COMBINING PHARMACOLOGICAL AND PSYCHOTHERAPEUTIC INTERVENTIONS FOR OBSESSIVE-COMPULSIVE DISORDER PATIENTS

Umberto Albert, Filippo Bogetto

Summary

Object: The aim of the present paper is to answer the following questions: 1) does combining medication and CBT add benefits as compared to CBT alone? 2) Does adding CBT to medication give further improvement as compared to medication alone? 3) Do benefits of combination treatments persist over the long-term?

Method: We reviewed available data concerning combining medications (SRIs) and cognitive-behavior therapy (CBT) in the treatment of Obsessive-Compulsive Disorder (OCD). 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 nine controlled studies which investigated the efficacy of combination treatments versus CBT alone and five which evaluated the efficacy of combination versus medications alone. Few studies investigated sequential treatments. Methodologies and results of these studies are presented and discussed.

Conclusions: The short-term or long-term treatment effect of CBT is not augmented by the addition of medication; a combination of CBT and medication might be superior to CBT alone when obsessions dominate the clinical picture and/or when a severe secondary depression is present. Children and adolescents with OCD could also benefit more from the combination treatment. The short-term treatment effect of antidepressants can be enhanced by the addition of CBT a) to augment the benefit from medication; b) to reduce the use of medication for those patients who are intolerant to side effects; 3) to prevent relapses for those patients who want to discontinue medication after short-term response. A sequential administration of CBT after medication might convert patients who failed to fully respond to medication in responders.

Key Words: Cognitive Behavior Therapy – Obsessive Compulsive Disorder – Combining Medications

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Umberto Albert, Filippo Bogetto
Department of Neuroscience, Anxiety and Mood Disorders Unit, University of Turin, Italy

Corresponding author: Umberto Albert
Department of Neurosciences, Anxiety and Mood Disorders Unit, University of Turin, Italy
Via Cherasco 11 – 10126 Torino, Italy
Tel. +39.011.6335425 - Fax +39.011.673473 - e-mail address: umberto_albert@hotmail.com

Introduction

Both cognitive behavior therapy (CBT) and pharmacotherapy (serotonin reuptake inhibitors - SRIs) have been recognized as effective treatments for obsessive-compulsive disorder (OCD) when compared with wait-list, inactive psychological treatments or placebo controls (March et al. 1997). However, a sizeable proportion of patients do not benefit from either treatment strategies alone, or drop out from treatment before attaining a full response. Even patients with a clinical response (generally defined as a reduction of the YBOCS total score below 16), moreover, often show residual symptoms which can impair their quality of life.

A question, then, arises concerning a) the possibility that a combination of both treatment strategies (CBT and medications) would result in a greater response or in a higher remission rate in patients who are provided *ab initio* this integrated treatment, and b) the possibility that patients who do not respond to one modality would benefit from adding the other treatment strategy.

Aim of the present paper

In the present paper we will review available data concerning combining medication and cognitive-behavior therapy (CBT) in the treatment of Obsessive-

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Compulsive Disorder (OCD).

In the first part of the paper we will review all published controlled studies on combination therapies trying to answer the following two questions: 1) does combining medication and CBT add benefits as compared to CBT alone? 2) Does adding CBT to medication gives further improvement as compared to medication alone? In case of positive answer the next question will be: 3) do benefits of combination treatments persist over the long-term?

In the second half of the paper we will review studies which investigated whether combination of CBT and medication is effective in converting partial or non responders to either monotherapy alone into responders (sequential combination strategies).

Combination treatments

Adding medication to CBT as compared to CBT alone

Nine studies investigated with appropriate methodology (controlled and/or randomized designs) whether adding ab initio a drug effective in the treatment of OCD to CBT (exposure and response prevention – ERP – with or without cognitive therapy) gives advantages as compared to CBT alone in efficacy or in time to response. Some of these studies also investigated whether the combination strategy is more effective on specific symptoms or in subgroups of OCD patients (with or without major depression or severe depressive symptomatology for example).

Rachman et al. 1979 (same study results published also in Marks et al. 1980) randomized 48 OCD patients to either clomipramine up to 225 mg/day or placebo for 4 weeks (mean CMI dose at the end of the study 183 mg/day); exposure (15 sessions) 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, although the combination yielded slightly superior results relative to the other conditions on most ratings, there was no statistically significant interaction between ERP and CMI. From week 7 to week 10 all patients received 15 sessions of ERP (additional sessions for those in the exposure group and new sessions for those in the relaxation arms), giving two comparisons groups (combination of CMI and ERP versus ERP and 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.

The same research group performed another controlled study a few years later (Marks et al. 1988). They included 55 patients (of whom only 11 were randomized) in four comparison groups: CMI+antiexposure 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). Self-exposure consisted of daily homework exercises (3 hours minimum duration); therapist-assisted exposure consisted in 15 ERP sessions. Clomipramine mean dosages were 157 mg/day at week 4 and 127 at week 17. Patients were assessed at week 8, 17, and 23. From week 23 to 27 (end of the study) patients received no exposure. 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 at week 17 and 23, suggesting that combination could lead to earlier improvement of symptoms than ERP alone but that benefits do not persist over the long-term.

Similar results (for rituals only) emerged from a French 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 (mean dosage at the end of the study 282 mg/day). Patients received weekly exposure sessions consisting of exposure in fantasy for the first 8 weeks followed by guided in vivo exposure and response prevention for the additional 16 weeks. Patients were followed-up for a total of 48 weeks. Overall, no differences were detected at week 8, at the end of the study (week 24) or at follow-up; a drug effect on mood only was detected at week 8 and 24, and a drug effect on rituals only was evident at week 8 but disappeared later on.

On the basis of preliminary results of a better efficacy in subjects with concomitant major depression, Foa and colleagues (1992) included 48 OCD subjects in a double-blind study comparing mildly versus severely depressed patients (based on the BDI). Patients were blindly assigned to either imipramine (mean 229 mg/day) or placebo for 6 weeks, and then received 15 daily, 2-hour sessions of 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 mildly depressed, IMI+ERP severely depressed, placebo+ERP mildly depressed, placebo+ERP severely depressed); at week 6 imipramine was better than placebo on depression only whereas no differences were evident at week 10 and 22 neither on mood nor on obsessive-compulsive symptoms. This study, however, is biased by the choice of imipramine, which is not an antiobsessional agent.

On the contrary, Hohagen et al. 1998 found combination more effective than CBT alone in subjects with predominant obsessive symptoms or concomitant severe depressive symptomatology (HAM-D greater than 18). Fourty-nine subjects were randomized to 10-week double-blind clomipramine (mean dose 288 mg/day) or placebo and simultaneous CBT consisting in therapist-aided exposure (3 times/week for 2 weeks) and cotherapist-aided and self-management exposure (daily for the remainder of the study period). 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.

Van Balkom et al. 1998 evaluated for the first time separately the combination of drug and cognitive versus drug and exposure and response prevention therapy and compared these two strategies to cognitive therapy alone and ERP alone for 16 weeks. They chose a sequential strategy for the combination arms: patients received 8 weeks of fluvoxamine (235 mg/day mean dose at week 8) prior to be randomized to additional 8 weeks of either cognitive therapy 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 week 16 no differences were detected among the four remaining groups, demonstrating that the sequential combination of fluvoxamine with CT or ERP is not superior to either CT or ERP alone.

O'Connor and colleagues (1999) compared medication (different SRIs)+CBT, CBT only, medication while on waiting-list for CBT and waiting-list. They included 29 subjects who were not randomized; all clients in the combination arm, moreover, were stabilized on medication (no change in dosages) for a minimum period of 1-2 months prior to study entry (mean 3.86 months), which represents a bias of the study. Patients received weekly ERP sessions for 20 weeks. At the end of the 20-week study period all treatments were more effective than the wait-list, without differences. Those patients who did not receive CBT in the first part of the study entered a 20-week CBT addition treatment. At the end of the study no differences were detected between patients who received CBT only, the combination *ab initio* (although with the abovementioned limitation) and those who received CBT following medication. The authors concluded that the further improvement of the medication only group after CBT suggests that administering CBT after a period of medication may be more advantageous than providing both at the same time, although this conclusion is not supported by their results.

The last study was recently performed in 122 adults with OCD randomized under double-blind conditions to a 12-week treatment with ERP, clomipramine (mean dose 196 mg/day), combination of ERP and clomipramine (mean dose 163 mg/day) and placebo (Foa et al. 2005). Subjects in the CBT arms received intensive ERP for 4 weeks (2-hour sessions each week day over a 3-week period with homeworks followed by 4 hours ERP in the fourth week). At week 4 both CBT groups had a significantly superior reduction in YBOCS scores than the clomipramine group, which did not differ from placebo. At the end of the study subjects in the ERP groups (whether or not combined with clomipramine) performed better than patients in the clomipramine only group; clomipramine, however, was superior to placebo. This study suggests that adding medication to CBT is not superior to CBT alone. It is possible, however, that the failure to detect a difference between the combined and the CBT alone groups could be attributed to the failure to maximize clomipramine doses in the combined groups as well as to the simultaneous investigation of intensive ERP and slow upward titration of clomipramine (so that the intensive phase of ERP was concluded before clomipramine could be effective).

Combination of CBT and medication performed better than CBT alone in a sample of children and adolescents with OCD (POTS Team, 2004). In a randomized, controlled, single-blind study, 112 subjects received CBT (consisting of 14 1-hour therapist-assisted ERP sessions), sertraline (mean dose 170 mg/day), CBT and sertraline (mean dose 133 mg/day) or placebo for 12 weeks. At week 12, the combination group showed a significantly higher YBOCS reduction as compared to both active treatment groups, which were different from the placebo group. The combination strategy, in terms of symptoms reduction, appeared more effective than CBT alone, although in terms of remission rates no differences were detected between the two groups. On the basis of these results, the Authors concluded that children and adolescents with OCD should start treatment with a combination of CBT and medication or with CBT alone.

Table 1 summarizes results of the abovementioned studies. In conclusion, nine controlled studies evaluated whether the combination of CBT and medication is superior in efficacy to CBT alone in the short-term for obsessive-compulsive disorder. In six of them the combination was simultaneous, that is patients in the combination arm started on both treatment strategies at the same time (Marks et al. 1988, Cottraux et al. 1990, Hohagen et al. 1998, O'Connor et al. 1999, POTS Team 2004, Foa et al. 2005); in the other three studies, patients in the combination arm received medication 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. These authors chose the sequential combination strategy because they considered that it better reflected routine clinical practice. We examined results of these studies together 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 medication and CBT as compared to CBT alone except for subgroups of patients with peculiar characteristics. Marks et al. 1980 found the combination more effective than CBT alone only in depressed OCD patients; this result is confirmed by Hohagen et al. 1998 who found the combination more effective in patients with severe depression or predominant obsessive symptomatology only. The fact that Foa et al. (1992) did not find the combination more effective than ERP alone on OC symptoms in depressed subjects is attributable to the choice of imipramine, which has no antiobsessional effect. Combination in that study was in effect more effective than ERP on depressive symptoms and only at week 6.

The combination strategy could also add benefit as compared to CBT alone in children and adolescents (POTS Team, 2004), although it was found more effective in YBOCS reduction and not in remission rates; based on their results, the authors of this study conclude cautiously that children and adolescents with OCD should begin treatment with combination of CBT and medication or with CBT alone. Future studies will highlight whether in this subgroup of patients with OCD it is worth combining the two strategies *ab initio*.

Combining *ab initio* medication and CBT could

Table 1. *Is adding ab initio medication to CBT more effective than CBT alone?*

Authors	***Sample size***	***Groups***	***Duration (weeks)***	***Assessments***	***Results***	***Combo versus CBT***
Rachman et al. 1979 Marks et al. 1980	48	a. Clomipramine+ERP b. Clomipramine+relaxation c. Placebo+ERP d. Placebo+ralaxation	10	7	a=b=c>d at w 7	Combo=ERP Combo>ERP only in depressed
Marks et al. 1988	55	a. Clomipramine+antiexposure (23w) b. Clomipramine+self-exposure (23 w) c. CMI+self-Exp(w1-8)+ther-ERP(w8-23) d. placebo+self-Exp(w1-8)+ther-ERP(w8-23)	27	8 17 23	c>d at w 8 c=d at w 17 and 23	Combo=ERP Combo faster than ERP
Cottraux et al. 1990	60	a. Fluvoxamine+antiexposure b. Fluvoxamine+ERP c. Placebo+ERP	24	8 24	a=b=c at w 24 a=b>c on rituals at w 8 only a=b>c on mood at w 8 and 24	Combo=ERP Combo faster than ERP
Foa et al. 1992	48	a. Imipramine+ERP(severely depressed) b. IMI+ERP(mildly depressed) c. Placebo+ERP(severely depressed) d. Placebo+ERP(mildly depressed)	22	6 10 22	a=b>c=d at w 6 on depression only a=b=c=d at w 10 and 22	Combo=ERP
Van Balkom et al. 1998	117	a. CT (1-16) b. ERP (1-16) c. Fluvoxamine (1-16) + CT (9-16) d. Fluvoxamine (1-16) + ERP (9-16) e. Waiting list (1-8)	16	8 16	a, b, c, d>e at w 8 a=b=c=d at w 16	Combo=CBT
Hohagen et al. 1998	49	a. CBT+placebo b. CBT+fluvoxamine	10	10	a=b on compulsions a<b on obsessions a<b in severely depressed	Combo>CBT in severely depressed and on obsessions only
O'Connor et al. 1999	29	a. Medication+CBT b. CBT c. Medication while on W-L d. Wait-list	20	20	a,b,c>d	Combo=CBT
POTS Team 2004	112	a. CBT b. Sertraline c. CBT+sertraline d. placebo	12	12	c>a=b>d at w 12	Combo>CBT
Foa et al. 2005	122	a. ERP b. Clomipramine c. ERP+clomipramine d. placebo	12	4 12	a=c>b=d at w 4 a=c>b>d at w 12	Combo=ERP

Table 2. *Is adding ab initio CBT to medication more effective than medication alone?*

Authors	***Sample size***	***Groups***	***Duration (weeks)***	***Assessments***	***Results***	***Combo versus medication***
Rachman et al. 1979 Marks et al. 1980	48	a. Clomipramine+ERP b. Clomipramine+relaxation c. Placebo+ERP d. Placebo+ralaxation	10	7	a=b=c>d at w 7	Combo=medication
Marks et al. 1988	55	a. Clomipramine+antiexposure (23w) b. Clomipramine+self-exposure (23 w) c. CMI+self-Exp(w1-8)+ther-ERP(w8-23) d. placebo+self-Exp(w1-8)+ther-ERP(w8-23)	27	8 17 23	b>a at w 8 and 17 b=a at w 23	Combo>medication at w 8 and 17 Combo=medication at w 23
Cottraux et al. 1990	60	a. Fluvoxamine+antiexposure b. Fluvoxamine+ERP c. Placebo+ERP	24	8 24	a=b at w 8 a=b=c at w 24	Combo=medication
O'Connor et al. 1999	29	a. Medication+CBT b. CBT c. Medication while on W-L d. Wait-list	20	20	a=b=c>d	Combo=medication
POTS Team 2004	112	a. CBT b. Sertraline c. CBT+sertraline d. placebo	12	12	c>a=b>d at w 12	Combo>medication
Foa et al. 2005	122	a. ERP b. Clomipramine c. ERP+clomipramine d. placebo	12	4 12	a=c>b=d at w 4 a=c>b>d at w 12	Combo>medication

also lead to earlier improvement for OC symptoms than Exposure and Response Prevention only, as suggested by results of the Marks et al. 1988 study (greater efficacy at week 8 but this difference disappeared later on). The study by Cottraux et al. 1990 suggests that the same could be true but for compulsive symptoms only, although the benefits do not last over the long-term.

A potential benefit for the combined treatment could also emerge in settings where ERP is not conducted intensively (and this could have a profound impact on the outpatient clinical practice where intensive treatments are difficult to be delivered), although this conclusion is tentative and not based on any study which directly addressed this issue. Our suggestion derives from the evaluation of effect sizes of ERP alone in two studies where CBT was differently delivered (Cottraux et al. 1990, Foa et al. 1992); although effect sizes of combination treatments were equivalent in both studies, effect size of ERP alone in the Cottraux et al. study, where ERP was delivered with a once in a week therapist-assisted format, was inferior to effect size of ERP alone in the Foa et al. study, where ERP was delivered intensively (5 sessions of assisted exposure/ week). The Cottraux et al. study better reflects routine clinical practice and thus efficacy of ERP in this setting could benefit from the addition of medication (effect size of the combination superior although not statistically significant).

Except for children and adolescents or severely depressed patients with OCD, then, it appears that there is no reason to combine CBT and medication when CBT is delivered *ab initio*.

Adding CBT to medication as compared to medication alone

The second question addressed in the present paper is whether adding CBT to medication is more effective than medication alone in those patients who, for any reasons, receive antiobsessional drugs as first-line interventions.

Only six of the nine abovementioned studies comprised a medication only arm, permitting to answer this question (Rachman et al. 1979, Marks et al. 1988, Cottraux et al. 1990, O'Connor et al. 1999, POTS Team, 2004, Foa et al. 2005). Methodologies of these studies have already been described in the previous paragraph; here we will only discuss results concerning the relative efficacy of the combination versus medication only arms.

The first study (Rachman et al. 1979, Marks et al. 1980) found the combination of ERP and clomipramine similar in efficacy at week 7 as compared to medication alone (clomipramine and relaxation). The same group found, a few years later (Marks et al. 1988), an advantage for the combination of clomipramine and exposure versus clomipramine and antiexposure instructions in the early phase of the study, while such difference did not persist at week 23. This could be only due to the latency of action of clomipramine, which, as all antiobsessional drugs, requires 6 to 8 weeks to manifest its efficacy.

Other two studies did not find an advantage for the combination over the pharmacologic monotherapy (Cottraux et al. 1990, O'Connor et al. 1999).

Evidence for a greater efficacy of the combination emerge, on the contrary, from the two more recent placebo-controlled studies (one of which performed in children and adolescents); the POTS Team (2004) found at the end of the 12-week study period, the combination of sertraline and CBT more effective than both sertraline alone and CBT alone. In the study by Foa and colleagues (2005), finally, although clomipramine was better than placebo at the end of the 12 weeks, the group receiving medication only showed a significantly lower symptoms reduction as compared to the combination group (intensive ERP and clomipramine). This suggests than combining intensive ERP and medication add benefit to medication. However, it is also possible that the greater effect of the combination compared to medication alone strategy would disappear later on as clomipramine antiobsessional effect become greater (all SRIs have a response latency of approximately 8 weeks while intensive ERP was concluded after 4 weeks only).

The same authors (Simpson et al. 2004) performed a 12-week follow-up of responder patients of the previous study with the aim of determine whether adults with OCD who respond to ERP with or without clomipramine fare better after treatment discontinuation than responders receiving clomipramine alone. Relapse rates 12 weeks after treatment discontinuation were 11% for the ERP group, 13% for the combined group and 45% for the clomipramine only group: the difference was statistically significant. This study highlights only that patients who responded to drug should be maintained on the same drug for longer periods of time, as demonstrated by several other authors (Maina et al. 2006). Moreover, it could suggest that ERP could be used (administered simultaneously in that case with medication) to prevent relapses for those patients who want to discontinue medications after the acute 12-week phase.

Table 2 summarizes results of the six studies. In conclusion, three of the studies suggest that adding CBT to medication does not augment or speed the response as compared to medication alone (Rachman et al. 1979, Cottraux et al. 1990, O'Connor et al. 1999); the two more recent studies, which included a placebo arm, on the contrary, indicate that the combination of drug and CBT is more effective than drug alone in reducing obsessive-compulsive symptoms (POTS Team 2004, Foa et al. 2005). The sixth study (Marks et al. 1988) found the combination faster in onset than drug alone, although one might argue that the faster onset of the combination strategy is to be attributed to the slow upward titration of clomipramine doses (the full effect of the drug is evident with a latency of 6-8 weeks from when the minimum therapeutic dose is reached).

Again, differences in study designs (time to reach appropriate drug dosages, for example) and in the intensity of CBT might explain discrepancies between different studies. There is preliminary evidence, however, that the effect of medication might be augmented, in terms of reduction of obsessive-compulsive symptoms, by the addition of CBT.

Another benefit of the combination strategy as compared to medication monotherapy is the use of lower mean drug dosages, which could be more tolerable for some patients: in the POTS Team study

(2004), mean dosages were 170 mg/day in the sertraline only group as compared to 133 mg/day in the CBT and sertraline group. In the Foa et al. study (2005), clomipramine mean dose was 196 mg/day in the medication only group and 163 mg/day in the combination one.

Long-term follow-up

Four follow-up studies evaluated whether the effect of combination treatments is maintained over the long-term in patients who participated to one of the previously described short-term studies (Sullivan et al. 1991, Cottraux et al. 1993, Rufer et al. 2005, Van Oppen et al. 2005).

Sullivan et al. (1991) followed-up 34 of the original 40 patients (85% of the sample) who completed the Marks et al. 1980 study: at the 6-year follow-up, the original clomipramine group was superior to the original placebo group (both had received ERP) on only one of the 16 measures, a result to be expected by chance according to the same authors. Although the combination of clomipramine and ERP was found more effective in depressed patients in the short-term, then, there was no longer a difference between the patients who originally received clomipramine or placebo in combination with CBT. It is worth mentioning, however, that only 10 patients out of the 34 had remained drug free throughout the 6 years of the study.

Cottraux et al. (1993) report on a follow-up of 33 patients from the original 60 (55%) who participated to their original short-tem study (Cottraux et al. 1990). These subjects were evaluated 1 year after the end of the previous trial (18 months from the beginning of treatment). At follow-up, the three groups (fluvoxamine+antiexposure, combination of fluvoxamine+exposure, and placebo+exposure) showed a similar YBOCS reduction (combination=medication only=ERP only). However, over 80% of patients who had received ERP with either placebo or fluvoxamine (combination) versus only 40% of those who had received fluvoxamine+antiexposure were free of antidepressant medications. This suggests that combining ERP with medication might allow discontinuation of drugs after the 6-month short-term treatment.

Rufer and colleagues (2005) followed-up 30 patients, 54% of the sample included in the short-term Hohagen trial (1998). Seven years after the end of the treatment (CBT with either fluvoxamine or placebo) there were no differences between the two groups in YBOCS scores, HAM-D scores or responder rates (combination=CBT alone). As in the Sullivan study, however, the vast majority of patients followed-up (70%) had needed additional drug treatment (only 9 subjects remained without medication during the entire follow-up period); unfortunately, this study did not specify the rate of antidepressant use in the two groups.

The follow-up study with the greater sample is the one by van Oppen et al. 2005; they naturalistically followed-up 102 of the original 122 patients (83.6%) who participated in the van Balkom study (1998). Five years after the end of the treatment patients were re-interviewed; results are presented giving three comparison groups: patients who had received cognitive therapy alone, ERP alone, and fluvoxamine with either cognitive therapy or ERP (presented together). The clinical benefits of the three treatments were maintained at follow-up both in terms of recovery and improvement rates (combination=CT=ERP). The rate of antidepressant use at follow-up, however, was higher in the combination group (51%) when compared with the cognitive therapy (19%; statistically significant difference) and with the ERP group (33%; difference not statistically significant). No differences were detected between the three groups in the proportion of subjects who had received additional psychological treatment during the follow-up.

These results, together with those from the Cottraux et al. 1993 study, suggest a potential role for combining CBT with medication in preventing relapses in those patients who prefer to discontinue medication after the short-term. It has to be mentioned, however, that the abovementioned studies did not evaluate relapse rates as one of the primary outcome measures of their studies.

This suggestion is further supported by results of two other trials: Hembree et al. (2003) in a long-term follow-up (6-43 months) of 62 patients who had received medication alone (fluvoxamine or clomipramine), ERP or both, found a benefit at follow-up for ERP or ERP combined with medication compared with medication only, mainly in the subgroup of those patients who had ceased medication.

Kordon and colleagues (2005), finally, followed-up for 2 years a total of 74 stable patients, divided in three groups: those who received CBT alone, those who received CBT combined with continuous SRI treatment during follow-up, and those who initially received combined treatment with discontinuation of SRI during the follow-up (at least 8 weeks prior to the 2-year evaluation). Relapse rates were not significantly different (31% versus 22% and 20%, respectively).

In conclusion, as for the short-term, no additional benefit in the long-term arises from adding medication to CBT as compared to CBT alone. The differences found by some short-term studies between the combination and the medication alone groups do not persist over the long-term. The lack of difference, in terms of relapse rates, between those who continued (22%) and discontinued (20%) medication at follow-up in the Kordon study, together with results from the Cottraux et al. 1993 and the van Oppen et al. 2005 studies, suggests that patients who might prefer stopping medication or with severe adverse effects may be protected against a worsening of symptoms by combining CBT in the acute phase of treatment.

The same protection may be achieved by planning psychotherapy to start after medication and end after drug discontinuation (sequential integrated treatment): Biondi and Picardi (2005) demonstrated a greater efficacy of an integrated sequential combination treatment of SRIs (of 12-24 months duration) and CBT (timed to start after drug treatment and end after medication discontinuation) as compared to medication 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 months vs. 25 months).

No evidence emerges for a negative effect of medication (in the short or long-term) on the efficacy of CBT; 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 (see Otto et al. 2005, for a complete review in other anxiety disorders).

Sequential treatments

Another approach is the sequential addition of CBT to medication or viceversa: the objective of a sequential treatment is, according to this definition, to augment the response to one strategy by adding the other treatment modality once the first is judged to be insufficient. Preliminary evidence suggests that this strategy might be effective in converting to responders patients who failed to improve on monotherapy and even that additional improvement might be obtained in patients who showed a full response, although not a remission, with medication only.

Although both adding CBT to medication non responders and adding medication to CBT non responders are routine clinical practices, little evidence is available from the literature review. The addition of a CBT trial, moreover, is considered by the Expert Consensus Guidelines as a first-line option in case of inadequate response to SRI alone together with the switching strategy (March et al. 1997); however, few studies examined this strategy in patients partially unresponsive to drug treatment (Simpson et al. 1999, Kampman et al. 2002, Albert et al. 2003, Tolin et al. 2004, Storch et al. 2006), while no studies, to our knowledge, have been published concerning the addition of medication to subjects not fully responding to CBT alone.

Simpson et al. (1999) used 17 sessions of ERP to augment the response in 7 patients who remained symptomatic (YBOCS≥16) despite an adequate 12-week trial of an SRI (retrospectively evaluated); the authors showed, although in an open-label manner, that CBT augmentation might lead to a significant decrease in obsessive-compulsive symptoms (mean YBOCS decrease 49%).

Kampman et al. (2002) prospectively evaluated the response to fluoxetine in drug-naïve OCD subjects; those patients who did not fully respond after 12 weeks of fluoxetine 60 mg/day (14 patients) received 12 ERP plus cognitive restructuring sessions; in the nine completers, the YBOCS decreased from 25.7 to 15.0 (highly significant), with a mean reduction in YBOCS scores of 41%.

Tolin and colleagues (2004) selected 20 OCD patients with a history of inadequate response to at least 2 previous trials of SRIs, given at adequate doses and for adequate periods of time, and with multiple comorbid disorders, 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 verify the failure to respond to pharmacotherapy; then they received 15 sessions of therapist-assisted in vivo or imaginal exposure plus homework ERP assignments. OCD severity (as measured with the YBOCS) decreased significantly after treatment and gains were maintained at the 6-month follow-up; analysis of clinical significance indicated that 53% of treatment completers met this criterion at posttreatment and 40% met the criterion at follow-up.

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, and in OCD response to SRIs occurs, at least in some cases, later during the course of the treatment.

On the basis of the preliminary results indicating the efficacy of a sequential combination strategy, we performed a study in order to evaluate the efficacy of the addition of CBT in OCD patients who had not responded adequately to a 6-month trial of SRIs, in order to be sure about attributing the eventual response to CBT addition and not to time elapsed. Patients with a principal DSM-IV diagnosis of OCD (SCID; YBOCS ≥16) who prospectively received a treatment with a first-line antiobsessional agent given for at least six months at adequate dosages were included. Subjects who had received a prior ineffective CBT trial and patients with current comorbid MDD (HAM-D≥16), lifetime comorbid schizophrenia, other psychotic disorders or bipolar disorders, or alcohol or substance abuse in the past six months were excluded. Subjects who failed to show, after six months, a Y-BOCS decrease ≥35% with respect to baseline but still exhibited a partial reduction in OC symptomatology were offered a CBT trial. CBT was added to the ongoing SRI, whose dosage was maintained fixed throughout the duration of the trial. We used the technique of ERP (weekly office visit + ERP homeworks – in some cases + out-of-office therapist assisted ERP). The primary outcome measure was the YBOCS, which was administered at least three times before the addition of CBT in order to assure that drug treatment was no more effective, at week 4 and at the end of the CBT trial. Nineteen patients were included; of them, six (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; $p<.001$). All patients who completed the study had washing or checking compulsions, which were the target of the ERP.

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. Our results confirm that this strategy might be effective in this subgroup of patients, although our data need to be replicated in controlled trials with different types of obsessive-compulsive symptoms to allow for a generalization of results (Albert et al. 2003).

Similar results emerge from another recent trial. O'Connor and colleagues (2006) presented results from two separate protocols; in the first one, 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 either fluvoxamine or placebo was maintained unchanged whilst on CBT).

During the first 5 months, a significantly greater change in YBOCS scores was observed in the medication as compared to the placebo group, as expected; however, the mean percentage reduction in YBOCS was clinically not significant in both groups (7% in the placebo and 15% in the fluvoxamine group, respectively); the sample which received 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 regardless of whether the subject was on medication or placebo prior to and during CBT (mean reduction in YBOCS scores: 44% in the placebo and 57% in the fluvoxamine group, respectively). In the second protocol (O'Connor et al. 2006), all patients were started immediately on CBT; the authors, however, 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 still >16 at CBT initiation). Both groups responded equally well to CBT (mean YBOCS reduction: 53% in drug-naïve patients and 43% in those stabilized on medications). Taken together, results from the two separate trials confirm that CBT is equally effective regardless of whether the subject has previously received medication or not (medication do not seem to interfere with CBT efficacy), and that sequential CBT addition to medication in patients unresponsive despite several months of SRI treatment is effective in inducing response.

CBT augmentation in subjects with inadequate response to medication might be a promising sequential treatment strategy also for children with OCD: a preliminary study found intensive CBT (5 sessions of ERP/week for 3 weeks) to reduce CY-BOCS mean scores from 32.0 to 11.2 in five children with a limited response to SRIs or unable to be titrated to a complete dose due to side effects (Storch et al. 2006).

A sequential addition of behavior therapy to medication has been found to be beneficial even for patients who have responded to drug treatment but showed residual symptoms (Tenneij et al. 2005): 96 OCD patients who had responded to 3 months of SRIs were randomized to either receive addition of 18 ERP sessions or continue on drug treatment alone for 6 months. The first group showed a significantly greater further reduction in YBOCS scores as compared to the other group, 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). Patients who received drug treatment alone were then offered the opportunity to receive CBT and evaluated another 6-month later (delayed combination therapy group); the comparison of response between the combination therapy (immediately after response) and the delayed combination therapy suggested that the effect is greater when behavior therapy is added immediately after attainment of the drug response.

The sequential delivery of CBT in patients partially or fully unresponsive to drug treatment with SRIs despite adequate dosages and duration of the trial (even 6 months at the highest tolerated doses) appears to be then effective. No study, to our knowledge, has investigated the efficacy of the sequential addition of medication to CBT in patients partially unresponsive to CBT alone.

Conclusions

The present paper was aimed at evaluating literature data concerning combination strategies of CBT and medication in OCD in order to identify those subjects who could benefit from this strategy implemented *ab initio* or sequentially administered. After having examined results of published studies we can try to draw some conclusions:

1) The short-term or long-term treatment effect of CBT (mainly ERP) is not augmented by the addition of medication; a combination of CBT and medication might be superior to CBT alone, regarding the short-term treatment results, when obsessions dominate the clinical picture and/or when a severe secondary depression is present. Children and adolescents with OCD could also benefit more from the combination treatment although it remains to be fully demonstrated that this strategy is more effective than CBT alone.

2) The short-term treatment effect of antidepressant medications can be enhanced by the addition of CBT in the form of ERP with or without cognitive therapy. CBT could be used a) to augment the benefit from medication in terms of obsessive-compulsive symptoms reduction (although negative studies also exist); b) to reduce the use of medication for those patients who are intolerant to side effects (mean drug doses were lower in the combination-treated subjects than in those who received medications only); c) to prevent relapses, over the long-term, for those patients who want to discontinue medication after short-term response.

3) A sequential administration of CBT in combination with medication might convert patients who failed to fully respond to medication in responders. Preliminary results also suggest that a sequential administration of CBT after response to medication might lead to further improvement in OC symptoms over the long-term.

4) There is no evidence for OCD that medications interfere, in the short-term or over the long-term, with CBT efficacy.

Future studies should confirm results of the present review and investigate whether medications are effective in patients not responding to CBT alone, which are the subjects who can benefit from a combination strategy *ab initio*, and which ingredients of CBT (ERP, cognitive therapy or both) is worth adding to medication when a combination of psychotherapy and pharmacotherapy is judged to be necessary.

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