Combining drug and psychological treatments for obsessive-compulsive disorder: What is the evidence, when and for whom

Combining drug and psychological treatments for Obsessive-Compulsive Disorder: what is the evidence, when and for whom

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Abstract

Background: serotonin reuptake inhibitors (SRIs) and cognitive-behavioral psychotherapy (CBT) are first-line treatments for obsessive-compulsive disorder (OCD). Since response is often inadequate, in recent years researchers investigated whether combining CBT and SRIs, either *ab initio* or sequentially, results in a greater reduction of obsessive-compulsive symptoms.

Objective: the aims of the present paper are to assess if combination treatment seems adding benefits as compared to either monotherapy alone and if sequential strategies may be effective in converting partial or non responders to a first-line treatment into responders.

Method: we reviewed available literature on pharmacological and CBT combination and sequential treatments for adult and pediatric OCD patients and then we conducted a separate analysis for studies concerning these two promising strategies. Search results included open-label trials and randomized controlled trials (RCTs).

Results: we identified ten controlled studies assessing the efficacy of combination treatments ab initio *versus* CBT alone and six evaluating combination strategies ab initio *versus* medications alone. Eleven studies, only two of which RCTs, have been published on sequential treatments. The combination *ab initio* of CBT and SRIs has not been found to be clearly superior to either monotherapy alone in most studies conducted on this topic, except for patients with severe depression who might benefit more from the combination *versus* only CBT. A sequential administration of CBT after medications has been found useful in promoting remission in patients who partially responded to drugs and in promoting response in resistant patients.

Conclusion: OCD patients with comorbid major depression should receive medication firstly, eventually associated with CBT; for all remaining patients there is clear evidence from the literature of no additive benefits of combining *ab initio* CBT and medication. Therefore, the routine use of a combination approach in all adult patients affected by OCD is not supported by the literature. The available evidence supports the effectiveness of the *sequential* addition of CBT to SRIs.

Keywords

Obsessive-Compulsive Disorder, cognitive behavioral therapy, augmentation treatment, combination treatments, serotonin reuptake inhibitors, treatment-resistant OCD, exposure and response prevention

1. INTRODUCTION

Obsessive-compulsive disorder (OCD) is a heterogeneous psychiatric illness with a lifetime prevalence in the general population of approximately 2-3%, making it a far more common disorder than previously believed [1]. The diagnosis is made by the presence of recurrent or persistent, upsetting thoughts, images, or urges, which are experienced as intrusive and unwanted (obsessions), and excessive repetitive behaviors or mental acts performed in response to these obsessions (compulsions) [2].

First line treatments for OCD include both serotonin reuptake inhibitors (SRIs) (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, and clomipramine), and cognitive behavior therapy (CBT) – in the forms of exposure and response prevention (ERP) and/or cognitive restructuring [3-11]. Both the above-mentioned pharmacological and psychological approaches have been recognized more effective than wait-list, inactive psychological treatments or placebo in individual randomized controlled trials (RCT) [12-15].

Despite advances in the treatment of OCD, 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 that can impair their quality of life [16].

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") [17, 18].

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

In the first part of the paper we will review all published controlled studies on combination therapies *ab initio* 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 give 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).

2. MATERIALS AND METHODS

We searched on Pubmed, Ovid, Scopus, PsycINFO, Cochrane Libraries from inception to August 2016. The search term "obsessive-compulsive disorder" was combined, using the boolean AND, with "treatment", "cognitive-behavior therapy", "resistant OCD", "sequential treatment" and "combined treatment". Then, a manual search for reference lists from articles selected in the previous search and for any relevant reviews was done. Search results included open-label trials and randomized controlled trials of both adults and children/adolescents with OCD.

3. RESULTS

3.1 Combination therapy *ab initio*

3.1.1 Acute studies: CBT plus medication *versus* CBT alone

Ten controlled and/or randomized studies investigated whether adding *ab initio* a drug effective in the treatment of OCD to CBT (exposure and response prevention ERP with or without cognitive therapy) provides an additional advantage 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.* (same study results published also in Marks *et al.* [20]) randomized 48 OCD patients to either clomipramine (CMI) 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) [19]. 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 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.

The same research group performed another controlled study a few years later [21]. Fifty-five (of whom only 11 were randomized) patients were included 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 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 subjects 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 conducted by Cottraux *et al.* [22]; 60 patients were randomized 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 imaginative exposure for the first 8 weeks followed by guided in vivo exposure and response prevention for the additional 16 weeks. Patients' follow-up lasted 48 weeks at all. 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 account of these preliminary results of a better efficacy in subjects with concomitant major depression, Foa and colleagues included 48 OCD subjects in a double-blind study comparing mildly versus severely depressed patients (based on the BDI) [23]. 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 behavioral therapy from week 10 to 22 (end of study). Patients were divided in 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.

Contrarily, Hohagen and colleagues found the combination more effective than CBT alone in subjects with predominant obsessive symptoms or concomitant severe depressive symptomatology (Hamilton Depression Rating Scale > 18) [24]. Forty-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 considerably 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.

A separate evaluation of the combination of drug and cognitive versus drug and exposure and response prevention therapy was done for the first time by Van Balkom *et al.* [25], who also compared these two strategies to cognitive therapy alone and ERP alone for 16 weeks. A sequential strategy was chosen 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. They added a waiting list comparison group 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 compared medication (different SRIs)+CBT, CBT only, medication while on waiting-list for CBT and waiting-list [26]. Twenty-nine non-randomized subjects were included in the study; 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. Without differences, all treatments were more effective than the waiting list at the end of the 20-week study period. 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 aforementioned 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.

Another study was conducted 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 [27]. 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 ERP and ERP

+ CMI groups showed a significantly greater reduction in YBOCS scores than CMI and placebo groups. CMI group did not significantly differ 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.

Only two studies were performed in samples of children and/or adolescents, with opposite results.

The first randomized, controlled, single-blind study found the combination of CBT and medication better than CBT alone [28]. 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. In terms of symptoms reduction, the combination strategy 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. Furthermore, the same Authors, using data from the same sample, found that in children and adolescent with OCD and a comorbid tic disorder treatment with sertraline did not differ from placebo: therefore patients with this type of comorbidity should begin treatment with CBT alone or the combination of CBT and medication [29]. The effectiveness of CBT can be significantly reduced by a family history of OCD: there is a six-fold difference in effect size for monotherapy CBT for those with and without a family history [30]. Thus those with a family history of OCD should be offered CBT only in combination with medication.

The efficacy of CBT alone or combined with sertraline in the treatment of pediatric obsessive-compulsive disorder was examined by another recent study performed by Storch and colleagues [31]. Forty-seven children and adolescents with OCD were randomized to 18-weeks of treatment in one of three arms: 1) sertraline at standard dosing + CBT (RegSert +CBT); 2) sertraline titrated slowly but achieving at least 8 weeks on the maximally tolerated daily dose + CBT (SloSert+CBT); or 3) pill placebo + CBT (PBO+CBT). Overall, results indicated significant improvement across primary and secondary outcomes, but that changes were comparable across groups: there was consistently no evidence that combination of sertraline with CBT in pediatric OCD was more effective than CBT alone.

Table 1 summarizes results of the abovementioned studies. In conclusion, ten controlled studies evaluated whether the combination of CBT and medication is superior in efficacy to CBT alone in the short-term treatment of OCD. In six of them the combination was simultaneous, which means that patients in the combination arm started on both treatment strategies at the same time [21, 22, 24, 26-28]; in the other four studies, patients in the combination arm received medication or placebo for 4 [20, 31], 6 [23], or 8 weeks [25] 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 *ab initio* as compared to CBT alone except for subgroups of patients with peculiar characteristics. Marks *et al.* [20] found the combination more effective than CBT alone only in depressed OCD patients; this result is confirmed by Hohagen *et al.*

[24], who found the combination more effective in patients with severe depression or predominant obsessive symptomatology only. Our conclusion is, so far, that OCD patients with comorbid major depression should receive medication, eventually associated with CBT; for all remaining patients there is clear evidence from the literature of no additive benefits of combining *ab initio* CBT and medication as compared to CBT alone. It remains unclear, on the contrary, whether combined treatment *ab initio* yields improved outcomes relative to CBT monotherapy alone in children and adolescents: the POTS trial [28] found that combined treatment was superior to CBT alone in children/adolescents with OCD, while Storch and colleagues did not find additional advantage of combined therapy over CBT monotherapy [31]. Future studies will highlight whether in this subgroup of patients with OCD it is worth combining the two strategies *ab initio*.

3.1.2 Acute studies: CBT plus medication versus medication alone

A different question to be answered is whether the combination *ab initio* of medication and CBT is more effective than medication alone in those patients who, for any reasons, receive antiobsessional drugs as first-line interventions. Only six of the ten abovementioned studies comprised a medication only arm, permitting to answer this question [19, 21, 22, 26-28]. 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 [19, 20] 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 [21], 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 [22, 26].

Evidence for a greater efficacy of the combination emerges, on the contrary, from the two more recent placebo-controlled studies (one of which performed in children and adolescents); the POTS Team [28] 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 [27], 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 that combining intensive ERP and medication adds 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 becomes greater (all SRIs have a response latency of approximately 8 weeks while intensive ERP was concluded after 4 weeks only).

Table 1 summarizes results of the abovementioned 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 [19, 22, 26]. The two more recent studies, which included a placebo arm, on the contrary, indicate that the combination of drug and CBT *ab initio* is more effective than drug alone in reducing obsessive-compulsive symptoms [27, 28]. The seventh study [21] 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 [28], 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 [27], clomipramine mean dose was 196 mg/day in the medication only group and 163 mg/day in the combination one.

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 therefore 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 *ab initio* as a routine clinical practice for all patients [8].

3.1.3 Long-term follow-up of acute studies

Four follow-up studies evaluated whether the effect of combination treatments *ab initio* is maintained over the long-term in patients who participated to one of the previously described short-term studies [32-35].

Sullivan *et al.* [32] followed-up 34 of the original 40 patients (85% of the sample) who completed the Marks *et al.* study [18]: 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*. [33] report on a follow-up of 33 patients from the original 60 (55%) who participated to their original short-tem study [22]. 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 [34] followed-up 30 patients, 54% of the sample included in the short-term Hohagen trial [24]. 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.* [35]; they naturalistically followed-up 102 of the original 122 patients (83.6%) who participated in the van Balkom study [25]. 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 anti-depressant 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.* study [33], 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.* [36] 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, 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) [37]. 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.* [33] and the van Oppen *et al.* [35] 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.

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.* [38], for a complete review in other anxiety disorders).

3.2 SEQUENTIAL COMBINATION

Another approach is the sequential combination strategy, consisting in the sequential addition of CBT to medication or vice versa, rather than applying the two optimal treatments for OCD patients simultaneously. The purpose of a sequential treatment is to augment the response to one approach by adding the other treatment modality once the first is considered to be insufficient. This might promote remission in patients who showed a reduction in symptoms with a

single treatment modality, satisfactory to meet criteria for response but still had clinically relevant residual OCD symptoms, and might promote response in patients unsuccessfully treated with first-line therapy (either SRIs or CBT).

We only consider studies that added behavior therapy or SRI after at least 12 weeks of first-line treatment (either CBT or drugs). This limitation is, to our opinion, necessary as response to both single therapies, especially as concerns SRIs, cannot be assessed before 6 to 8 weeks and several patients usually achieve response criteria between 8 to 12 weeks of drug treatment [39]. Methodologically, adding CBT before week 12 would not warrant clinicians to discriminate between the true additive effect of the sequential combination treatment and the simple effect of continuing the drug treatment for a longer period.

Although both adding CBT to medication non responders and adding medication to CBT non responders are routine clinical practices, several studies have been published concerning the sequential addition of CBT to those patients who partially responded or failed to respond to SRIs (and continued to take the drug while on CBT), while only 2 studies evaluated the effectiveness of switching to pharmacotherapy versus continued CBT or switching to cognitive therapy among OCD patients who did not respond to an initial course of CBT [40, 41].

The rationale of the sequential combination strategy is to maintain and increase the effect of another first-line treatment (SRIs) when this outcome is judged to be poor, with a different strategy (CBT) whose efficacy in OCD has been demonstrated.

3.2.1. Sequential combination treatment in partial responders

Tenneij *et al.* firstly assessed whether the addition of behavior therapy to SRIs is really more effective than just the continuation of drug treatment among subjects who already responded to drug monotherapy but exhibited residual symptoms [42]. Secondly, they evaluated 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 responded to 3 months of drug treatment were 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. Patients who received combination therapy exhibited significantly higher remission rates compared to those who continued on drug treatment alone (53% *versus* 11%, $p<.0001$ for completers). Subsequently, patients who received drug treatment alone were offered the opportunity to receive CBT and were evaluated another 6-month later (delayed combination therapy group). The comparison of response between the combination therapy (immediately after response, namely 3 months after starting 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.

Therefore, a sequential addition of CBT to drugs (that are maintained) might lead patients who partially respond to drug treatment alone to further improvement in OC symptoms. This is a clinically relevant issue since only a minority of subjects accomplishes remission using a single treatment modality, although both CBT and SRIs have been recognized as effective treatment.

Biondi and Picardi evaluated another sequential combination strategy, based on scheduling behavior therapy to start after medications and end after drug discontinuation (sequential integrated treatment) [43]. The purpose of this

approach is to maintain benefits of pharmacotherapy once drugs are discontinued. The sequential integrated treatment of SRIs (12-24 months) and CBT (timed to start after drug treatment and end after medication discontinuation) showed greater efficacy 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 vs. 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.

Franklin *et al*. selected 124 pediatric OCD outpatients, between the ages of 7–17, who showed a partial response (CY-BOCS score ≥ 16) despite an adequate SRI trial [44]. All patients received medication management, which included maintenance treatment with SRIs for the duration of the study. Participants were randomized to receive 12 weeks of adjunctive CBT (which included 14 hour-long sessions administered by a study psychologist) or instructions in CBT (consisting in introducing the procedures of CBT in seven 45 minutes sessions delivered by child and adolescent psychiatrists in the context of medication management) or no adjunctive treatment. Adding CBT to medication management compared with medication management alone improves response rate (defined as a CY-BOCS reduction of 30% or more from baseline to week 12) and reduces symptoms severity, whereas, augmentation of medication management with the addition of instructions in CBT did not have a significant effect.

In conclusion, the sequential combination of CBT to SRIs in both children/adolescents and adults who partially responded to medications alone is associated with a further improvement even when drugs are discontinued.

3.2.2. Sequential combination treatment in resistant patients

Several open-label, naturalistic studies (all except one performed in adults) indicated that the sequential combination of CBT to SRIs is subjects not responding to medications alone is effective, with YBOCS total score mean decrease of 17.9-49% depending on the intensity of ERP and the degree of resistance (number of previous failed SRI trials). Designs and results of all the studies [45-55], which used CBT to augment the response to medication in OCD patients, are displayed in Table 2.

Two RCTs provided clear evidence of the effectiveness of the sequential combination strategy. In the first one, stress management training (SMT) was used as the control condition [51]. Participants were 108 adult OCD patients; those assigned to the CBT arm received 17 twice-weekly ERP sessions, while SMT 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), 74% of patients receiving ERP were responders *versus* 22% of patients receiving SMT ($p<.001$). These findings strongly support the use of ERP as an SRI augmentation strategy for OCD non-responders to medication.

In the second RCT [54], while continuing their SRI at the same dose, patients were randomized to the addition of 8 weeks of risperidone (up to 4 mg/d), ERP (17 sessions delivered twice weekly), or pill placebo. Patients randomized to ERP had significantly greater reduction in week 8 Y-BOCS scores compared to those treated with risperidone and placebo, while patients on risperidone did not differ from those receiving placebo. More patients receiving ERP achieved clinical response (80% for ERP, 23% for risperidone, and 15% for placebo; $p<.001$) and minimal symptoms (Y-BOCS ≤12: 43% for ERP, 13% for risperidone, and 5% for placebo; $p=.001$). Indeed, the authors concluded that the

addition of ERP to SRIs was superior not only to placebo but also to risperidone, the other strongly supported strategy for resistant OCD [56].

Responders to risperidone and ERP augmentation were then followed-up for additional 6 months [57]: ITT analyses indicated that ERP yielded superior OCD outcomes than risperidone (Y-BOCS: 10.95 versus 18.70; p=.009). More patients randomized to ERP met response criteria (Y-BOCS decrease ≥25%: 70% versus 22.5%; p<.001) and achieved minimal symptoms (Y-BOCS ≤12: 50% versus 5%; p<.001).

O'Connor and colleagues sustained the previous conclusion examining the efficacy of CBT in OCD subjects who had previously or not received a pharmacological treatment (and continued this treatment while on CBT) [58]. 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. Both groups benefited significantly from CBT addition, with no difference in the degree of response regardless of whether the patients were previously on fluvoxamine or placebo (mean YBOCS total score reduction 57% *vs.* 44%). In the second protocol, all patients (n=22) immediately received CBT. The authors identified two subgroups, one drug-naïve at the moment of CBT initiation and the other stabilized on SRI treatment but still symptomatic despite a partial response (YBOCS total score >16). 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. Therefore, CBT augmentation of SRIs appears to be a valuable option for both OCD patients who respond to medications but still have OC symptomatology and resistant patients.

To our knowledge, only 2 studies investigated the effectiveness of the sequential addition of medication to CBT in patients unresponsive to CBT alone, one examining a sample of adults and the other considering children and adolescents [40, 41].

A 12-week RCT compared the effectiveness of second-step treatment with cognitive therapy versus fluvoxamine (titrated up to 300 mg/day) in 48 OCD patients considered non-responders to a previous first-step treatment with 12-week ERP [40]. Fluvoxamine as a second-step treatment was significantly superior to CT, which did not appear to be effective. OCD patients who are nonresponsive to ERP may then benefit more from a switch to treatment with an antidepressant instead of switching to CT.

The second RCT investigated the effectiveness of sertraline (100-200 mg/day) versus continued CBT (10 additional sessions) in 54 children and adolescents that did not respond to an initial course of 14-week CBT [41]. No differences between the 2 groups were detected: continued treatment for CBT non-responders was as effective as switching to sertraline (response rates: 50% in the continued CBT group vs. 45.4% in the sertraline one).

In conclusion, the available evidence supports the sequential addition of CBT to SRIs for both OCD patients who respond to medications but still have residual obsessive-compulsive symptoms (2 positive randomized controlled studies) [42, 44] and for resistant patients (2 positive randomized controlled studies) [51, 54]. Two other RCTs support the effectiveness of switching to medications after non-response to CBT [40, 41].

4. CONCLUSIONS AND FUTURE DIRECTIONS

In conclusions, the *combination ab initio* of CBT and SRIs has not been found to be clearly superior to either medication alone or CBT alone in most studies conducted in adult patients; the only exception is for patients with comorbid major depression, where the combination *ab initio* appeared superior to CBT alone. Our conclusion is, then, that OCD patients with comorbid major depression should receive medication firstly, eventually associated with CBT; for all remaining patients there is clear evidence from the literature of no additive benefits of combining *ab initio* CBT and medication. Therefore, the routine use of a combination approach in all adult patients affected by OCD is not supported by the literature.

It remains unclear, on the contrary, whether combined treatment *ab initio* yields improved outcomes relative to CBT monotherapy alone or drug alone in children and adolescents. Thus, future studies in children and adolescents are strongly needed.

The available evidence supports the effectiveness of the *sequential* addition of CBT to SRIs for both OCD patients who respond to medications but still have residual obsessive-compulsive symptoms and for resistant patients; however, these conclusions are supported by only 2 RCTs for partial responders and 2 other RCTs for resistant patients. Two other RCTs support the effectiveness of switching to medications after non-response to CBT. The sequential combination of CBT and medication, then, is advisable in routine clinical practice, based also on results of naturalistic effectiveness studies [53], although positive findings need to be replicated in large and controlled trials.

Another promising combination strategy consists in combining CBT with D-cycloserine (DCS). In this case the combination is made between a psychological and a pharmacological approach, although the drug used, DCS, is not used alone to treat OCD (as in the case of SRIs). DCS affects the glutamate system by acting as a partial agonist at the N-methyl-D-aspartate (NMDA) receptor, which is crucially implicated in fear learning and fear extinction in both rats and humans [59]. As CBT/ERP is based on learning theories, DCS has been largely investigated as a valuable augmentation strategy for anxiety disorders and/or OCD patients treated with CBT.

A recent Cochrane systematic review investigated this approach in children, adolescents and adults with anxiety and related disorders, including OCD [60]. All RCTs (n=6) assessing DCS *versus* placebo as augmentation strategy of CBT for OCD were included. Although DCS augmentation of CBT was efficacious in individual studies, there was no difference *versus* placebo in children, adolescents and adults at the end of the treatment. DCS, then, does not enhance the treatment effects of ERP at post-treatment.

However, results of a re-analysis of data from a 10-session RCT of ERP+DCS versus ERP+placebo indicated that the course of ERP was 2.3 times faster over the full 10 sessions for the DCS compared to the placebo group, and nearly six times quicker in the first half of ERP. These results suggest that DCS does not amplify the effects of ERP, but instead initiates treatment effects sooner in treatment [61].

This conclusion is supported by results of another recent meta-analysis [62], incorporating all 6 RCTs simultaneously examined by the Cochrane authors, but evaluating also the effects of DCS at mid-treatment. Results suggested that with the careful optimization of DCS-augmented ERP therapy by fine-tuning timing and dosing of DCS administration and number and frequency of ERP sessions, DCS may enhance the efficacy of ERP therapy in reducing the symptomatic

severity of OCD patients, especially at early stage of the treatment; therefore, DCS augmentation could possibly reduce treatment cost, reduce treatment drop and refusal rate, and help to improve access to the limited number of experienced therapists [62].

Furthermore, a 12-week RCT has been published concerning not only the efficacy of DCS *versus* placebo as adjunct to CBT but also the interaction with concomitant antidepressant medication. Adult OCD patients (n=128) were included with a score of Y-BOCS $\geq$ 16 and concurrent psychotropic medication at a stable dose for at least 2 months prior to enrollment, which did not change for the duration of the trial. Since the authors found that antidepressants may interact with DCS to block its facilitating effect on fear extinction, they suggested the use of DCS only in antidepressant-free patients with OCD [63].

In conclusion, the combination of DCS and ERP does not universally enhance the treatment outcomes of ERP, but remains a promise for a better tailoring of treatments for OCD patients. Distinct treatment moderators, including the concomitant use of antidepressants, may account for discrepant findings across RCTs and disorders.

Future studies are strongly required in order to better integrate psychological and pharmacological treatments, including both SRIs (medications used as monotherapy to treat OCD) and DCS (a medication not used to treat OCD but instead to enhance learning processes).

Conflict of interest

The authors confirm that this article content has no conflict of interest.

REFERENCES

[1] Ruscio, A.M.; Stein, D.J.; Chiu, W.T.; Kessler, R.C. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. *Mol. Psychiatry*, **2010**, 15(1), 53-63.

[2] American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 5th ed*. Washington, DC: American Psychiatric Press **2013**.

[3] March, J.; Frances, A.; Carpenter, D.; Kahn, D. The Expert Consensus Guidelines Series. Treatment of obsessive-compulsive disorder. *J. Clin. Psychiatry*, **1997**, 58(4), 2-72.

[4] Baldwin, D.S.; Anderson, I.M.; Nutt, D.J.; Bandelow, B.; Bond, A.; Davidson, J.R.; den Boer, J.A.; Fineberg, N.A.; Knapp, M.; Scott, J.; Wittchen, H.U. British Association for Psychopharmacology. British Association for Psychopharmacology. Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology. *J. Psychopharmacol.,* **2005,** 19, 567-96.

[5] Baldwin, D.S.; Anderson, I.M.; Nutt, D.J.; Allgulander, C.; Bandelow, B.; den Boer, J.A.; Christmas, D.M.; Davies, S.; Fineberg, N.; Lidbetter, N.; Malizia, A.; McCrone, P.; Nabarro, D.; O'Neill, C.; Scott, J.; van der Wee, N.; Wittchen, H.U. Evidence-based pharmacological treatment of anxiety disorders, post-traumatic stress disorder and obsessive-compulsive disorder: a revision of the 2005 guidelines from the British Association for Psychopharmacology. *J. Psychopharmacol.,* **2014,** 28(5), 403-39.

[6] Canadian Psychiatric Association. Clinical practice guidelines. Management of anxiety disorders. *Can. J. Psychiatry*, **2006**, 51(8 Suppl 2), 9S-91S.

[7] American Psychiatric Association. *Practice Guideline for the treatment of patients with obsessive-compulsive disorder*. Arlington, VA: American Psychiatric Association **2007**.

[8] American Psychiatric Association. *Guideline Watch (March 2013): Practice Guideline for the treatment of patients with obsessive-compulsive disorder*. Arlington, VA: American Psychiatric Association **2013**.

[9] Bandelow, B.; Zohar, J.; Hollander, E.; Kasper, S.; Möller, H.J. WFSBP Task Force on Treatment Guidelines for Anxiety, Obsessive-Compulsive and Post-Traumatic Stress Disoders, Zohar, J.; Hollander, E.; Kasper, S.; Möller, H.J.; Bandelow, B.; Allgulander, C.; Ayuso-Gutierrez, J.; Baldwin, D.S.; Buenvicius, R.; Cassano, G.; Fineberg, N.; Gabriels, L.; Hindmarch, I.; Kaiya, H.; Klein, D.F.; Lader, M.; Lecrubier, Y.; Lépine, J.P.; Liebowitz, M.R.; Lopez-Ibor, J.J.; Marazziti, D.; Miguel, E.C.; Oh, K.S.; Preter, M.; Rupprecht, R.; Sato, M.; Starcevic, V.; Stein, D.J.; van Ameringen, M.; Vega, J. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders-first revision. *World. J. Biol. Psychiatry*, **2008**,9(4), 248-312.

[10] Bandelow, B.; Sher, L.; Bunevicius, R.; Hollander, E.; Kasper, S.; Zohar, J.; Möller, H.J. WFSBP Task Force on Mental Disorders in Primary Care; WFSBP Task Force on Anxiety Disorders, OCD and PTSD. Guidelines for the pharmacological treatment of anxiety disorders, obsessive-compulsive disorder and post-traumatic stress disorder in primary care. *Int. J. Psychiatry Clin. Pract.,* **2012**, 16, 77-84.

[11] Katzman, M.A.; Bleau, P.; Blier, P.; Chokka, P.; Kjernisted, K.; Van Ameringen, M. Canadian Anxiety Guidelines Initiative Group on behalf of the Anxiety Disorders Association of Canada/Association Canadienne des troubles anxieux and McGill University, Antony, M.M.; Bouchard, S.; Brunet, A.; Flament, M.; Grigoriadis, S.; Mendlowitz, S.; O'Connor, K.; Rabheru, K.; Richter, P.M.; Robichaud, M.; Walker, J.R. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. *BMC Psychiatry*, **2014**, 14, S1.

[12] Deacon, B.J.; Abramowitz, J.S. Cognitive and behavioural treatments for anxiety disorders: a review of meta-analytic findings. *J. Clin. Psychol.,* **2004**, 60(4), 429-41.

[13] Eddy, K.T.; Dutra, L.; Bradley, R.; Westen, D. A multidimensional meta-analysis of psychotherapy and pharmacotherapy for obsessive-compulsive disorder. *Clin. Psychol. Rev.,* **2004**, 24(8),1011-30.

[14] Fisher, P.L.; Wells, A. How effective are cognitive and behavioural treatments for obsessive-compulsive disorder? A clinical significance analysis. *Behav. Res. Ther.*, **2005**, 43(12), 1543-58.

[15] Rodrigues, H.; Figueira, I.; Gonçalves, R.; Mendlowicz, M.; Macedo, T.; Ventura, P. CBT for pharmacotherapy non-remitters--a systematic review of a next-step strategy. *J. Affect. Disord.*, **2011**, 129(1-3), 219-28.

[16] Goodman, W.K.; McDougle, C.J.; Barr, L.C.; Aronson, S.C.; Price, L.H. Biological approaches to treatment-resistant obsessive compulsive disorder. *J. Clin. Psychiatry*, **1993**, 54(6), 16–26.

[17] Albert, U.; Bogetto, F. Treatment of obsessive-compulsive disorder: drugs, psychotherapy or combined treatments? *Riv. Psichiatr.*, **2015**, 50(4), 153-4.

[18] Albert, U.; Barbaro, F.; Aguglia, A.; Maina, G.; Bogetto, F. Combined treatments in obsessive-compulsive disorder: current knowledge and future prospects. *Riv. Psichiatr.*, **2012,** 47(4), 255-68.

[19] Rachman, S.; Cobb, J.; Grey, S.; McDonald, B.; Mawson, D.; Sartory, G.; Stern, R. The behavioural treatment of obsessional-compulsive disorders, with and without clomipramine. *Behav. Res. Ther.*, **1979**, 17(5), 467-78.

[20] Marks, I.M.; Stern, R.S.; Mawson, D.; Cobb, J.; McDonald, R. Clomipramine and exposure for obsessive-compulsive rituals: i. *Br. J. Psychiatry*, **1980**, 136, 1-25.

[21] Marks, I.M.; Lelliott, P.; 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, 522-34.

[22] Cottraux, J.; Mollard, E.; Bouvard, M.; Marks, I.; Sluys, M.; Nury, A.M.; Douge, R.; Cialdella, P. A controlled study of fluvoxamine and exposure in obsessive-compulsive disorder. *Int. Clin. Psychopharmacol.*, **1990**, 5(1), 17-30.

[23] Foa, E.B.; Kozak, M.J.; Steketee, G.S.; McCarthy, P.R. Treatment of depressive and obsessive-compulsive symptoms in OCD by imipramine and behaviour therapy. *Br. J. Clin. Psychol.*, **1992**, 31, 279-292.

[24] Hohagen, F.; Winkelmann, G.; Rasche-Rüchle, H.; Hand, I.; König, A.; Münchau, N.; Hiss, H.; Geiger-Kabisch, C.; Käppler, 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), 71-8.

[25] Van Balkom, A.J.; de Haan, E.; van Oppen, P.; Spinhoven, P.; Hoogduin, K.A.; 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(8), 492-9.

[26] O'Connor, K.; Todorov, C.; Robillard, S.; Borgeat, F.; Brault, M. Cognitive-behaviour therapy and medication in the treatment of obsessive-compulsive disorder: a controlled study. *Can. J. Psychiatry*, **1999**, 44(1), 64-71.

[27] Foa, E.B.; Liebowitz, M.R.; Kozak, M.J.; Davies, S.; Campeas, R.; Franklin, M.E.; Huppert, J.D.; Kjernisted, K.; Rowan, V.; Schmidt, A.B.; Simpson, H.B.; 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(1), 151-61.

[28] Pediatric OCD Treatment Study (POTS) Team. Cognitive-behavior therapy, sertraline, and their combination for children and adolescents with obsessive- compulsive disorder: the Pediatric OCD Treatment Study (POTS) randomized controlled trial. *JAMA*, **2004**, 292, 1969-76.

[29] March, J.S.; Franklin, M.E.; Leonard, H.; Garcia, A.; Moore, P.; Freeman, J.; Foa, E. Tics moderate treatment outcome with sertraline but not cognitive-behavior therapy in pediatric obsessive-compulsive disorder. *Biol. Psychiatry*, **2007**, 1, 61(3), 344-7.

[30] Garcia, A.M.; Sapyta, J.J.; Moore, P.S.; Freeman, J.B.; Franklin, M.E.; March, J.S.; Foa E.B. Predictors and moderators of treatment outcome in the Pediatric Obsessive Compulsive Treatment Study (POTS I). *J. Am. Acad. Child. Adolesc. Psychiatry*, **2010**, 49(10), 1024-33.

[31] Storch, E.A.; Bussing, R.; Small, B.J.; Geffken, G.R.; McNamara, J.P.; Rahman, O.; Lewin, A.B.; Garvan, C.S.; Goodman, W.K.; Murphy, T.K. Randomized, placebo-controlled trial of cognitive-behavioral therapy alone or combined with sertraline in the treatment of pediatric obsessive-compulsive disorder. *Behav. Res. Ther*., **2013**, 51(12), 823-9.

[32] O'Sullivan, G.; Noshirvani, H.; Marks, I.; Monteiro, W.; Lelliott, P. Six-year follow-up after exposure and clomipramine therapy for obsessive-compulsive disorder. *J. Clin. Psych.,* **1991**, 52, 150-155.

[33] Cottraux, J.; Mollard, E.; Bouvard, M.; Marks, I. Exposure therapy, fluvoxamine, or combination treatment of obsessive-compulsive disorder: one-year follow-up. *Psych. Res.,* **1993**, 49, 63-75.

[34] Rufer, M.; Hand, I.; Alsleben, H.; Braatz, A.; Ortmann, J.; Katenkamp, B.; Fricke, S.; Peter, H. Long-term course and outcome of obsessive-compulsive patients after cognitive-behavioral therapy in combination with either fluvoxamine or placebo. A 7-year follow-up of a randomized double-blind trial. *Psychiatry Clin. Neurosci*., **2005**, 255, 121-128.

[35] Van Oppen, P.; van Balkom, A.J.L.M.; de Haan, E.; van Dych, R. Cognitive therapy and exposure in vivo alone and in combination with fluvoxamine in obsessive-compulsive disorder: a 5-year follow-up. *J. Clin. Psych.,* **2005**, 66, 1415-1422.

[36] Hembree, E.A.; Riggs, D.S.; Kozak, M.J.; Franklin, M.E.; Foa, E.B. Long-term efficacy of exposure and ritual prevention therapy and serotonergic medications for obsessive-compulsive disorder. *CNS Spectr.*, **2003**, 8, 5, 363-371.

[37] Kordon, A.; Kahl, K.G.; Brooks, A.; Voderholzer, U.; Rasche–Räuchle, H.; Hohagen, F. Clinical outcome in patients with obsessive-compulsive disorder after discontinuation of SRI treatment: results from a two-year follow-up. *Psychiatry Clin. Neurosci*., **2005**, 255, 48-50.

[38] Otto, M.W.; Smits, J.A.; Reese, H.E. Combined psychotherapy and pharmacotherapy for mood and anxiety disorders in adults: review and analysis. *Clinical Psychology: Science and Practice*, **2005**, 12, 72-86.

[39] Bloch, M.H.; Landeros-Weisenberger, A.; Kelmendi, B.; Coric, V.; Bracken, M.B.; Leckman, J.F. A systematic review: antipsychotic augmentation with treatment refractory obsessive-compulsive disorder. *Mol. Psychiatry*, **2006**, 11, 622-632.

[40] Van Balkom, A.J.; Emmelkamp, P.M.; Eikelenboom, M.; Hoogendoorn, A.W.; Smit, J.H.; van Oppen, P. Cognitive therapy versus fluvoxamine as a second-step treatment in obsessive-compulsive disorder nonresponsive to first-step behavior therapy. *Psychother. Psychosom*., **2012**, 81(6), 366-74.
632.

[41] Skarphedinsson, G.; Weidle, B.; Thomsen, P.H.; Storch, E.A.; Lewin, A.B.; Ivarsson, T. Continued cognitive-behavior therapy versus sertraline for children and adolescents with obsessive-compulsive disorder that were non-responders to cognitive-behavior therapy: a randomized controlled trial. *Eur. Child. Adolesc. Psychiatry*, **2015**, 24(5), 591-602.

[42] Tenneij, N.H.; van Megen, H.J.G.M.; Denys, D.A.; Westenberg, H.G. Behavior therapy augments response of patients with obsessive-compulsive disorder responding to drug treatment. *J. Clin. Psychiatry*, **2005**, 66, 1169-1175.

[43] Biondi, M; Picardi, A. Increased maintenance of obsessive- compulsive disorder remission after integrated serotonergic treatment and cognitive psychotherapy compared with medication alone. *Psychother. Psychosom.,* **2005**, 74, 2, 123-8.

[44] Franklin, M.E.; Sapyta, J.; Freeman, J.B.; Khanna, M.; Compton, S.; Almirall, D.; Moore, P.; Choate-Summers, M.; Garcia, A.; Edson, A.L.; Foa, E.B.; March, J.S. Cognitive behavior therapy augmentation of pharmacotherapy in pediatric obsessive-compulsive disorder: the Pediatric OCD Treatment Study II (POTS II) randomized controlled trial. *JAMA*, **2011**, 306(11), 1224-32.

[45] Simpson, H.B.; Gorfinkle, K.S.; Liebowitz, M.R. Cognitive-behavioral therapy as an adjunct to serotonin reuptake inhibitors in obsessive-compulsive disorder: an open trial. *J. Clin. Psychiatry*, **1999**, 60, 584-90.

[46] Kampman, M.; Keijsers, G.P.; Hoogduin, C.A.; Verbraak, M.J. Addition of cognitive-behaviour therapy for obsessive-compulsive disorder patients non-responding to fluoxetine. *Acta Psychiatr. Scand.,* **2002**, 106, 314-9.

[47] Albert, U.; Maina, G.; Forner, F.; Bogetto, F. Cognitive-behavioral therapy in obsessive-compulsive disorder patients partially unresponsive to SRIs. *Eur. Neuropsychopharmacol.,* **2003**, 13 (suppl 4), S357.

[48] Tolin, D.F.; Maltby, N.; Diefenbach, G.J.; Hannan, S.E.; Worhunsky, P. Cognitive-behavioral therapy for medication nonresponders with obsessive-compulsive disorder: a wait-list-controlled open trial. *J. Clin. Psychiatry*, **2004**, 65, 922-31.

[49] Storch, E.A.; Bagner, D.M.; Geffken, G.R.; Adkins, J.W.; Murphy, T.K.; Goodman, W.K. Sequential cognitive-behavioral therapy for children with obsessive-compulsive disorder with an inadequate medication response: a case series of five patients. *Depress. Anxiety*, **2006**.

[50] Tundo, A.; Salvati, L.; Busto, G.; Di Spigno, D.; Falcini, R. Addition of cognitive-behavioral therapy for nonresponder to medication for obsessive-compulsive disorder: a naturalistic study. *J. Clin. Psychiatry*, **2007**, 68, 1552-6.

[51] Simpson, H.B.; Foa, E.B.; Liebowitz, M.R.; Ledley, D.R.; Huppert, J.D.; Cahill, S.; Vermes, D.; Schmidt, A.B.; Hembree, E.; Franklin, M.; Campeas, R.; Hahn, C.G.; Petkova, E. A randomized, controlled trial of cognitive-behavioral therapy for augmenting pharmachoterapy in obsessive-compulsive disorder. *Am. J. Psychiatry*, **2008**, 165, 621-30.

[52] Anand, N.; Sudhir, P.M.; Math, S.B.; Thennarasu, K.; Janardhan Reddy, Y.C. Cognitive behavior therapy in medication non-responders with obsessive-compulsive disorder: a prospective 1-year follow-up study. *J. Anxiety Disord.*, **2011,** 25, 939-45.

[53] Albert, U.; Aguglia, A.; Bogetto, F.; Cieri, L.; Daniele, M.; Maina, G.; Necci, R.; Parena, A.; Salvati, L.; Tundo, A. Effectiveness of cognitive-behavioral therapy addition to pharmacotherapy in resistant obsessive-compulsive disorder: a multicenter study. *Psychother. Psychosom.*, **2012**, 81(6), 383-5.

[54] Simpson, H.B.; Foa, E.B.; Liebowitz, M.R.; Huppert, J.D.; Cahill, S.; Maher, M.J.; McLean, C.P.; Bender, J.Jr.; Marcus, S.M.; Williams, M.T.; Weaver, J.; Vermes, D.; Van Meter, P.E.; Rodriguez, C.I.; Powers, M.; Pinto, A.; Imms, P.; Hahn, C.G.; Campeas, R. Cognitive-behavioral therapy vs risperidone for augmenting serotonin reuptake inhibitors in obsessive-compulsive disorder: a randomized clinical trial. *JAMA*, **2013,** 70(11), 1190-9.

[55] McLean, C.P.; Zandberg, L.J.; Van Meter, P.E.; Carpenter, J.K.; Simpson, H.B.; Foa, E.B. Exposure and response prevention helps adults with obsessive-compulsive disorder who do not respond to pharmacological augmentation strategies. *J. Clin. Psychiatry*, **2015**, 76(12), 1653-7.

[56] Albert, U.; Carmassi, C.; Cosci, F.; De Cori, D.; Di Nicola, M.; Ferrari, S.; Poloni, N.; Tarricone, I.; Fiorillo, A. Role and clinical implications of atypical antipsychotics in anxiety disorders, obsessive-compulsive disorder, trauma-related, and somatic symptom disorders: a systematized review. *Int. Clin. Psychopharmacol.*, **2016,** Mar 11. [Epub ahead of print]

[57] Foa, E.B.; Simpson, H.B.; Rosenfield, D.; Liebowitz, M.R.; Cahill, S.P.; Huppert, J.D.; Bender, J.Jr.; McLean, C.P.; Maher, M.J.; Campeas, R.; Hahn, C.G.; Imms, P.; Pinto, A.; Powers, M.B.; Rodriguez, C.I.; Van Meter, P.E.; Vermes, D.; Williams, M.T. Six-month outcomes from a randomized trial augmenting serotonin reuptake inhibitors with exposure and response prevention or risperidone in adults with obsessive-compulsive disorder. *J. Clin. Psychiatry*, **2015**, 76(4), 440-6.

[58] O'Connor, K.; Aardema, F.; Robillard, S.; Guay, S.; Pélissier, M.C.; Todorov, C.; Borgeat, F.; Leblanc, V.; Grenier, S.; Doucet, P. Cognitive-behaviour therapy and medication in the treatment of obsessive-compulsive disorder. *Acta Psychiatr. Scand.*, **2006**, 113, 408-19.

[59] Ressler, K.J.; Rothbaum, B.O. Augmenting obsessive-compulsive disorder treatment: from brain to mind. *JAMA*, **2013**, 70(11), 1129-1131.

[60] Ori, R.; Amos, T.; Bergman, H.; Soares-Weiser, K.; Ipser, J.C.; Stein, D.J. Augmentation of cognitive and behavioural therapies (CBT) with d-cycloserine for anxiety and related disorders. *Cochrane Database Syst. Rev*., **2015**, (5).

[61] Chasson GS, Buhlmann U, Tolin DF, Rao SR, Reese HE, Rowley T, Welsh KS, Wilhelm S. Need for speed: evaluating slopes of OCD recovery in behavior therapy enhanced with d-cycloserine. Behav Res Ther. 2010 Jul;48(7):675-9.

[62] Xia, J.; Du, Y.; Han, J.; Liu, G.; Wang, X. D-cycloserine augmentation in behavioral therapy for obsessive-compulsive disorder: a meta-analysis. *Drug Des. Devel. Ther*., **2015**, 21, 9, 2101-17.

[63] Andersson, E.; Hedman, E.; Enander, J.; Radu Djurfeldt, D.; Ljótsson, B.; Cervenka, S.; Isung, J.; Svanborg, C.; Mataix-Cols, D.; Kaldo, V.; Andersson, G.; Lindefors, N.; Rück, C. D-Cycloserine vs Placebo as Adjunct to Cognitive Behavioral Therapy for Obsessive-Compulsive Disorder and Interaction With Antidepressants: A Randomized Clinical Trial. *JAMA*, **2015**, 72(7), 659-67.