 48 appeared to be nonresponders (Y-BOCS improvement score of less than one third). These nonresponders were randomized to CT (n = 22) or fluvoxamine (n = 26). The main outcome measure was the Y-BOCS severity scale. Statistical analyses were conducted in the intention-to-treat sample (n = 45) on an 'as randomized basis' and in the per-protocol sample (n = 30). Due to selective dropout in the fluvoxamine group, two additional sensitivity analyses were performed. **Results:** Complete data could be obtained

from 45 subjects (94%) after 12 weeks. Fifty percent of the patients refused fluvoxamine after randomization compared to 13% who refused CT [$\chi^2(1) = 7.10$; $p = 0.01$]. CT as a second-step treatment did not appear to be effective in this sample of nonresponders. Fluvoxamine was significantly superior to CT in the intention-to-treat sample, in the per-protocol sample and in the two separately defined samples in which the sensitivity analyses were performed. **Conclusions:** OCD patients who are nonresponsive to ERP may benefit more from a switch to treatment with an antidepressant instead of switching to CT. In clinical practice, it may be important to motivate this subgroup of patients to undergo psychopharmacological treatment, as this may improve their outcome considerably.

Copyright © 2012 S. Karger AG, Basel

Background

In recent decades the development of treatments for obsessive-compulsive disorder (OCD) has radically changed the prognosis for patients from poor to good. A major body of research has shown that OCD may be

successfully treated with two types of first-line treatments: behavior therapy, consisting of exposure in vivo with response prevention (ERP), and serotonergic reuptake inhibitors (SRIs) [1–3]. However, only 50% of all patients remit completely with these first-line treatments in the long term [4]. In an effort to optimize outcome in the treatment of OCD, three strategies have been studied: switching, combining and augmenting treatments.

In clinical guidelines for the treatment of OCD, clinicians are advised to switch from one first-line treatment (either ERP or an SRI) to another first-line treatment in cases of nonresponse [5]. The evidence base for such advice is remarkably thin. The common practice of switching from SRIs to ERP after nonresponse in OCD appeared to be effective in two studies [6, 7]. At present, no systematic studies of patients with OCD who are nonresponsive to ERP have been published.

The effectiveness of switching the first-line treatment of OCD after initial nonresponse to SRIs has been examined only once before. About 40% of patients who were treatment resistant to a first-line SRI and were switched to another SRI became responders after the switch [8].

Another strategy to increase the effectiveness of first-line treatments is to combine them. A growing number of articles evaluating the effectiveness of the combination of ERP and SRIs have been published. Combination studies have shown that the effectiveness of SRIs may be enhanced by the addition of ERP [9–11]. The reverse may not be true: the outcome of ERP usually did not improve when SRIs were added [12–15]. After several months of treatment, the superior results of the combination treatment over ERP alone disappeared [16–18].

Another branch of research into the optimization of the effectiveness of OCD treatments has been dedicated to the augmentation of first-line treatments. This type of research has predominantly been performed in studies of patients with OCD resistant to SRIs [19–21]. The augmentation of SRIs with lithium, buspirone, naltrexone and pindolol has failed to demonstrate effectiveness. The evidence base for the augmentation of SRIs with low dosages of antipsychotics indicates that the proportion of response after augmentation with these drugs increases by 20–50% [22].

The current study examined the question of how to further treat a patient with OCD after nonresponse to treatment with ERP. As a second step, the effectiveness of cognitive therapy (CT) versus the SRI fluvoxamine was compared. In previous trials CT has been found to be as

effective as ERP [23, 24]. We chose ERP as a first step in OCD treatment because of its superiority over pharmacotherapy [9], its relatively easy applicability compared with CT [23] and the preference of OCD patients for non-pharmacological treatment [25]. Because no other second-step studies have been published [26], we based our hypothesis on former first-step studies and hypothesized that CT would be superior to fluvoxamine in decreasing OCD symptoms.

Methods

Design

In the present study we conducted a randomized controlled trial (RCT) to evaluate the efficacy of CT versus fluvoxamine as second-step treatments in a sample of subjects with OCD who were nonresponsive to 12 weeks of ERP as a first-step treatment. This study was conducted between 1999 and 2005 and was accredited by the Ethics Committee of the VU University Medical Center.

Subjects

Subjects included were older than 17 years and had a diagnosis of OCD according to DSM-IV. The diagnosis was confirmed with the Structured Clinical Interview on DSM-IV axis I diagnoses [27], and written informed consent was obtained. Subjects were informed before the start of the first-step treatment that in the case of nonresponse to ERP they would be randomized over treatment with CT or fluvoxamine in the second step. Excluded were subjects with obsessions only, suicidal intent, organic brain disease, past or present psychosis and substance use disorder. In addition, patients were excluded who (i) were treated concomitantly elsewhere, (ii) had been treated with behavior therapy or CT in the 6 months preceding baseline or (iii) used psychoactive drugs. However, the use of benzodiazepines of less than 15 mg diazepam equivalents per day was allowed.

Procedure

Before the start of the first-step treatment, subjects ($n = 146$) were assessed for eligibility for the trial by means of an intake session with an experienced clinician who performed a psychiatric assessment. A total of 118 subjects started 12 weekly sessions comparing the effectiveness of four modes of ERP: (i) therapist-controlled ERP performed by experienced behavior therapists; (ii) therapist-controlled ERP performed by graduate students in clinical psychology; (iii) self-controlled ERP performed by experienced behavior therapists, and (iv) self-controlled ERP performed by graduate students in clinical psychology. The results of this first-step study will be briefly discussed here. Further details are provided elsewhere [28]. Only exposure in vivo was used. In all four treatment conditions patients spent 3 h/week undergoing exposure exercises. In the four conditions, the severity of OCD measured with the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) [29] was significantly decreased. No significant differences were found across these four modes of ERP.

After treatment with ERP (first-step treatment), the patients were assessed again with the Y-BOCS to determine their response status. Response was defined as an improvement equal to or greater than one third (33.3%) on the Y-BOCS. This definition was based on the literature in which response rates in OCD range from more than 20 to 35% on the Y-BOCS [3]. Y-BOCS scores for the responders ($n = 70$) were: mean pretest score = 25.8 (SD = 5.8); mean posttest score = 11.9 (SD = 7.8). The Y-BOCS scores for the nonresponders ($n = 48$) were: mean pretest score = 26.9 (SD = 5.2); mean posttest score = 21.3 (SD = 5.7).

Nonresponders ($n = 48$) were informed of their status and randomized over CT ($n = 22$) or fluvoxamine ($n = 26$). The randomization code was developed by an independent statistician. The details of the series were unknown to any of the researchers. All nonresponders were shifted to a therapist different from the one they had had in the first-step treatment.

Treatments and Therapists

CT and fluvoxamine were administered in an open fashion. No double-blind, placebo-controlled condition was included in the design because the placebo effect in OCD is known to be small [1–3, 30] and the superiority of fluvoxamine over placebo in OCD is well known [31].

Cognitive Therapy. Subjects received twelve 45-min sessions with CT. The protocol was based on Beck's model consisting of the application of techniques that are especially suitable for OCD. The general strategies were: firstly, to consider intrusions as stimuli; secondly, to identify negative automatic thoughts; thirdly, to challenge these automatic thoughts, and finally, to change these distressing thoughts into nondistressing thoughts. The therapist challenged misinterpretations associated with beliefs in the main domains identified by the Obsessive Compulsive Cognition Working Group [32]. Furthermore, patients were instructed to monitor and challenge automatic thoughts in diaries at home. The main focus in this treatment was on potentially biased reasoning styles such as inflated personal responsibility, overestimation of danger, perfectionism and the overimportance of thoughts [33, 34]. After session 6, behavioral experiments were introduced and were used to test the empirical basis of the dysfunctional assumptions.

Fluvoxamine. Subjects underwent seven 30-min sessions in 12 weeks (week 1, 2, 3, 4, 6, 8, 12). Fluvoxamine was started at 50 mg/night. In the absence of adverse events, the dosage was increased to 300 mg/day after 3 weeks of treatment and further kept at a constant level [31]. The mean daily dosage was 200 mg (SD = 86.6 mg; 50–300 mg) at week 12. After 12 weeks, fluvoxamine plasma levels were measured. One subject refused to have blood taken. The mean fluvoxamine plasma level was 231.3 mg/l (SD = 76.7 mg/l; range 45–276 mg/l). At every session, concomitant illnesses, concomitant medications and adverse events were recorded. Neither formal exposure exercises nor cognitive treatment were provided.

Therapists. Four experienced therapists (3 women, 1 man) provided CT. All therapists had broad experience with CT in anxiety disorders and were specially trained for this RCT by P.v.O. and P.E. Each had a Master's degree in clinical psychology and was certified as supervisor by the Netherlands Association of Behavior Therapy and CT. Three experienced senior psychiatrists (1 woman, 2 men) provided treatment with fluvoxamine. Each cognitive behavioral therapist and psychiatrist had approximate-

ly 15 years of experience with the treatment of OCD. They were also experienced in the delivery of CT-protocolized treatments within the framework of other RCTs [12, 23].

Treatment Delivery. Extensive manuals were used to guide both treatment conditions. All CT sessions were recorded on audiotape. The therapists attended weekly supervision sessions with P.v.O. and P.E. In these supervision sessions, adherence to the treatment protocol was checked to ensure fidelity to the method and principles of CT. No formal fidelity ratings were used. The supervisors reviewed parts of all audiotapes from all patients. The supervisors assisted in planning the content of future sessions. In the vast majority of cases, the therapists adhered strictly to the manual and the therapeutic methodology.

Measures

Subjects were assessed at pretest and posttest sessions with self-rated and assessor-rated measurement instruments. All interviewers were trained, certified, monitored and supervised in the assessment techniques and blind to the treatment being evaluated.

The primary outcome measure was the clinician-rated Y-BOCS ranging from 0 to 40 [29].

Secondary outcome measures included: (i) *responder status* – subjects were considered responders when their posttest score measured with the Y-BOCS had decreased equal to or greater than one third (33.3%) compared with their pretest score; (ii) *presence and severity of obsessive-compulsive symptoms* were measured with the self-rated 41-item Padua Inventory-Revised ranging from 0 to 164 [35] and the assessor-rated Anxiety Discomfort Scale [36]; the latter scale consists of 5 idiosyncratic situations that are scored on a 9-point scale measuring the level of anxiety and discomfort in the specific OCD situation (range 0–40); (iii) *presence and severity of depressive and anxiety symptoms* – the severity of depressive symptoms was assessed with the self-rated 21-item Beck Depression Inventory, ranging from 0 to 63 [37]; in addition, the Beck Anxiety Inventory [38], a 21-item measure of the severity of anxiety symptoms ranging from 21 to 84, was used. Furthermore, the Comprehensive Psychopathological Rating Scale, a 67-item assessor rating addressing a wide range of psychiatric signs and symptoms, was administered; two of its subscales were used: depression symptoms were measured with the Montgomery-Åsberg Depression Rating Scale ([39] 21 items, range 0–126), while anxiety symptoms were assessed with the Brief Anxiety Rating Scale (6 items, range 0–36) [40]; (iv) *adverse events* were rated every session with the Fawcett side effect scale by the psychiatrists treating patients with fluvoxamine [41].

Statistical Analyses

Pretreatment differences in demographic and clinical status variables between CT and fluvoxamine were analyzed with non-parametric and parametric tests. Statistical analyses were performed with the intention-to-treat samples on an 'as randomized' basis ($n = 45$) and were repeated in the per-protocol sample ($n = 30$).

The differential treatment outcome after 12 weeks was analyzed with repeated measures analyses of variance with Y-BOCS as the primary outcome measure, two assessments (pretest and posttest) and two conditions (CT and fluvoxamine). Time effects were analyzed with paired *t* tests. In the statistical analysis of the

secondary outcome variables, the variables measuring (i) obsessive compulsive symptoms, (ii) anxiety symptoms and (iii) depression symptoms were analyzed in three separate repeated measures multivariate analyses of variance (MANOVA).

The difference in the proportion of responders between the two conditions was analyzed with Fisher's exact test. The presence and severity of side effects were presented with summarizing statistics. Data were analyzed with SPSS version 15.0 and with Stata version 11.0 (multiple imputation part).

Selective Dropout and Missing Data. Due to selective dropout in the condition fluvoxamine, missing data in the per-protocol sample appeared to be *not* missing completely at random [42]. Little's missing completely at random test statistic [43] showed significant differences between the per-protocol sample versus treatment dropouts or refusers on the pretest score on the Y-BOCS: $\chi^2(1) = 5.0$, $p = 0.025$. We chose to address the selective dropout problem in the per-protocol analysis by presenting sensitivity analyses in two additionally defined intent-to-treat samples. To sum up, for the primary outcome variable, four analyses will be presented: (i) intent-to-treat sample A ($n = 45$): after 12 weeks, all subjects enrolled in this study were invited to the posttest assessment; 3 subjects were not willing to complete this assessment, resulting in the following complete pretest and posttest data: CT $n = 20$; fluvoxamine $n = 25$; (ii) per-protocol sample ($n = 30$): subjects were included in this sample when they used medication for the complete 12-week period or when they attended all 12 scheduled CT sessions: CT $n = 17$; fluvoxamine $n = 13$. Two sensitivity analyses in additionally defined intent-to-treat samples: (iii) intent-to-treat sample B, construed with the conservative last observation carried forward analysis ($n = 48$; CT $n = 22$; fluvoxamine $n = 26$), including the completers, refusers and dropouts. For the latter two groups, the pretest score served as the posttest score; (iv) intent-to-treat sample C with multiple imputation ($n = 48$; CT $n = 22$; fluvoxamine $n = 26$), including the completers, refusers and dropouts; the missing posttest score was imputed with Stata's 'mi impute' procedure with the option that uses multivariate normal distribution as a probability model for the complete data [42, 43].

Results

Attrition

The initial intake procedure yielded 146 eligible subjects. Of these, 118 (81%) entered the first-step treatment consisting of 12 weeks of ERP. The flow of subjects from initial recruitment through final analysis is presented in figure 1. After the first-step treatment, 48 subjects were considered nonresponders and randomized to CT ($n = 22$) or fluvoxamine ($n = 26$).

As indicated in figure 1, complete data after 12 weeks could be obtained for 45 subjects (94%), who were included in the intent-to-treat sample A. The per-protocol sample included 30 subjects (62%): 16 (33%) refused the treatment condition they had been assigned to and 2 (5%) dropped out prematurely. The proportion of refusing

subjects differed significantly over the two conditions [Fisher's exact test: $\chi^2(1) = 7.10$; $p = 0.01$]. All subjects refusing fluvoxamine indicated they were reluctant to take prescriptions for their obsessive-compulsive symptoms. In CT, subjects refused treatment because they wanted to stop symptom-specific psychotherapy, for example because of the homework assignments.

The per-protocol sample was compared with dropouts and refusers on all relevant demographic and clinical variables measured at the pretest assessment. No significant differences were found with respect to gender, marital status, education level, comorbidity with anxiety or depressive disorders, duration of OCD and number of previous treatments (all $p > 0.10$). However, some analyses of the clinical ratings suggested that dropouts and refusers suffered from less severe symptoms than the per-protocol sample: Y-BOCS, refusers/dropouts: mean = 21.6 (SD = 3.5); per protocol: mean = 24.4 (SD = 5.4); $t(d.f. = 46) = 1.94$; $p = 0.06$; Brief Anxiety Rating Scale, refusers/dropouts: mean = 7.2 (SD = 4.1); per protocol: mean = 10.4 (SD = 4.5); $t(d.f. = 46) = 2.4$; $p = 0.02$.

Pretest Characteristics

Demographic and clinical status variables of the intent-to-treat sample are presented in table 1. No significant differences emerged between the two conditions in any of the demographic data or in the primary and the secondary outcome measures.

Primary Outcome Measure

In table 2 the means and standard deviations of the Y-BOCS at pretest and posttest sessions for the two treatment conditions are presented, as well as the results of the repeated measures analyses conducted in the four differently defined samples. In all four analyses, the results indicated that fluvoxamine was superior to CT.

Secondary Outcome Measures

Responder Status. Subjects were considered responders when their posttest Y-BOCS score decreased equal to or greater than one third (33.3%) compared with the pretest score. In the intent-to-treat A sample ($n = 45$), 8 of 25 subjects (32%) randomized to fluvoxamine could be considered as responders versus 1 of 20 subjects (5%) randomized to CT [Fisher's exact test: $\chi^2(1) = 5.07$; $p = 0.03$].

Obsessive-Compulsive Symptoms, Anxiety and Depression Symptoms. Three separate multivariate repeated measures analyses of variance were carried out: (i) with two OCD measures, (ii) with two anxiety measures and (iii) with two depression measures. Means, standard de-

Fig. 1. Flow of the patients from initial recruitment to final analysis. EXP = Exposure; SCID = Structured Clinical Interview for DSM-III-R. Due to differential dropout rates in the fluvoxamine condition, sensitivity analyses were conducted in two differently defined intent-to-treat samples, B and C; see text for the definition of these samples.

viations and outcomes of the MANOVAs are presented in table 3. As this table shows, after 12 weeks no significant differences between the two treatment conditions were found for any of the measures. To investigate how the scores on these measurements differed between respond-

ers and nonresponders, repeated measures analyses of variance were carried out for all the measurements, indicating that responders improved significantly more than nonresponders on all outcome measures (all $p < 0.05$).

Table 1. Demographic and clinical status variables at the pretest assessment

	CT (n = 22)	Fluvoxamine (n = 26)	Statistics
Male gender	10 (45%)	10 (38%)	$\chi^2(1) = 0.24$; $p = 0.62$
Single	6 (27%)	12 (46%)	$\chi^2(1) = 1.81$; $p = 0.18$
Paid employment	11 (50%)	13 (50%)	$\chi^2(1) = 0.00$; $p = 1.00$
OCD only ¹	10 (45%)	9 (35%)	$\chi^2(2) = 0.58$; $p = 0.44$
Comorbid anxiety disorders ¹	8 (36%)	8 (31%)	$\chi^2(2) = 0.17$; $p = 0.68$
Comorbid affective disorders ¹	5 (23%)	10 (38%)	$\chi^2(2) = 1.17$; $p = 0.24$
Age, years	37.4 (14.4)	36.1 (9.3)	$t(46) = 0.40$; $p = 0.69$
Education, years	12.9 (3.6)	13.3 (3.3)	$t(44) = 0.40$; $p = 0.69$
Duration of OCD, years	19.9 (13.1)	18.3 (10.1) ²	$t(41) = 0.44$; $p = 0.66$
Number of comorbid disorders ¹	2.0 (1.1)	1.9 (0.8)	$t(46) = 0.38$; $p = 0.71$
Number of previous treatments	2.2 (2.1)	2.1 (1.3)	$t(46) = 0.21$; $p = 0.83$

Results are presented as means (SD) or numbers (%).

¹ Assessed using the Structured Clinical Interview for DSM-IV disorders.

² n = 23; data missing for 3 subjects.

Table 2. Means $\pm$ SD and outcomes of the statistical analyses of the primary outcome measure Y-BOCS in (i) the a priori defined intent-to-treat sample A, (ii) the a priori defined per-protocol sample, and two sensitivity analyses in (iii) intent-to-treat sample B and (iv) intent-to-treat sample C

	Pretest assessment	Posttest assessment	Repeated-measures ANOVA
Intent-to-treat sample A			
CT (n = 20)	22.1 $\pm$ 4.6	22.3 $\pm$ 7.0	Time: $F(1, 43) = 3.83$; $p = 0.057$
Fluvoxamine (n = 25)	23.9 $\pm$ 5.4	19.8 $\pm$ 6.9*	Time $\times$ cond.: $F(1, 43) = 4.65$; $p = 0.037$
Per-protocol sample			
CT (n = 17)	23.0 $\pm$ 4.2	23.1 $\pm$ 4.7	Time: $F(1, 28) = 7.40$; $p = 0.013$
Fluvoxamine (n = 13)	26.2 $\pm$ 6.4	19.2 $\pm$ 8.0*	Time $\times$ cond.: $F(1, 28) = 7.92$; $p = 0.005$
Intent-to-treat sample B ¹			
CT (n = 22)	22.4 $\pm$ 4.9	22.7 $\pm$ 7.0	Time: $F(1, 46) = 3.39$; $p = 0.072$
Fluvoxamine (n = 26)	23.9 $\pm$ 5.3	19.9 $\pm$ 6.8*	Time $\times$ cond.: $F(1, 46) = 5.41$; $p = 0.025$
Intent-to-treat sample C ²			
CT (n = 22)	22.7 $\pm$ 4.5	23.1 $\pm$ 7.2	Time: $F(1, 34.88) = 3.65$; $p = 0.064$
Fluvoxamine (n = 26)	23.9 $\pm$ 5.3	17.7 $\pm$ 8.1*	Time $\times$ cond.: $F(1, 37.0) = 4.84$; $p = 0.034$

Cond. = Condition. * $p = 0.01$, paired t test (pretest vs. posttest data). ¹ Missing posttest data obtained by imputation with pretest (last observation carried forward). ² Missing posttest data obtained by multiple imputation: means and SDs are averaged over 50 imputed data sets. Repeated-measures ANOVA test statistics are derived from a corresponding regression analysis.

Adverse Events. Adverse events were inventoried at each treatment session. None of the patients dropped out prematurely due to side effects. The most frequently reported side effects were: nausea and anorexia (n = 5); sexual dysfunction (n = 3); headache (n = 2); sleeplessness (n = 2).

Conclusions

This study addresses the question of how to further treat patients with OCD after nonresponse to treatment with ERP and compares the effectiveness of CT with the SRI fluvoxamine. Fluvoxamine appeared to be signifi-

Table 3. Means $\pm$ SD and outcomes of MANOVA of the secondary outcome measures in the intent-to-treat sample A

Measure	CT (n = 20)		Fluvoxamine (n = 25)		MANOVA	
	pretest	posttest	pretest	posttest	F(1, 36)	p
ADS	22.9 $\pm$ 10.8	22.4 $\pm$ 11.4	25.4 $\pm$ 6.0	22.8 $\pm$ 9.7	0.69	0.41
PI-R	59.5 $\pm$ 23.7	57.7 $\pm$ 28.9	66.7 $\pm$ 26.0	60.5 $\pm$ 30.3	2.4	0.13
BDI	16.8 $\pm$ 10.0	15.8 $\pm$ 11.2	16.6 $\pm$ 11.5	15.4 $\pm$ 11.5	0.97	0.33
BAI	18.4 $\pm$ 12.0	17.8 $\pm$ 15.4	17.0 $\pm$ 8.7	15.7 $\pm$ 9.3	0.20	0.66
MADRS	30.1 $\pm$ 14.9	27.7 $\pm$ 18.6	33.8 $\pm$ 17.5	29.2 $\pm$ 17.2	0.06	0.81
BAS	8.4 $\pm$ 3.7	7.8 $\pm$ 5.2	9.9 $\pm$ 5.2	8.4 $\pm$ 4.5	0.04	0.84

ADS = Anxiety Discomfort Scale; PI-R = Padua Inventory Revised; BDI = Beck Depression Inventory; BAI = Beck Anxiety Inventory; MADRS = Montgomery-Åsberg Depression Rating Scale; BAS = Brief Anxiety Rating Scale.

cantly superior to treatment with CT. In addition, although subjects had been informed before the start of the first step, consisting of ERP, that in the case of nonresponse they would be randomized over treatment with CT or fluvoxamine, many patients refused treatment with fluvoxamine after they had been informed that they had been randomized to that treatment in the second step.

In this second-step study, fluvoxamine was found to be superior to CT. This finding is not in line with previous first-step findings, in which psychotherapy in OCD is usually superior to treatment with SRIs [9, 44]. In addition, CT did not appear to be effective at all in patients who were nonresponsive to ERP. A potential reason for nonresponse to CT is the fact that CT is a demanding treatment, one that might be experienced as even more difficult by patients who have just completed ERP. Moreover, patients might have felt less confident about CT after being nonresponders to ERP. Unfortunately, we did not collect data that evaluated the degree of motivation of the patients when starting CT. Finally, a possible explanation for the nonresponse to CT may be found in the similar underlying mechanisms of change of CT and ERP [45].

Our finding that treatment of OCD with an SRI may be efficacious after nonresponse to behavior therapy corroborates the findings of a predictor study using a pretreatment scan with 18-fluorodeoxyglucose positron emission tomography [46]. Higher metabolic activity in the left orbitofrontal cortex was associated with a better response to behavior therapy, while lower activity was associated with a superior effect by fluoxetine. It was con-

cluded that subjects with different patterns of metabolism preferentially respond to one type of treatment versus the other. This suggests a neurobiological underpinning to differential treatment reactions, stressing the importance of a radical change of treatment modality in the case of nonresponse.

If SRIs and CT or ERF are indeed complementary, with some patients responding to one modality and other patients responding to the other, it is remarkable that no additive treatment effects have been observed in combination treatments [12–15]. These apparently conflicting findings may be caused by the attenuation of glucocorticoid activity by antidepressants which may interfere with extinction learning in ERP when these treatments are combined [47]. In other words: the combination of antidepressants with CT or ERF may be qualitatively different from antidepressants alone as a second-step strategy.

To our knowledge, this is the first study of evidence-based choice in a sample of behavior therapy for nonresponders with OCD. The present study showed that a switch to medication may be problematic for some patients initially treated with psychotherapy. In panic disorder patients it was shown that those who did not respond to exposure showed poor tolerance of and compliance with second-step pharmacological treatment [48]. It is possible that in the present study the inclusion of subjects with a preference for behavior therapy versus drug treatment has influenced the characteristics of the present sample. However, in general, patients with OCD have a preference for psychotherapy [25].

Studies comparing drug and nondrug treatments must take into account the distribution of the therapists

over the conditions and the number and duration of the sessions [30]. The starting point in addressing these problems was clinical practice. Therefore, fluvoxamine was administered by psychiatrists, and CT was administered by cognitive behavioral therapists. Not only did the treatment conditions differ in the disciplines of the therapists, they differed in their number and duration (fluvoxamine: 7 sessions of 30 min; CT: 12 sessions of 45 min). It cannot be ruled out that these differences have influenced our findings. However, where attention would have been an important element in treatment, we would have expected to find superior results from CT since it meant that therapists paid more attention to patients. This was definitely not the case.

Some limitations of the present study need to be addressed. We did not include a placebo condition but compared two active treatments in an open fashion. Thus, the design did not control for a nonspecific pharmacological treatment effect. However, the placebo effect of OCD is known to be small [1–3, 49, 50]. This was corroborated in this RCT by the absence of an effect of CT.

Furthermore, this study might be criticized because of the selective dropout rate in the fluvoxamine condition. We dealt with the selective dropout rate in the fluvoxamine condition as follows: (i) the intent-to-treat analysis was done on an ‘as randomized basis’ with complete post-test measures of 94% of the included subjects; (ii) in addition to the a priori intent-to-treat and per-protocol analyses, two additional sensitivity analyses were per-

formed with differently defined samples. In all four types of analyses and in the responder analysis, the same conclusion was shown: fluvoxamine was superior to CT, indicating that the results are robust.

Other potential criticisms involve the absence of an independent fidelity rating of adherence of the therapists to the CT manual. Although the supervisors (P.v.O. and P.E.) did not notice adherence problems during supervision when audiotapes were used, adherence problems cannot be precluded entirely.

We may conclude that the present study of OCD non-responders to ERP has demonstrated that instead of switching to CT, patients could benefit more from switching to an SRI. Since little to no research has been done on ERP nonresponders, a good avenue of research for future studies could be trying a second course of ERP after patients have been stabilized on a second-step SRI. In addition, the study has shown that it may be difficult for some patients to make a switch from ERP to antidepressants. A challenging task for further research is to investigate whether motivational strategies are able to increase the feasibility of the use of SRIs as a second step in patients with OCD nonresponsive to first-step ERP.

Disclosure Statement

None of the authors report financial or personal relationships or affiliations that could inappropriately influence (or bias) their decisions, work or this article.

References

- 1 Abramowitz JS: Effectiveness of psychological and pharmacological treatments for obsessive-compulsive disorder: a quantitative review. *J Consult Clin Psychol* 1997;65:44–52.
- 2 Kobak KA, Greist JH, Jefferson JW, Katelnick DJ, Henk HJ: Behavioral versus pharmacological treatments of obsessive compulsive disorder: a meta-analysis. *Psychopharmacology (Berl)* 1998;136:205–216.
- 3 Eddy KT, Dutra L, Bradley R, Westen D: A multidimensional meta-analysis of psychotherapy and pharmacotherapy for obsessive-compulsive disorder. *Clin Psychol Rev* 2004;24:1011–1030.
- 4 Van Oppen P, van Balkom AJ, de Haan E, van Dyck R: Cognitive therapy and exposure in vivo alone and in combination with fluvoxamine in obsessive-compulsive disorder: a 5-year follow-up. *J Clin Psychiatry* 2005;66:1415–1422.
- 5 Koran LM, Hanna GL, Hollander E, Nestadt G, Simpson HB: Practice guideline for the treatment of patients with obsessive-compulsive disorder. *Am J Psychiatry* 2007;164(suppl):5–53.
- 6 Tolin DF, Hannan S, Maltby N, Diefenbach GJ, Worhunsky P, Brady RE: A randomized controlled trial of self-directed versus therapist-directed cognitive-behavioral therapy for obsessive-compulsive disorder patients with prior medication trials. *Behav Ther* 2007;38:179–191.
- 7 Anand N, Sudhir PM, Math SB, Thennarasu K, Janardhan Reddy YC: Cognitive behavior therapy in medication non-responders with obsessive-compulsive disorder: a prospective 1-year follow-up study. *J Anxiety Disord* 2011;25:939–945.
- 8 Denys D, van Megen HJ, van der Wee N, Westenberg HG: A double-blind switch study of paroxetine and venlafaxine in obsessive-compulsive disorder. *J Clin Psychiatry* 2004;65:37–43.
- 9 Foa EB, Liebowitz MR, Kozak MJ, Davies S, Campeas R, Franklin ME, Huppert JD, Kjernisted K, Rowan V, Schmidt AB, Simpson HB, Tu X: Randomized, placebo-controlled trial of exposure and ritual prevention, clomipramine, and their combination in the treatment of obsessive-compulsive disorder. *Am J Psychiatry* 2005;162:151–161.
- 10 Tenneij NH, van Megen HJ, Denys DA, Westenberg HG: Behavior therapy augments response of patients with obsessive-compulsive disorder responding to drug treatment. *J Clin Psychiatry* 2005;66:1169–1175.
- 11 Simpson HB, Foa EB, Liebowitz MR, Ledley DR, Huppert JD, Cahill S, Vermees D, Schmidt AB, Hembree E, Franklin M, Campeas R, Hahn CG, Petkova E: A randomized, controlled trial of cognitive-behavioral therapy for augmenting pharmacotherapy in obsessive-compulsive disorder. *Am J Psychiatry* 2008;165:621–630.

- 12 Van Balkom AJ, de Haan E, van Oppen P, Spinhoven P, Hoogduin KA, van Dyck R: Cognitive and behavioral therapies alone versus in combination with fluvoxamine in the treatment of obsessive compulsive disorder. *J Nerv Ment Dis* 1998;186:492–499.
- 13 Marks IM, Stern RS, Mawson D, Cobb J, McDonald R: Clomipramine and exposure for obsessive-compulsive rituals: *Br J Psychiatry* 1980;136:1–25.
- 14 Marks IM, Lelliot PT, Basoglu M, Noshirvani H, Monteiro W, Cohen D, Kasvikis Y: Clomipramine, self-exposure and therapist-aided exposure for obsessive-compulsive rituals. *Br J Psychiatry* 1988;152:522–534.
- 15 Cottraux J, Mollard E, Bouvard M, Marks I, Sluys M, Nury AM, Douge R, Cialdella P: A controlled study of fluvoxamine and exposure in obsessive-compulsive disorder. *Int Clin Psychopharmacol* 1990;5:17–30.
- 16 Cottraux J, Mollard E, Bouvard M, Marks I: Exposure therapy, fluvoxamine, or combination treatment in obsessive-compulsive disorder: one-year follow-up. *Psychiatry Res* 1993;49:63–75.
- 17 Hohagen F, Winkelmann G, Rasche-Ruchle H, Hand I, Konig A, Munchau N, Hiss H, Geiger-Kabisch C, Kappler C, Schramm P, Rey E, Aldenhoff J, Berger M: Combination of behaviour therapy with fluvoxamine in comparison with behaviour therapy and placebo. Results of a multicentre study. *Br J Psychiatry Suppl* 1998;35:71–78.
- 18 Aderka IM, Anholt GE, van Balkom AJLM, Smit JH, Hermesh H, van Oppen P: Sudden gains in the treatment of obsessive-compulsive disorder. *Psychother Psychosom* 2012;81:44–51.
- 19 Bloch MH, Landeros-Weisenberger A, Kelmendi B, Coric V, Bracken MB, Leckman JF: A systematic review: antipsychotic augmentation with treatment refractory obsessive-compulsive disorder. *Mol Psychiatry* 2006;11:622–632.
- 20 Ipser JC, Carey P, Dhansay Y, Fakier N, Seedat S, Stein DJ: Pharmacotherapy augmentation strategies in treatment-resistant anxiety disorders. *Cochrane Database Syst Rev* 2006;4:CD005473.
- 21 Walsh KH, McDougle CJ: Pharmacological augmentation strategies for treatment-resistant obsessive-compulsive disorder. *Expert Opin Pharmacother* 2004;5:2059–2067.
- 22 Fineberg NA, Gale TM, Sivakumaran T: A review of antipsychotics in the treatment of obsessive compulsive disorder. *J Psychopharmacol* 2006;20:97–103.
- 23 Van Oppen P, de Haan E, van Balkom AJ, Spinhoven P, Hoogduin K, van Dyck R: Cognitive therapy and exposure in vivo in the treatment of obsessive compulsive disorder. *Behav Res Ther* 1995;33:379–390.
- 24 Cottraux J, Note I, Yao SN, Lafont S, Note B, Mollard E, Bouvard M, Sauteraud A, Bourgeois M, Dartigues JF: A randomized controlled trial of cognitive therapy versus intensive behavior therapy in obsessive compulsive disorder. *Psychother Psychosom* 2001;70:288–297.
- 25 Prins MA, Verhaak PF, Bensing JM, van der Meer K: Health beliefs and perceived need for mental health care of anxiety and depression – the patients' perspective explored. *Clin Psychol Rev* 2008;28:1038–1058.
- 26 Tomba E: Nowhere patients. *Psychother Psychosom* 2012;981:69–72.
- 27 Spitzer RL, Williams JB, Gibbon M, First MB: The Structured Clinical Interview for DSM-III-R (SCID). I. History, rationale, and description. *Arch Gen Psychiatry* 1992;49:624–629.
- 28 Van Oppen P, van Balkom AJ, Smit JH, Schuurmans J, van Dyck R, Emmelkamp PM: Does the therapy manual or the therapist matter most in treatment of obsessive-compulsive disorder? A randomized controlled trial of exposure with response or ritual prevention in 118 patients. *J Clin Psychiatry* 2010;71:1158–1162.
- 29 Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, Heninger GR, Charney DS: The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. *Arch Gen Psychiatry* 1989;46:1006–1011.
- 30 Elkin I, Pilkonis PA, Docherty JP, Sotsky SM: Conceptual and methodological issues in comparative studies of psychotherapy and pharmacotherapy. II. Nature and timing of treatment effects. *Am J Psychiatry* 1988;145:1070–1076.
- 31 Goodman WK, Price LH, Delgado PL, Palumbo J, Krystal JH, Nagy LM, Rasmussen SA, Heninger GR, Charney DS: Specificity of serotonin reuptake inhibitors in the treatment of obsessive-compulsive disorder. Comparison of fluvoxamine and desipramine. *Arch Gen Psychiatry* 1990;47:577–585.
- 32 Obsessive Compulsive Cognitions Working Group: Psychometric validation of the Obsessive Beliefs Questionnaire and the Interpretation of Intrusions Inventory. Part I. *Behav Res Ther* 2003;41:863–878.
- 33 Van Oppen P, Arntz A: Cognitive therapy for obsessive-compulsive disorder. *Behav Res Ther* 1994;32:79–87.
- 34 Steketee G, Siev J, Fama JM, Keshaviah A, Chosak A, Wilhelm S: Predictors of treatment outcome in modular cognitive therapy for obsessive-compulsive disorder. *Depress Anxiety* 2011;28:333–341.
- 35 Anholt GE, van Oppen P, Emmelkamp PM, Cath DC, Smit JH, van Dyck R, van Balkom AJ: Measuring obsessive-compulsive symptoms: Padua Inventory-Revised vs Yale-Brown Obsessive Compulsive Scale. *J Anxiety Disord* 2009;23:830–835.
- 36 Watson JP, Marks IM: Relevant and irrelevant fear in flooding – a crossover study of phobic patients. *Behav Ther* 1971;2:275–293.
- 37 Beck AT, Ward CH, Mendelson M, Mock JE, Erbaugh J: An inventory for measuring depression. *Arch Gen Psychiatry* 1961;4:561–571.
- 38 Beck AT, Epstein N, Brown G, Steer RA: An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol* 1988;56:893–897.
- 39 Davidson J, Turnbull CD, Strickland R, Miller R, Graves K: The Montgomery-Asberg Depression Scale: reliability and validity. *Acta Psychiatr Scand* 1986;73:544–548.
- 40 Goekoop JG, Hoeksema T, Knoppert-Van der Klein EA, Klinkhamer RA, Van Gaalen HA, van Londen L, De Weme R, Zwinderman AH: Multidimensional ordering of psychopathology. A factor-analytic study using the Comprehensive Psychopathological Rating Scale. *Acta Psychiatr Scand* 1992;86:306–312.
- 41 Fawcett S: Symptoms, signs, side effects checklist. *Psychopharmacol Bull* 1987;23:322–323.
- 42 Hamer RM, Simpson PM: Last observation carried forward versus mixed models in the analysis of psychiatric clinical trials. *Am J Psychiatry* 2009;166:639–641.
- 43 Little RJA: A test of missing completely at random for multivariate data with missing values. *J Am Stat Assoc* 1988;83:1198–1202.
- 44 Schruers KR: Group cognitive behavioural therapy increases complete remission of obsessive-compulsive disorder symptoms compared with sertraline, but not response. *Evid Based Ment Health* 2007;10:25.
- 45 Anholt GE, Kempe P, de Haan E, van Oppen P, Cath DC, Smit JH, van Balkom AJ: Cognitive versus behavior therapy: processes of change in the treatment of obsessive-compulsive disorder. *Psychother Psychosom* 2008;77:38–42.
- 46 Brody AL, Saxena S, Schwartz JM, Stoessel PW, Maidment K, Phelps ME, Baxter LR Jr: FDG-PET predictors of response to behavioral therapy and pharmacotherapy in obsessive compulsive disorder. *Psychiatry Res* 1998;84:1–6.
- 47 Otto M, McHugh RK, Kantak KM: Combined pharmacotherapy and cognitive-behavioral therapy for anxiety disorders: medication effects, glucocorticoids, and attenuated treatment outcomes. *Clin Psychol Sci Pract* 2010;17:91–103.
- 48 Fava GA, Savron G, Zielesny M, Grandi S, Rafanelli C, Conti S: Overcoming resistance to exposure in panic disorder with agoraphobia. *Acta Psychiatr Scand* 1997;95:306–312.
- 49 Van Balkom AJLM, van Oppen P, Vermeulen AWA, van Dyck R, Nelson A, Vorst HCM: Meta-analysis on the treatment of obsessive-compulsive disorder: a comparison of antidepressants, behavior, and cognitive therapy. *Clin Psychol Rev* 1994;14:359–381.
- 50 Hembree EA, Riggs DS, Kozak MJ, Franklin ME, Foa EB: Long-term efficacy of exposure and ritual prevention therapy and serotonergic medications for obsessive-compulsive disorder. *CNS Spectr* 2003;8:363–381.