OBSESSIVE-COMPULSIVE DISORDER IN ADULTS: EFFICACY OF COMBINED AND SEQUENTIAL TREATMENTS

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Abstract

Objective: the aims of the present paper are to review literature data on pharmacological and cognitive behavioral therapy (CBT) combination treatments for adult patients with OCD and answer the following questions: 1) does combination treatment add benefits as compared to either monotherapy? 2) is a sequential combination useful for patients with residual symptoms or resistant patients?

Method: we reviewed available data concerning combining Serotonin Reuptake Inhibitors (SRIs) and CBT in the treatment of OCD. Only studies performed in adults were selected. A separate analysis was made for studies which investigated combined treatments *ab initio* and for those which evaluated the efficacy of sequential treatments.

Results: we identified eight controlled studies which investigated the efficacy of combination treatments versus CBT alone and five which evaluated the efficacy of combination versus medications alone. Six studies, one of which double-blind, investigated sequential treatments. Methodologies and results of these studies are presented and discussed.

Conclusions: the combination *ab initio* of CBT, or better Exposure and Response Prevention techniques (ERP), and SRIs has not been found to be clearly superior to either therapy alone in most studies that have examined this question, except for patients with severe depression who might benefit more from the combination than from CBT only. A sequential administration of CBT after medications is useful in promoting remission in patients who responded to drugs and in promoting response in patients who failed to respond to medication.

Key Words: cognitive behavioral therapy, combination treatments, obsessive-compulsive disorder, exposure and response prevention techniques, serotonin reuptake inhibitors

Declaration of interest: None

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Introduction

The treatment of adult patients with Obsessive-Compulsive Disorder (OCD) entails both cognitive-bahavioural treatments (CBT) and pharmacological treatments: first-line approaches, according to the recent Practice Guideline for the Treatment of Patients with OCD (American Psychiatric Association 2007), are exposure and response prevention techniques (ERP), among CBT strategies, and Serotonin Reuptake Inhibitors (SRIs - clomipramine and Selective Serotonin Reuptake Inhibitors), among pharmacological approaches. Both CBT and SRIs, in fact, have been recognized as effective treatments when compared with wait-list, inactive psychological treatments or placebo (March et al. 1997, Deacon & Abramowitz 2004, Eddy et al. 2004, Cottraux et al. 2005, Baldwin et al. 2005, Fisher & Wells 2005, National Institute for Health and Clinical Excellence 2006; American Psychiatric Association 2007).

Despite advances in the treatment of OCD in adults, however, response is often inadequate, or patients do not tolerate and/or discontinue the treatment (both CBT and drugs) prematurely. Even patients with full clinical response as defined by criteria currently used in clinical trials (a reduction of the YBOCS total score greater or equal to 25% or 35% as compared to baseline), often show residual symptoms which can impair their quality of life.

In recent years, then, the attention of researchers has moved to investigate whether combining CBT incorporating ERP and SRIs results in a greater reduction of obsessive-compulsive symptoms in adults. The combination may be done *ab initio*, i.e. CBT and drugs simultaneously started at the beginning of the treatment, or sequentially, i.e. one approach may be started several weeks after the beginning of the other ("sequential treatment").

Submitted January 2009, Accepted February 2009

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Aims

In the present paper we will review available data concerning combining medication and CBT in the treatment of adults with OCD. Data on combination therapies in children and adolescents with OCD will be reviewed by Kaiser and Bouvard in a separate paper in this issue.

Firstly, we will review available data on combination treatments *ab initio* in adults to verify whether combining two treatment approaches is more effective than each of the treatment alone. Secondly, we will review literature data on sequential treatments consisting in CBT addiction in patients who failed to fully respond to SRIs (resistant patients). To our knowledge, no data exist on patients who failed to fully respond to CBT and received the addition of drugs while continuing CBT.

1. Combination treatments *ab initio*

Nine controlled and/or randomized studies are available in the literature on this topic. One of them (POTS Team 2004) was conducted in children and adolescents, so will be reviewed in details the other eight studies in the present paragraph.

We will present results of these studies trying to answer the two following questions: 1) does CBT plus medication work better than CBT alone? 2) does CBT plus medication work better than medication alone? 3) does combination of CBT and medication reduce the efficacy of CBT? Not all studies, in fact, were designed to answer both questions and comprised a placebo arm, a combination arm and two separate medication only and CBT only arms.

1.1 CBT plus medication versus CBT alone

Rachman et al. 1979 (same study results published also in Marks et al. 1980) randomized 48 OCD patients to either clomipramine (CMI) up to 225 mg/day or placebo for 4 weeks; exposure or relaxation was then added from week 4 to week 7, giving four comparison groups at the end of week 7 (CMI+exposure; CMI+relaxation; placebo+exposure; placebo+relaxation). At week 7 there was no statistically significant interaction between ERP and CMI. From week 7 to week 10 all patients received ERP (additional sessions for those in the exposure group and new sessions for those in the relaxation arms), giving two comparisons group (CMI + ERP versus ERP + placebo). Patients were then followed-up until week 36. Clomipramine was superior to placebo on most ratings of OCD symptoms, mood, and social adjustment. Post hoc analyses revealed that these CMI-placebo differences were mainly caused by the superior effect of CMI in the subgroup consisting of the most depressed patients.

A few years later Marks and colleagues (1988) performed another controlled study including 55 patients in four comparison groups: CMI+ antiexposure instructions for 23 weeks; CMI+self-exposure for 23 weeks; double-blind CMI+self-exposure (weeks 1 to 8)+therapist-assisted exposure (week 8 to 23); double-blind placebo+self-exposure (weeks 1 to 8)+therapist-assisted exposure (week 8 to 23). Concerning the efficacy of combination versus CBT alone, at week 8 patients in the combination arm performed better than those in the placebo+exposure group; this difference disappeared later on, suggesting that combination could lead to earlier improvement of symptoms than ERP alone but that benefits of the combination do not persist over the long-term.

A similar earlier improvement of symptoms in the combination group as compared to CBT alone group emerged from a different study. Cottraux et al. (1990) randomized 60 patients to three parallel treatment arms: the first group received single-blind fluvoxamine and antiexposure indications for 24 weeks; the other two groups received ERP and double-blind placebo or fluvoxamine up to 300 mg/day. Overall, no differences between groups were detected at week 8, at the end of the study (week 24) or at follow-up (week 48). However, fluvoxamine-ERP combination resulted in a significantly greater effect on mood only at week 8 and 24, and in a significantly greater effect on rituals only at week 8 (this effect disappeared later on).

This earlier improvement of affective symptoms in patients receiving the combination of drugs and CBT as compared to CBT only was not evident in another study specifically designed to enrol subjects with different severity of depression. Foa and colleagues (1992) included 48 OCD subjects in a double-blind study comparing mildly versus severely depressed patients (based on the Beck Depression Inventory). Patients were blindly assigned to either imipramine (IMI) or placebo for 6 weeks, and then received ERP from week 7 to 10, followed by "supportive behavioural therapy" from week 10 to 22 (end of study). The study gave four comparison groups (IMI+ERP in mildly depressed subjects, IMI+ERP in severely depressed subjects, placebo+ERP in mildly depressed subjects, placebo+ERP in severely depressed subjects). Results indicated that imipramine improved depressive symptoms in depressed patients, but it did not affect OC symptoms and did not potentiate the effects of behaviour therapy. ERP markedly reduced OC symptoms. No differences between highly depressed and mildly depressed patients on OC symptoms were found in their responses to behavioural or supportive therapy.

On the contrary, Hohagen and colleagues (1998) found the combination more effective than CBT alone in subjects with predominant obsessive symptoms or concomitant severe depressive symptomatology (Hamilton Depression Rating Scale > 18). Fourty-nine subjects were randomized to 10-week double-blind fluvoxamine + CBT or placebo + CBT. The combination group performed significantly better on obsession measures while no differences were detected on compulsions. Severely depressed subjects responded preferentially (in terms of obsessive-compulsive symptoms reduction) to combination than to CBT alone.

Three recent studies, finally, found no advantages of combining drugs and CBT (either ERP or cognitive therapy, CT) as compared to CBT alone in the treatment of adults with OCD (Van Balkom et al. 1998, O'Connor et al. 1999, Foa et al. 2005). The first one (Van Balkom

Table 1. *Drugs-CBT combination in adults with OCD: controlled studies*

Authors	*Sample size*	*Treatment Groups*	*Duration (weeks)*	*Combo versus CBT*	*Combo versus medications*
Rachman et al. 1979 Marks et al. 1980	48	CMI+ERP CMI+relaxation Placebo+ERP Placebo+relaxation	10	Combo=ERP Combo>ERP only in depressed	Combo=medications
Marks et al. 1988	55	CMI+antiexposure (23w) CMI+self-exposure (23 w) CMI+self-Exp(w1-8)+ther-ERP(w8-23) placebo+self-Exp(w1-8)+ther-ERP(w8-23)	27	Combo=ERP Combo faster than ERP	Combo>medications at w 8 and 17 Combo=medications at w 23
Cottraux et al. 1990	60	Fluvoxamine+antiexposure Fluvoxamine+ERP Placebo+ERP	24	Combo=ERP Combo faster than ERP on mood and rituals	Combo=medications
Foa et al. 1992	48	IMI+ERP(severely depressed) IMI+ERP(mildly depressed) Placebo+ERP(severely depressed) Placebo+ERP(mildly depressed)	22	Combo=ERP	-
Hohagen et al. 1998	49	CBT+placebo CBT+fluvoxamine	10	Combo>CBT in severely depressed and on obsessions only	-
Van Balkom et al. 1998	117	CT (1-16w) ERP (1-16w) Fluvoxamine (1-16w) + CT (9-16w) Fluvoxamine (1-16w) + ERP (9-16w) Waiting list (1-8w)	16	Combo=CBT	-
O'Connor et al. 1999	29	Medications+CBT CBT Medications while on wait-list Wait-list	20	Combo=CBT	Combo=medications
Foa et al. 2005	122	ERP CMI ERP+CMI placebo	12	Combo=ERP	Combo>medications

CMI=Clomipramine; IMI=Imipramine; ERP=Exposure and Response Prevention; Combo=Combination of drugs and behavior therapy; CBT=Cognitive-Bahevaior Therapy; Self-Exp=Self-Exposure; ther-ERP=Therapist-assisted exposure; CT=Cognitive Therapy

et al. 1998) evaluated the efficacy of SRIs + CT versus SRIs + ERP versus CT, versus ERP for 16 weeks. Subjects included in the combination arms received 8 weeks of fluvoxamine prior to be randomized to additional 8 weeks of either CT or ERP. A waiting list comparison group was added for the first 8 weeks. At week 8 all treatment groups performed better than the wait-list comparison sample. At the end of the study no differences were detected among the four remaining groups, demonstrating that the combination of fluvoxamine with CT or ERP is not superior to either CT or ERP alone.

O'Connor and colleagues (1999) compared four treatments: SRIs +CBT, CBT, SRIs while on a waiting-list for CBT and waiting-list. Subjects included (N=29), however, were not randomized; moreover, patients in the combination arm were requested to have a stable dosage of their SRI for a minimum period of 1-2 months prior to enrolment. Despite these limitations, this study showed that at the end of the 20-weeks study period all treatments were more effective than the wait-list, without significant differences between the three other groups.

The last study included 122 adults with OCD randomized under double-blind conditions to a 12-week treatment with four different treatments: ERP, CMI, ERP + CMI, and placebo (Foa et al. 2005). At week 4 both ERP and ERP + CMI groups groups showed a significantly greater reduction in YBOCS scores than CMI and placebo groups. CMI group did not significantly differs from placebo group. At the end of the study (week 12) subjects in the ERP groups (whether or not combined with CMI) performed better than patients in the CMI only group; CMI, as expected, was superior to placebo. Concerning the relative efficacy of combination versus ERP only, this study confirmed that adding medication to CBT is not superior to CBT alone.

In conclusion, eight controlled studies evaluated whether the combination of CBT and medications is superior in efficacy to CBT alone in adults with OCD. Only 5 out 8 studies were designed to have patients in the combination arm starting with both treatments at the same time (Marks et al. 1988, Cottraux et al. 1990, Hohagen et al. 1998, O'Connor et al. 1999, Foa et al. 2005); in the other three studies, patients in the combination arm received medications or placebo for 4 (Marks et al. 1980), 6 (Foa et al. 1992) or 8 weeks (van Balkom et al. 1998) prior to CBT initiation. However, we examined results of these studies in this paragraph as CBT was added whether or not patients had previously responded to medication treatment and because all these studies aimed at evaluating whether the combination treatment was more effective than the monotherapy strategy. Taken together, results of these studies suggest no additive benefit for combining *ab initio* medications and CBT as compared to CBT alone in adult patients with OCD except for severely depressed patients. Combining *ab initio* medications and ERP may also result, as compared to ERP alone, in an earlier improvement of obsessive-compulsive symptoms, although this effect is not maintained after the first 8 weeks of treatment.

1.2 CBT plus medication versus medication alone

A different question to be answered is whether the combination *ab initio* of medications and CBT is more effective than medications alone in the treatment of adults with OCD. Five of the abovementioned studies were designed to answer this question, having both a combination and a medication only arms. Table 1 summarizes designs and results of these trials. Four studies (Rachman et al. 1979, Marks et al. 1988, Cottraux et al. 1990, O'Connor et al. 1999) did not find an advantage of combining the two treatment approaches as compared to SRIs alone; one of these studies (Marks et al. 1988) only found the combination of clomipramine and exposure more effective than clomipramine and antiexposure instructions in the early phase of the study, while such difference did not persist at the end of the trial.

Only the study by Foa and colleagues (2005) found that the group receiving clomipramine only showed a significantly lower symptoms reduction at the end of the 12-week trial as compared to the combination group (intensive ERP and clomipramine). This suggests than combining intensive ERP and medications adds benefit to medications. However, it is also possible that the greater effect of the combination compared to the medications alone strategy would disappear later on as clomipramine antiobsessional effect becomes greater (all SRIs have a response latency of approximately 8 weeks while intensive ERP was concluded after 4 weeks only).

In conclusion, the combination of CBT (or better ERP) and SRIs has not been found to be clearly superior to either therapy alone in most studies that have examined this question, as evident from the first paragraph of this review. Using both approaches *ab initio* is, moreover, expensive and thus is not justified in terms of benefits versus costs. Consequently, the most recent international guidelines for the treatment of OCD do not recommend combining SRIs and ERP in all patients (American Psychiatric Associations, 2007).

1.3 Does combination of CBT and medication reduce the efficacy of CBT?

Another important point to be raised is whether the addition of medications to ERP (or CBT in general) prevents ERP to be fully effective, or whether benefits of the combination disappear when drugs are discontinued (due to a change in the internal context), as appears to be the case for other Anxiety Disorders such as Panic Disorder (see Barlow et al. 2000; Otto et al. 2005a, Otto et al. 2005b; Watanabe et al. 2007).

Four follow-up studies were performed of the original patients included in the short-term trials summarized in table 1 (O'Sullivan et al. 1991, Cottraux et al. 1993, Rufer et al. 2005, Van Oppen et al. 2005); although methodological biases have to be taken into account when examining results, these studies suggest that for OCD patients the addition of medications to CBT (ERP mainly) does not interfere with the learning process of CBT over the long-term. In other words, there

is no evidence for OCD that medications prevent CBT to be fully effective or that CBT needs to be continued beyond medication discontinuation in order to prevent the context shift effect (see Otto et al. 2005b, for a complete review in other anxiety disorders). Some evidence emerges, moreover, that combining ERP with medications in the acute phase might allow discontinuation of drugs after the 6-month short-term treatment (Cottraux et al. 1993, Hembree et al. 2003, Kordon et al. 2005).

2. Sequential combination

A sequential combination strategy has been used to augment treatment outcome in those patients who showed a reduction in symptoms with SRIs sufficient to meet criteria for response but still had residual symptoms (Tenneij et al. 2005), or to induce response in patients unsuccessfully treated with SRIs. In this latter case CBT techniques were used to boost the effect of drugs when at least a partial response to these agents was shown. The rationale, as in the case of antipsychotic augmentation for SRI-resistant patients (Maina et al. 2005, 2008), is then to support and increment with a different strategy (whose efficacy in OCD has been demonstrated) the effect of another first-line treatment (SRIs) when this effect is judged to be poor.

We will consider in this section only studies which added CBT after at least 12 weeks of drug treatment monotherapy. This limitation is, to our opinion, necessary as response to SRIs is not evident before 6 to 8 weeks and several patients usually satisfy response criteria between 8 to 12 weeks of drug treatment (Bloch et al. 2006). Methodologically, adding CBT before week 12 would not permit clinicians to distinguish between the true additive effect of the combination treatment and the simple effect of continuing the drug treatment for a longer period.

Although adding medications to CBT non responders are routine clinical practices, to our knowledge no studies have been published concerning the addition of medications to subjects not fully responding to CBT alone.

2.1 Sequential treatment in responders

The first study (Tenneij et al. 2005) sought to examine whether the combination of CBT and drugs, advocated by several authors as the optimal treatment for OCD patients, including those who have already responded to drug treatment, is really more effective than just the continuation of drug treatment, and, secondly, whether the timing of the addition of behavior therapy (namely 3 or 9 months after the start of drug treatment) has an effect on treatment outcome. Ninety-six OCD patients who showed a reduction of at least 25% on the YBOCS total score after 3 months of drug treatment (paroxetine 60 mg/d or venlafaxine 300 mg/d) were initially randomized to either receive addition of 18 ERP sessions or continue on drug treatment alone for additional 6 months. The patients on SRIs + ERP showed a significantly greater further reduction in YBOCS total score (-3.9 points) as compared to the patients on SRIs which, on the contrary, had a mean increase of 3.9 points in the YBOCS total score (mean difference of 7.8 points in completers and 5.8 in the ITT sample). The remission rate was significantly higher in patients who received combination therapy than in patients who continued on drug alone (53% versus 11%, $p < .0001$ for completers). After 9 months patients who received drug alone were treated with CBT and evaluated another 6-month later ("delayed combination therapy group"). The comparison of response between the combination therapy (immediately after response – 3 months after the start of drug treatment) and the delayed combination therapy (9 months after) suggested that the effect is greater when behavior therapy is added immediately after attainment of the drug response.

Thus, a sequential addition of CBT to drugs (that are maintained) might promote remission in those patients who respond to drug treatment alone but still show residual symptoms. This is a clinically relevant issue in view of the notion that only a minority of subjects join remission on a single treatment modality (either CBT or drugs).

Another way of integrating psychological and pharmacological approaches is planning psychotherapy to start after medications and end after drug discontinuation ("sequential integrated treatment"). The purpose of this approach is to stabilizing benefits of drug treatment once drugs are discontinued. Biondi and Picardi (2005) demonstrated a greater efficacy of the integrated sequential combination treatment of SRIs (12-24 months) and CBT (timed to start after drug treatment and end after medication discontinuation) as compared to medications alone in maintaining remission of OCD over the long-term, with an estimated mean survival time significantly higher in the first as compared to the latter group (132 versus 25 months).

Thus, the sequential combination of CBT and SRIs seems to be useful in promoting remission in responders and maintaining benefits of drug treatment over the long-term despite medication discontinuation.

2.2 Sequential treatment in resistant patients

The vast majority of studies using a sequential combination strategy, however, had the objective of evaluating whether the addition of CBT is effective in converting a partial or non responder to drug treatment alone in responder. Designs and results of all the studies which used CBT to augment the response to SRIs in adult patients with OCD are reported in tables 2 and 3.

Simpson et al. (1999) used 17 sessions of ERP to augment the response in 7 patients who remained symptomatic (YBOCS total score ≥16) despite a 12-week trial of an SRI at adequate doses (clomipramine ≥225 mg/d; fluoxetine ≥60 mg/d; paroxetine ≥60 mg/d; sertraline ≥200 mg/d; fluvoxamine ≥250 mg/d). The evaluation of resistance, however, was retrospective and based upon patients' verbal report, although the failure to respond to these high doses makes this sample a true resistant one. The authors showed for the first time in the literature, although in an open-label manner, that CBT augmentation might lead to a significant decrease in obsessive-compulsive symptoms (mean YBOCS total

Table 2. *Sequential addition of CBT to medications in adults with OCD drugs non responders*

Authors	*Design*	*Definition of resistance*	*Evaluation of resistance*	*CBT technique*	*Number of sessions (N/w)*
Simpson et al. 1999	o-l	Some improvement (by verbal report) but still YBOCS≥16 despite SRI (adequate dose) ≥12 weeks	Retrospective	ERP	17 (twice/w)
Kampman et al. 2002	o-l	<25% decrease in YBOCS despite 12 weeks of fluoxetine 60 mg/d	Prospective	ERP + CT	12 (one/w)
Albert et al. 2003	o-l	<35% decrease in YBOCS despite 6 months of SRI (adequate dose)	Prospective	ERP	15 (one/w)
Tolin et al. 2004	Wait-list-controlled o-l	YBOCS≥16 despite ≥2 unsuccessfully SRI trials	Retrospective	ERP	15 (1 to 5/w)
Tundo et al. 2007	o-l	YBOCS≥16 despite 1 unsuccessfully SRI trial	Retrospective	ERP + CT	Mean 30.4 hours (one/w)
Simpson et al. 2008	RCT (vs. stress management training)	YBOCS≥16 despite 1 unsuccessfully SRI trial	Retrospective	ERP	17 (twice/w)

o-l=open label
SRI=Serotonin Reuptake Inhibitor
ERP=Exposure and Response Prevention
CT=Cognitive Therapy
RCT=Randomized Controlled Trial
YBOCS=Yale-Brown Obsessive-Compulsive Scale

Table 3. *Sequential addition of CBT to medications in adults with OCD drugs non (continued)*

	Sample size		***YBOCS total score***		
Authors	***Patients included (N)***	***Completers (N)***	***At baseline***	***At the end of CBT***	***Mean % decrease***
Simpson et al. 1999	6	5	23.8±2.6 (ITT)	12.2±4.3 (ITT)	49
Kampman et al. 2002	14	9	25.7±5.3 (completers) 26.4±5.4 (ITT)	15.0±6.5 (completers) 19.0±8.1 (ITT)	41
Albert et al. 2003	19	13	26.5±3.3 (completers)	17.3±5.3 (completers)	-
Tolin et al. 2004	20	15	25.1±5.5 (completers) 25.4±5.5 (ITT)	15.9±9.0 (completers) 18.2±8.9 (ITT)	39.5 29.6
Tundo et al. 2007	36	28 at 6 months 21 at 12 months	28.2±4.4 (ITT)	24.8±5.2 (ITT, 6 month) 22.9±5.9 (ITT, 12 month)	19 -
Simpson et al. 2008	108	94	ERP: 25.4±4.7 SMT: 26.2±4.4	ERP: 14.2±6.6 SMT: 22.4±6.3	-

ERP=Exposure and Response Prevention
SMT=Stress Management Training
ITT=Intention-To-Treat sample

score decrease 49%). Patients were then followed-up for a mean length of 9 months, and 5/6 completers remained much improved with a ≥6 point decrease in their YBOCS total score compared to beginning of CBT.

On the basis of these preliminary results, Kampman and colleagues (2002) designed a prospective study in which they administered fluoxetine (60 mg/d) to drug-naïve OCD subjects and examined resistance after 12 weeks. Those patients who showed a less than 25% decrease in their YBOCS total score at the end of this phase (14 patients) received 12 weekly ERP plus cognitive restructuring sessions; in the nine completers, the YBOCS total score significantly decreased from 25.7 to 15.0, with a mean reduction of 41%. This study, however, did not conduct a follow-up.

Another step towards the demonstration of the efficacy of sequential combination strategies for resistant patients was made by Tolin and colleagues (2004) who designed a wait-list-controlled open trial; they selected 20 OCD patients with a history of inadequate response (retrospectively evaluated) to at least 2 previous trials of SRIs, given at adequate doses (clomipramine ≥150 mg/d; fluoxetine ≥40 mg/d; paroxetine ≥40 mg/d; sertraline ≥50 mg/d; fluvoxamine ≥200 mg/d; citalopram ≥60 mg/d; venlafaxine ≥375 mg/d) and for adequate time (at least 10 weeks). Patients with multiple comorbid disorders were permitted to entry the study to test the efficacy of CBT augmentation in a difficult-to-treat patient sample. All patients were placed in a 1-month wait-list while on medication, to confirm the failure to respond to pharmacotherapy; then they received 15 sessions of therapist-assisted exposure plus homework ERP assignments. OCD severity (as measured with the YBOCS) decreased significantly after treatment both in the completer and in the intention-to-treat samples. Patients were followed-up at 1, 3, and 6 months after the end of the ERP: no relapses were evident at 1 and 3 months, while there was some increase in symptoms at 6 months; YBOCS total score decreased to 35.7%, 31.8% and 30.2% at 1, 3, and 6 months of follow-up, respectively. This study showed that the sequential administration of a CBT trial to severe patients with multiple drug treatment failures and Axis I comorbidity is effective, although it seems somewhat less effective than previously shown.

At least the first two abovementioned studies (Simpson et al. 1999, Kampman et al. 2002) examined the addition of CBT to patients not responding after 12 weeks of treatment. However, OCD response to SRIs occurs, at least in some cases, later during the course of the treatment. For example De Haan and colleagues (1997) showed that 38% of patients who had not improved after 16 weeks of treatment with CBT or SRI could be classified as treatment responders after 6 months of continued treatment. We then designed an open-label study consisting of two phases; in the first one, OCD patients prospectively received 6 months of SRI (Albert et al. 2003). Subjects who failed to show, after six months, a Y-BOCS total score decrease ≥35% with respect to baseline but still exhibited a partial reduction in OC symptomatology were offered a CBT trial consisting in ERP (weekly office visit + ERP homeworks – in some cases + out-of-office therapist assisted ERP); CBT was added to the ongoing SRI, whose dosage was maintained fixed throughout the duration of the trial. The primary outcome measure was the YBOCS, which was administered at least three times before the addition of CBT in order to ensure that drug treatment was no more effective, at week 4 and at the end of the CBT trial. Nineteen patients were included; 6 out 19 (31.6%) withdrew prematurely from the study because of non-compliance with therapists' indications. The remaining patients showed at the end a significant reduction in mean YBOCS total score (17.3 versus 26.5 at beginning of the study; $p<.001$). Our study prospectively evaluated, although in an open-label manner, the efficacy of the addition of CBT in subjects who showed a partial response to SRIs but failed to improve further after six months of continued treatment at the highest tolerated dosages.

A fifth naturalistic study confirmed the efficacy of the addition of CBT for nonresponders to medication; Tundo and colleagues (2007) enrolled 36 OCD patients unresponsive to at least 1 adequate SRI trial (retrospective evaluation although all patients had been treated by one of the Authors). Patients were allowed to enter the study only if they had been non responders to elevated dosages of SRIs (citalopram, fluoxetine and paroxetine 60 mg/d; fluvoxamine 300 mg/d; sertraline 200 mg/d; venlafaxine 375 mg/d and clomipramine 225 mg/d); moreover the sample included was made of severely ill patients with long-term illnesses, high frequency of comorbidity and failure to respond to ≥2 trials in 72% of cases. Patients were offered CBT incorporating ERP, with cognitive therapy and other ad hoc interventions to supplement ERP strategies; therapy sessions were scheduled flexibly to promote treatment adherence, with a mean of 30 CBT hours/patient. Twenty-four patients were evaluated six months after beginning CBT and 21 after 12 months: the combination of SRIs and CBT resulted in a modest yet significant reduction of the YBOCS total score (from 28 to 25 at six months and 23 at 12 months in the ITT sample). This study, to our opinion, had the strength of having incorporated severe real-world patients; although the effectiveness of CBT is lower in this population (mean reduction in YBOCS total score at final assessment only 19%), this study provides support to the effectiveness of CBT addition to drugs in nonresponders.

Simpson and colleagues (2008), finally, demonstrated the efficacy of CBT for augmenting pharmacotherapy in OCD resistant subjects in a 8-week, randomized, controlled trial in which stress management training was used as the control condition. Participants were 108 adult OCD patients with a YBOCS total score ≥16 despite a therapeutic SRI dose for at least 12 weeks prior to enrollment (retrospective evaluation; citalopram, fluoxetine and paroxetine 60 mg/d; fluvoxamine 250 mg/d; sertraline 200 mg/d; escitalopram 30 mg/d and clomipramine 225 mg/d). Patients assigned to the CBT arm received 17 twice-weekly ERP sessions; stress management training included 17 sessions in which patients were taught deep breathing, progressive muscle relaxation, positive imagery, assertiveness training and problem solving. At the end of the study (week 8), significantly more patients receiving ERP than patients receiving stress management training were responders (decrease ≥25%

in the YBOCS total score): 74% versus 22% (p<.001). The mean YBOCS score decreased from 25.4 to 14.2 in patients assigned to ERP and from 26.2 to 22.6 only in those assigned to the control condition. These findings strongly support the use of ERP as an SRI augmentation strategy for OCD nonresponders to medication.

This conclusion is further supported by O'Connor and colleagues (2006) who examined the efficacy of CBT in OCD subjects who had previously or not received a pharmacological treatment (and continued this treatment while on CBT). They presented results from two separate protocols. In the first one, 21 OCD patients received 5 months of double-blind treatment with either fluvoxamine or placebo and then CBT was added for a further 5-month period (the dose of fluvoxamine was maintained unchanged whilst on CBT). During the first 5 months, a significantly greater change in YBOCS total score was observed in the medication (15%) as compared to the placebo group (7%); however, the reduction was clinically not significant in both groups. The sample on fluvoxamine may be then considered a resistant one as a whole (although the proportion of responders is not reported). Both groups benefited further and significantly from CBT addition, with no difference in the degree of response between patients previously treated with fluvoxamine (mean YBOCS total score reduction 57%) or with placebo (mean YBOCS total score reduction 44%). In the second protocol, 22 patients received CBT. The authors identified two separate groups, one drug-naïve at the moment of CBT initiation and the other stabilized on SRI treatment (adequate for duration and dosage) but still symptomatic despite a partial response (YBOCS total score >16 at CBT initiation). Both groups responded equally well to CBT (mean YBOCS total score reduction: 53% in drug-naïve patients and 43% in those stabilized on medications). Taken together, results from the two separate trials confirm that: a) CBT is equally effective regardless of whether the subject has previously received medications or not; b) medications do not seem to interfere with CBT efficacy; and c) the sequential CBT addition to medications in patients unresponsive to SRI treatment is effective in inducing response.

In conclusion, CBT augmentation of SRIs appears to be a valuable option both for OCD patients who respond to medications but still have obsessive-compulsive symptoms and for resistant patients. Unfortunately, no study, to our knowledge, investigated the efficacy of the sequential addition of medication to CBT in patients partially unresponsive to CBT alone who continued to receive CBT. Given that CBT response rates are, on average, 70 to 90% but up to 25% of patients refuse it and 13% to 20% do not complete it (Foa et al. 1983, Perse 1988, Greist 1994, Abramowitz 1997, Kozak et al. 2000, Kobak et al. 1998), the latter question is of high clinical relevance.

Conclusions and future directions

In conclusions, the combination *ab initio* of Cognitive-Behavior Therapy (or better Exposure and Response Prevention, as the vast majority of studies investigated this technique) and SRIs has not been found to be clearly superior to either therapy alone in most studies that have examined this question. The only exception is the treatment of patients with severe depression who might benefit more from the combination than from CBT only. The evidence of the literature, thus, do not support the routine use of a combination approach in all adult patients with OCD. There is no evidence for OCD, on the contrary, that medications interfere, in the short-term or over the long-term, with CBT efficacy.

A sequential administration of CBT after medications has been found useful in promoting complete remission of symptoms in patients who responded to drugs (with the currently used definition of response that is a reduction ≥25% of the YBOCS total score); this conclusion, however, is drawn from a single, although well-conducted, study and needs to be replicated.

There is a clear evidence that a sequential combination strategy is useful in medication-resistant patients.

There are now two evidence-based strategies for OCD subjects unresponsive to a medication trial: the sequential addition of ERP and the addition of antipsychotics (Maina et al. 2005, 2008). Although there are no studies directly comparing these two strategies under controlled conditions in OCD patients, comparisons of results across studies suggest that both strategies are equally effective. The choice between the two approaches might then depend upon the availability of CBT therapists, patients' preferences, and side-effects associated with antipsychotics.

Two promising combination strategies are now under investigation. The first one consists in combining CBT with D-cycloserine. In this case the combination is made between a psychological and a pharmacological approach as in the case of the studies reviewed in the first paragraph; however, the drug used, D-cycloserine (partial agonist at the NMDA receptor), is not used to treat OCD (as in the case of SRIs) but to enhance the effect of learning, which is the scope of CBT. This strategy, then, may be more appropriately termed an augmentation treatment than a combination treatment. Several studies have investigated this approach in adults with Anxiety Disorders, three (two positive and one negative) in OCD (Kushner et al. 2007; Storch et al. 2007; Wilhelm et al. 2008; see Deveney et al. 2009 for a complete review).

The second one consists in combining two approaches but not in the same patient: we (among others) are investigating the role of family members in maintaining obsessive-compulsive symptoms and the effectiveness of a multifamily psychoeducational intervention aimed at reducing accommodating behaviors in family members of adult patients with OCD who are currently receiving pharmacological treatment (Albert et al. 2006; Maina et al. 2006; Albert et al. 2007, 2008, 2009). Although it is still to be demonstrated that reducing accommodating behaviors in family members may promote a greater reduction of obsessive-compulsive symptoms in the patient, this is the hypothesis which is currently under investigation.

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