

## TREATMENT-RESISTANT OBSESSIVE-COMPULSIVE DISORDER (OCD): CURRENT KNOWLEDGE AND OPEN QUESTIONS

Umberto Albert, Andrea Aguglia, Stefano Bramante, Filippo Bogetto, Giuseppe Maina

### Abstract

**Objective:** Obsessive-compulsive disorder (OCD) is a common psychiatric illness with a lifetime prevalence in the general population of approximately 2-3%. Serotonin reuptake inhibitors (SRIs) and cognitive-behavioral therapy (CBT) in the form of exposure and response prevention (ERP) both represent first-line treatments for OCD. However, unsatisfactory response to these treatments is very common and the evaluation of next-step treatment strategies is highly relevant. The purpose of this paper is to review available data on treatment-resistant OCD and to build a treatment algorithm for those patients who fail to respond to a first SRI trial.

**Method:** We carried out a search on MEDLINE/PUBMED database, selecting meta-analyses, systematic reviews and randomized controlled studies written in English on treatment-resistant OCD. We also considered open-label studies and case series and/or reports, written in English. We reviewed the available evidence for different strategies and tried to delineate an evidence-based treatment algorithm for clinicians.

**Results:** Antipsychotic addition to SRIs and CBT augmentation of drug treatment both are supported by a number of double-blind studies, although differences between antipsychotics seem to exist and the effectiveness of routinely delivered CBT as an adjunct to medication in real world OCD patients with incomplete response to medication need to be replicated. The switch to IV administration of clomipramine may be clinically useful in some cases, although the return to oral formulation often is associated with a relapse. Switching to other first-line agents or to other compounds (such as venlafaxine) is supported by open-label studies or by double-blind studies without a placebo arm.

**Conclusions:** Several evidence-based effective strategies are available to clinicians in case of treatment-resistant OCD. Strengths and limitations of each of the effective strategies are still under study and will be the focus of future comparative trials. There is also a strong need for alternative therapeutic options for OCD patients.

**Key words:** obsessive-compulsive disorder, treatment-resistant OCD, augmentation, switch

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**Declaration of interest:** none

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### 1. Introduction

Obsessive-compulsive disorder (OCD) is a heterogeneous disorder of unknown etiology, characterized by the presence of upsetting, persistent worries, images, or impulses, which are experienced as intrusive and senseless (obsessions), and/or excessive repetitive behaviors or mental acts (compulsions), performed in response to these obsessions (APA 2000).

Epidemiological studies conducted in the last 20 years have established a prevalence rate in the general population of approximately 2-3%, making it a far more common disorder than previously believed (Ruscio et al. 2010). OCD has a significant impact on human and social functioning, quality of life, family

relationships, and socio-economic status (Albert et al. 2010, Fontenelle et al. 2010, Hollander et al. 2010, Wittchen et al. 2011). The World Health Organization listed this disorder among the 10 most disabling illnesses (Nolen 2002), while the National Comorbidity Survey-Replication study indicated that OCD is the anxiety disorder with the highest percentage (50.6%) of serious cases (Kessler et al. 2005). Moreover, it has been estimated that most individuals with OCD spend an average of 17 years before receiving an appropriate diagnosis and treatment for their illness (Jenike 2004).

According to several recent treatment guidelines, 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 – are considered first-line treatments for OCD (March 1997, Baldwin et al. 2005, Canadian Psychiatric Association 2006, APA 2007, Bandelow et al. 2008, Bandelow et al. 2012). Both CBT and SRIs have been in fact recognized more effective than wait-list, inactive psychological treatments or placebo in individual randomized controlled trials (RCT) (Deacon and Abramowitz 2004, Eddy et al. 2004, Fisher and Wells 2005, Rodrigues et al. 2011, Marazziti et al. 2012a). Concerning the relative efficacy between different SRIs, a Cochrane review comprising 17 RCTs could not identify any significant difference between citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline (Soomro et al. 2008). Equally, escitalopram improved obsessive-compulsive symptoms without any significant difference as compared to paroxetine (Fineberg et al. 2007, Stein et al. 2007).

Given the equivalence of both psychological and pharmacological approaches, the severity of the disorder and the age of the subject might guide the physician's choice: when treating an adult affected by a severe OCD, clinicians should prefer drug treatment with SRIs, eventually associating CBT. Conversely, childhood OCD should be first treated with ERP or cognitive therapy, eventually adding pharmacotherapy in the most severe cases. The selection might also be affected by patient preferences, and of course by the local availability of services able to offer evidence-based psychological interventions.

Unfortunately, 40-60% of OCD patients do not respond adequately to SRIs therapy and an even greater proportion of patients fail to experience complete remission of their symptoms after a first trial (Alacron et al. 1993, Ravizza et al. 1995, Erzegovesi et al. 2001). Even those patients who are judged to be clinical responders based on stringent response criteria (i.e., typically a greater than 25 or 35% decline in Yale-Brown Obsessive Compulsive Scale rating) continue to experience significant impairment from their residual obsessive-compulsive symptoms (Goodman et al. 1993). Because of the high number of patients with obsessive-compulsive disorder not responding satisfactorily to the initial SRIs monotherapy, the evaluation of additional treatment options is highly relevant.

The purpose of this paper is to review available data on treatment-resistant OCD and to build a treatment algorithm for those patients who fail to respond to a first SRIs trial. A necessary premise to the current review is that the vast majority of available studies investigated the efficacy of various possible strategies for patients not responding to a first trial with drugs, while very few examined next step strategies in the case of non-response to CBT. We will then focus our attention on literature data on next step options for patients failing to respond to a first drug treatment.

## 2. Definition of treatment resistance

Treatment-resistant OCD patients are defined as those who undergo adequate trials of first-line therapies without achieving a satisfactory response, usually defined by a reduction in the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) score  $\geq 35\%$  or  $\geq 25\%$  with respect to baseline (Rauch and Jenike 1994). The International Treatment Refractory OCD Consortium has recently proposed stages of response to treatment; full response is defined as 35% or greater reduction of Y-BOCS and Clinical Global Impression (CGI) 1 or

2; partial response as greater than 25% but less 35% Y-BOCS reduction; non response as less than 25% Y-BOCS reduction and CGI 4 (Rauch and Jenike 1994, Pallanti et al. 2002a, Pallanti and Quercioli 2006). Furthermore, recovery is defined as a complete and objective disappearance of symptoms, corresponding to Y-BOCS value of 8 or below; remission can indicate a response that reduces symptoms to a minimal level, i.e. Y-BOCS score of 16 or less, being this value the minimum threshold one for a patient to be included in a clinical trial.

Before defining a patient as resistant to a pharmacological treatment, several issues have to be considered:

1. clinicians have to be sure that the diagnosis of OCD is correct and that other symptoms are not incorrectly considered as obsessions or compulsions (obsessive-compulsive personality disorder; ruminations occurring in major depressive disorder or other anxiety disorders; repetitive stereotyped behaviors encountered in psychoses or in mental retardation, organic mental disorders; obsessive concern about body shape or ritualized eating behaviors in eating disorders; patterns of behaviors, interests or restricted and repetitive activities in autism);

2. has the pharmacological treatment been taken adequately in terms of doses and time? Clinicians should evaluate the response to first-line treatment in OCD patients after at least 12 weeks with moderate-high dosages of SRIs, as illustrated in **table 1** (Bloch et al. 2010). The pattern of response in OCD, moreover, is quite dissimilar to that seen in Major Depression: first signs of improvement do not correspond to remission of symptoms but they consist in a slow and progressive reduction of obsessive-compulsive symptoms;

3. clinicians have to assess the potential presence of medical or psychiatric comorbidity that could affect treatment response; paradigmatic the case of OCD comorbid with Bipolar Disorder, where treatment with high doses of SRIs could worsen both bipolar disorder (mixed episodes, rapid cycling, switch) and OCD (Ghaemi et al. 2008, Salvi et al. 2008);

4. some individuals who fail to improve after three months of treatment at adequate doses may turn into treatment responders after additional months of continued treatment: this suggests that the first available strategy could be just waiting for the treatment to produce a full response. This strategy should be reserved to patients who showed at least a partial response during the treatment (De Haan et al. 1997, McDonough et al. 2002).

Another issue that should be kept in mind in the assessment of treatment-resistant OCD is the potential role of the family in reinforcing the disorder and reducing patient compliance. Family members tend to become emotionally over-involved, neglecting their own needs and at the same time perpetuating the cycle of obsessions and compulsions. On the other hand, family members might express criticism by voicing expectations that the patient “just snaps out of it”. Both attitudes, besides worsening relatives' quality of life (Albert et al. 2007, Grover and Dutt 2011), contribute to the maintenance of patient's symptoms as well (van Noppen and Steketee 2003). Psychoeducational interventions directed to the families might help to establish a therapeutic alliance, to provide education about the disorder and its treatment, to improve family problem solving skills, and to ameliorate compliance to drug treatments (van Noppen et al. 1997, Albert et al. 2006, Maina et al. 2006).

Once all these questions have been addressed and a

condition of treatment-resistance of OCD is confirmed, several therapeutic options are available, that can be classified in augmentation or switching strategies.

### 3. Augmentation strategies

The first strategy given to clinicians in case of unsatisfactory response with a SRIs is to add another therapeutic agent. Alternative augmentation strategies after an adequate trial of first-line medications involve the addition of psychotherapy (CBT) or drugs.

#### 3.1. Psychotherapy augmentation

This strategy consists in adding to the failed SRIs treatment a cognitive-behavioral therapy in the form of exposure and response prevention, either alone or associated with cognitive restructuring.

Before considering this strategy, it is very important to consider the following essential conditions: willingness of the patient to undergo a CBT trial, good collaboration and motivation of the subject, good intellectual capacity to understand the rationale of the psychotherapy, and, possibly, a collaborative familiar milieu.

Several open-label and case report studies emphasized the efficacy of psychotherapy as an augmentation strategy for OCD patients resistant to drug treatment: approximately 50% of resistant patients do respond to the addition of CBT (Simpson et al. 1999, Kampman et al. 2002, Albert et al. 2003, Tolin et al. 2004, Tundo et al. 2007, Anand et al. 2011). The efficacy of CBT addition to pharmacotherapy has been validated in a well-conducted 8-week, randomized, controlled trial with stress management training as the control condition. At the endpoint, the mean Y-BOCS total score decreased from 25.4 to 14.2 in patients assigned to ERP (n=54) and from 26.2 to 22.6 in the other group (n=54); moreover, patients receiving ERP

had a significantly higher response rate than patients receiving stress management training (decrease  $\geq 25\%$  in the Y-BOCS total score 74% and 22%, respectively;  $p < .001$ ) (Simpson et al. 2008). Evidence from this randomized, controlled study strongly supports the use of CBT incorporating ERP as an SRI augmentation strategy for OCD non-responders to medication.

However, while randomized, controlled studies have very strong internal validity (they allow the elimination of biases and confounding factors effects), the generalizability of their findings to the real world could be limited by several factors such as rigid inclusion/exclusion criteria and therapy use under ideal conditions. In Simpson and colleagues' study (2008), for example, comorbid diagnoses were allowed if clearly secondary, mania, psychosis, prominent suicidal ideation, substance abuse or dependence in the previous 6 months were exclusion criteria. Moreover, ERP protocol, consisted in 17 twice-weekly sessions (each 90-120 minutes), daily homework assignments, between-session phone calls (twice per week), and included at least two sessions in the patients' home environment to promote generalization. Although ERP was not really intensive, one might ask if patients in the real world can follow this CBT format and if therapists in the real world can follow these rules. So, it could be useful for clinicians to know if Simpson and colleagues' randomized, controlled study results are confirmed in large multicenter effectiveness studies.

We performed a multicenter study to investigate the effectiveness of CBT as an augmentation strategy to medication in severe, real-world, SRIs non-responder OCD patients. 119 OCD subjects resistant to SRIs (resistance was prospectively evaluated) were offered a CBT trial. Subjects were representative of a severe, real-world sample of resistant patients, with multiple comorbidities and several previous ineffective trials. CBT was delivered in a naturalistic setting. Patients were assessed at baseline, at 6 and 12 months. Responder rates at 6 and 12 months were 32.8% and 58%, respectively;

**Table 1.** Dosing of Serotonin Reuptake Inhibitors (SRIs) in the treatment of obsessive-compulsive disorder (from APA. Practice guideline for the treatment of patients with obsessive-compulsive disorder. American Psychiatric Association, Arlington, VA: 2007)

SRI	Starting dose and incremental dose (mg/day) (a)	Usual target dose (mg/day)	Usual maximum dose (mg/day)	Occasionally prescribed maximum dose (mg/day) (b)
Citalopram	20	40-60	80	120
Clomipramine	25	100-250	250	— (c)
Escitalopram	10	20	40	60
Fluoxetine	20	40-60	80	120
Fluvoxamine	50	200	300	450
Paroxetine	20	40-60	60	100
Sertraline (d)	50	200	200	400

(a): some patients may need to start at half this dose or less to minimize undesired side effects such as nausea or to accommodate anxiety about taking medications.

(b): these doses are sometimes used for rapid metabolizers or for patients with no or mild side effects and inadequate therapeutic response after 8 weeks or more at the usual maximum dose.

(c): combined plasma levels of clomipramine plus desmethylclomipramine 12 hours after the dose should be kept below 500 ng/mL to minimize risk of seizures and cardiac conduction delay

(d): sertraline, alone among the selective serotonin reuptake inhibitors, is better absorbed with food.



remitter rates were 15.1% and 31.1%, respectively (Albert et al. 2012a). Our multicenter, prospective, naturalistic study indicates that the positive results of the controlled study concerning the efficacy of CBT addition to medication non-responder OCD patients can be generalized, although at a lesser degree, to routine clinical practice.

For the future, further controlled trials employing OCD patients with various patterns of symptoms are required to allow for a generalization of results.

### 3.2. Pharmacotherapy augmentation

When the first-line SRIs treatment provides an unsatisfactory response and CBT augmentation is not available or acceptable to the patient, another available and evidence-based option is pharmacotherapy augmentation, which consists in adding to the ongoing SRIs another drug. Several augmenting agents have been studied, some of them in open-label and other in single or double blind conditions. The most studied effective strategy is antipsychotic augmentation.

#### 3.2.1. Antipsychotic augmentation

Following the hypothesis of dopaminergic hyperactivation in OCD (Denys et al. 2004a, Koo et al. 2010), many research projects focused on the examination of antipsychotic compounds in this disorder. Because the serotonergic metabolism is supposed to be centrally involved in the pathophysiology of OCD (Zohar et al. 1987, Goddard et al. 2008), most studies were aimed at determining whether the co-administration of SRIs and antipsychotics is effective in patients unresponsive to SRIs alone (Vulink et al. 2011).

Several randomized, double-blind, placebo-controlled studies exist, to date, supporting the use of this strategy; review and meta-analytical studies also confirm that, as a class, antipsychotics are effective when added to SRIs in resistant patients (Sareen et al. 2004, Bloch et al. 2006, Skapinakis et al. 2007, Komossa et al. 2010, Dold et al. 2012). However, not all antipsychotics have been studied in double-blind conditions and differences in efficacy exist between antipsychotics.

Early studies added typical antipsychotics (haloperidol and pimozide) to SRIs (McDougale et al. 1990, McDougale et al. 1994); only haloperidol, however, among the typical antipsychotics, proved to be effective in a double-blind, placebo-controlled study, particularly for patients with comorbid tic disorders (McDougale et al. 1994). The side effect profile of haloperidol, with dose-dependent extrapyramidal symptoms, limits the potential benefit of this strategy in resistant OCD patients. By comparison, the atypical antipsychotics may be better tolerated in the short-term, although concerns exist regarding long-term metabolic side effects (Marazziti et al. 2005, Fineberg et al. 2006, Matsunaga et al. 2009).

Recently, Dold and colleagues published a meta-analysis of results of all double-blind studies on antipsychotic augmentation of SRIs in treatment-resistant OCD (Dold et al. 2012). Concerning second-generation antipsychotics, five RCTs examined the addition of quetiapine (Denys et al. 2004b, Carey et al. 2005, Fineberg et al. 2005, Kordon et al. 2008, Diniz et al. 2011), three risperidone (McDougale et al. 2000, Hollander et al. 2003a, Erzegovesi et al. 2005), two olanzapine (Bystritsky et al. 2004, Shapira et al.

2004) and one aripiprazole (Muscattello et al. 2011). The authors conclude that antipsychotic augmentation, overall, significantly improved obsessive-compulsive symptoms refractory to SRIs monotherapy in at least one-third of cases. Due to its favorable risk-benefit ratio, risperidone can currently be considered as the compound of first choice for such treatment strategy. No evidence could be identified for the efficacy of adjunctive quetiapine (no difference in response between quetiapine and placebo in four of the five studies) and olanzapine (one positive study – Bystritsky et al. 2004 – and one negative – Shapira et al. 2004). However, the negative study with olanzapine (Shapira et al. 2004) was biased by the fact that the Authors included patients not responding to only 8 weeks of SRIs monotherapy; thus patients in both the placebo and the olanzapine arms showed a significant response rate. Our single-blind study comparing olanzapine with risperidone addition showed similar response rates (Maina et al., 2008). We then think that olanzapine may be a valid alternative to risperidone as an augmentation strategy in resistant patients. A very recent study, not included in meta-analysis published by Dold and colleagues, evaluated the efficacy of aripiprazole (10 mg/day, fixed-dose) in 39 patients with treatment-resistant OCD: aripiprazole augmentation was significantly more effective than placebo (Sayyah et al., 2012). This study confirmed the efficacy of aripiprazole in treatment-resistant OCD. **Table 2** summarizes results of studies investigating antipsychotic augmentation.

In positive studies, response rates were around 50%; when response to antipsychotic addition occurs it is evident within the first 4-6 weeks (Bloch et al. 2006).

Further research is needed to clarify the relative efficacy of different antipsychotics in OCD by conducting RCTs that directly compare the different antipsychotics (head-to-head comparisons). Only two 8-weeks, single-blind RCTs exist (Maina et al. 2008, Selvi et al. 2011). Maina and colleagues (2008) compared directly risperidone and olanzapine addition to SRIs in resistant OCD patients (n=50); as previously mentioned, the two compounds were equally effective in improving obsessive-compulsive symptoms. Selvi and coworkers (2011) compared risperidone (3 mg/day) and aripiprazole (15 mg/day) augmentation; both drugs proved to be effective strategies in resistant patients, although a significantly higher response rate was found with risperidone (72.2%) compared to aripiprazole (50%).

Another unresolved question is how long clinicians should maintain the antipsychotic in combination with the serotonergic drug, once response is achieved. Maina and colleagues showed that the discontinuation of the antipsychotic in patients previously responsive only to the augmentation strategy leads to an exacerbation of obsessive-compulsive symptoms (relapse) in the vast majority of patients (83.3% within the 24-week follow-up); 72.2% of patients relapsed within the first 8 weeks from discontinuation (Maina et al. 2003). Although retrospective, our study provides initial evidence that antipsychotic augmentation has to be maintained for patients who respond to this strategy, because the vast majority of subjects who discontinue the antipsychotic relapse within 2 months. On the other hand, however, if such treatment is carried out over the long-term, patients are exposed to the common and serious adverse effects associated with long-term antipsychotic administration, especially metabolic ones: increased glucose, triglycerides, abdominal circumference, blood pressure and decreased cholesterol HDL (Matsunaga et al. 2009, Albert et al. 2012b). Antipsychotic-induced

weight gain may influence patients' adherence to medication, and places them at risk for a broad range of medical problems such as cardiovascular diseases, type 2 diabetes, stroke, premature mortality (Khang et al. 2010, Gupta et al. 2011, Joseph et al. 2011, Tanner et al. 2011, Novelletto et al. 2012).

Some evidence exists in favor of the combination of SRIs and antipsychotic from beginning of treatment, in non-refractory OCD patients (Vulink et al. 2009). In our opinion, given the adverse effect profile of long-term antipsychotic use, antipsychotic augmentation should be reserved for patients not responding adequately after 12 weeks of SRIs monotherapy.

Further research is still required regarding the optimal dose of several antipsychotics, the ideal duration of add-on treatment, its long-term tolerability and the evaluation of predictors of response. Further investigations should also assess which SRIs are the most suitable for an antipsychotic augmentation strategy.

### 3.2.2. Other augmentation strategies

Other less evaluated augmentation strategies include the combination of two SRIs or the addition to the current SRIs of a compound other than the antipsychotic; the evidence regarding these treatment approaches is considerably weaker.

Several double-blind, placebo-controlled studies evaluated the potential efficacy of different drugs used as augmentation strategies in treatment-resistant OCD patients; among these, ineffective (and not recommended on the basis of current knowledge) are lithium (McDougle et al. 1991, Pigott et al. 1991), buspirone (Pigott et al. 1992, McDougle et al. 1993, Grady et al. 1993), desipramine (Barr et al. 1997), inositol (Fux et al. 1999), clonazepam (Crockett et al. 2004), naltrexone (Amiaz et al. 2008). Some

compounds showed preliminary evidence of efficacy as compared to placebo: caffeine and d-amphetamine (Koran et al. 2009), lamotrigine (Bruno et al. 2012), topiramate, which was effective only on compulsions and not on obsessions and Y-BOCS total score (Mowla et al. 2010, Berlin et al. 2011), pindolol (beta-adrenergic antagonist with pre-synaptic 5-HT<sub>1A</sub> antagonist activity), ineffective in reducing the latency of response of antiobsessive agents (Mundo et al. 1998) but effective in treatment-resistant patients (Dannon et al. 2000). Although potentially effective, we consider these drugs as a last chance option to be reserved for patients refractory to other evidence-based alternatives.

### 3.2.3. SRIs augmentation (combination)

This strategy is a combination therapy, and consists in associating two serotonergic compounds (usually clomipramine – CMI, added to the ongoing selective serotonin reuptake inhibitors – SSRI trial). Of all the SSRI, sertraline and citalopram, having a lower metabolic interference with the cytochrome P450, should be considered the first-choice drugs to associate to CMI in order to empower the serotonin reuptake inhibition. Results from open trials support the efficacy of this strategy (Simeon et al. 1990, Ravizza et al. 1996, Figueroa et al. 1998, Marazziti et al. 2008, Diniz et al. 2010). In our study, for example, the addition of sertraline 50 mg/day to clomipramine 150 mg/day yielded a greater reduction in Y-BOCS scores than the increase of clomipramine dosage up to 250 mg/day, being also associated with a more favorable side-effect profile (Ravizza et al. 1996). However, all the aforementioned studies were performed in an open-label fashion and involved few patients per trial.

Diniz and colleagues recently performed a double-blind, placebo-controlled trial comparing the efficacy of adding quetiapine (≤200 mg/day) or clomipramine

**Table 2.** Double-blind, placebo-controlled studies on antipsychotic augmentation in treatment-resistant OCD

Antipsychotic	Authors	N	Length (weeks)	Dose range (mg/day)	Mean Final Dose (mg/day)	Results
<i>Haloperidol</i>	McDougle et al. 1994	34	4	2-10	6.2 ± 3.0	Haloperidol > Placebo
	McDougle et al. 2000	36	6	1-6	2.2 ± 0.7	Risperidone > Placebo
<i>Risperidone</i>	Hollander et al. 2003	16	8	0.5-3	2.25 ± 0.86	Risperidone > Placebo
	Erzegovesi et al. 2005	39	6	0.5 (fixed-dose)	0.5 (fixed-dose)	Risperidone > Placebo
	Bystritsky et al. 2004	26	6	5-20	11.2 ± 6.5	Olanzapine > Placebo
<i>Olanzapine</i>	Shapira et al. 2004	44	6	5-10	6.1 ± 2.1	Olanzapine = Placebo
	Atmaca et al. 2002*	27	8	50-200	91 ± 41	Quetiapine > Placebo
	Denys et al. 2004	40	8	200-300	300	Quetiapine > Placebo
	Fineberg et al. 2005	21	16	50-400	215 ± 124	Quetiapine = Placebo
<i>Quetiapine</i>	Carey et al. 2005	42	6	25-300	168.8 ± 120.8	Quetiapine = Placebo
	Kordon et al. 2008	40	12	400-600	-	Quetiapine = Placebo
	Diniz et al. 2011	54	12	≤200	-	Quetiapine = Placebo
<i>Aripiprazole</i>	Muscattello et al. 2011	40	16	15 (fixed-dose)	15 (fixed-dose)	Aripiprazole > Placebo
	Sayyah et al. 2012	39	12	10 (fixed-dose)	10 (fixed-dose)	Aripiprazole > Placebo

\* single-blind, placebo-controlled study

( $\leq 75$  mg/day) to a treatment regimen consisting of fluoxetine ( $\leq 40$  mg/day). The clomipramine-fluoxetine combination resulted a safe and effective treatment for fluoxetine non-responders, while the addition of quetiapine was not; results of this double-blind trial support the use of this strategy, which may be reserved especially for those patients who cannot tolerate high doses of fluoxetine (Diniz et al. 2011).

There is, however, the need for additional double-blind studies to support this combination strategy and determine which, among combination and augmentation strategies, is more effective.

#### 4. Switching strategies

The option to switch to another first-line drug might be preferred when, after an adequate trial, there is no sign of improvement in obsessive-compulsive symptoms. This strategy involves switching to a different route of administration (from oral to intravenous formulation), when possible, to a second first-choice medication, or to a different compound.

##### 4.1. Switch to intravenous (iv) route of administration

The rationale of IV clomipramine is to avoid first-pass metabolism, assuming that partial or no clinical response with the oral formulation may be due to inadequate plasma levels of clomipramine or to low clomipramine/desmethylclomipramine ratio, which is normally around 1:2 (Greist and Jefferson 1998, Marazziti et al. 2012b). The switch to IV clomipramine seems to be an effective option in treatment-resistant OCD patients. In the early open-label reports, this therapeutic strategy has proved good tolerability and a rapid relief of obsessional symptoms in resistant OCD (Warneke 1989, Fallon et al. 1992, Koran et al. 1997, Koran et al. 2006). In order to rule out the hypothesis that the efficacy of IV clomipramine was a placebo effect (invasive treatment), Fallon and colleagues performed a double-blind study of IV clomipramine versus IV placebo (14 infusions over a time span of 18 days) in 54 resistant patients. Therapeutic effects were seen after the last infusion was performed: 21% of the patients treated with IV clomipramine responded as compared 0% of patients treated with IV placebo. One month after, response rate was 58% in patients continuing on open-label oral CMI (Fallon et al. 1998).

Citalopram is the only SSRI currently available in the IV formulation. Pallanti and colleagues, in an open study, examined the efficacy of IV citalopram in subjects with OCD who failed at least two adequate oral SRIs trials, other than citalopram. The findings showed a discrete clinical efficacy of IV citalopram after three weeks (59% of patients had a decrease in the Y-BOCS score  $\geq 25\%$ ); the IV citalopram administration may be viewed as a mean of accelerating OCD symptom relief and eventually predicting response to oral citalopram treatment (Pallanti et al. 2002b). Data on the efficacy of IV citalopram in patients resistant to oral citalopram are lacking.

##### 4.2. Switch to a second first-choice compound

A second option consists in switching to another serotonergic compound, although data from published studies are still scarce. After a previous unresponsive SRIs trial, response rate to a second SRIs has been

reported as low as 27-33% (Rasmussen et al. 1993, Ackerman et al. 1998). These response rates are even lower if patients failed two previous SRIs trials: only 19% of patients responded to fluvoxamine after failure to respond to clomipramine and fluoxetine (Goodman et al. 1997). Data over the use of citalopram are conflicting: in one study, only a patient out of 7 (14%) responded to citalopram after two previous unsuccessful trial with SRIs (Pallanti et al. 1999), while another open-label trial with a similar design showed that 14 OCD patients out of 18 achieved a good therapeutic response (Marazziti et al. 2001), suggesting that non response to a single SSRI does not necessarily imply a lack of response to another SSRI.

Published studies have not clarified whether clinicians should switch from a first failed SSRI to CMI, to another SSRI, or to a different compound. The Expert Consensus Guidelines on the Treatment of OCD (March et al. 1997) recommends switching to another SSRI after a non-response to a first SSRI, and switching to clomipramine only after 2 to 3 failed SSRI trials. Pigott and colleagues treated 11 OCD patients with either fluoxetine or CMI during 10 weeks, and then switched therapy to the other drug for an additional period of 10 weeks. The authors found that 5 patients responded preferentially to CMI, two to fluoxetine and four to both drugs, thus indicating that individuals not responding to one drug may still respond to the other (Pigott et al. 1990). In an open study presented at the 4<sup>th</sup> IOCDC we observed that switching from CMI to an SSRI or vice-versa yields higher response rates (33 to 40%) than switching from one SSRI to another (0 to 20%) (Koran et al. 2000).

The better tolerability profile of SSRI supports the choice of a second SSRI trial before switching to clomipramine, which may be reserved as a third choice. However, these considerations are based on open label trials and should be viewed as preliminary.

##### 4.3. Switch to another compound in monotherapy

Given that preliminary evidence stands for a potential role of venlafaxine in the treatment of OCD, switching to a drug other than the approved SSRI and clomipramine may be an option in some resistant cases.

Venlafaxine has been studied in patients with OCD in one small, placebo-controlled trial versus placebo (Yaryura-Tobias et al. 1996) and in two active comparator controlled studies versus clomipramine (Albert et al. 2002) and paroxetine (Denys et al. 2003). In the first study venlafaxine failed to separate from placebo, probably because the study lasted only 8 weeks (Yaryura-Tobias et al. 1996); moreover, this study did not use the Y-BOCS as the outcome measure. We performed a single-blind study comparing venlafaxine  $\geq 225$  mg/day versus clomipramine  $\geq 150$  mg/day in 73 drug-naïve patients through a 12-week trial. At the endpoint, the two compounds showed similar response rates without any statistically significant difference (Albert et al. 2002). Another positive study is a double-blind trial where venlafaxine (300 mg/day) was compared to paroxetine (60 mg/day) in a large cohort of patients (150 patients); both treatments appeared equally effective in reducing Y-BOCS scores, with a response rate of almost 40% in both groups (Denys et al. 2003). On the basis of such preliminary results, venlafaxine was used to treat resistant cases. A single-blind study investigated the efficacy of venlafaxine 225-300 mg versus CMI 150-225 mg and citalopram 40-60



mg in patients resistant to at least two SSRI: responder rates at the end of the study were 42.8% for venlafaxine, 37.5% for CMI and 14.3% with citalopram (Maina et al. 2001). Hollander and coworkers demonstrated the efficacy of venlafaxine (mean dose 232.2 mg/day) in 39 patients with OCD, 29 of which had previously completed one or more therapeutic attempts with SSRI; 76% of patients had a clinical benefit from the switch to venlafaxine (Hollander et al. 2003b). These preliminary results seem to indicate that, beside clomipramine, after two failed SSRI trials clinicians should consider switching OCD patients to venlafaxine.

Other non-serotonergic drug with potential antiobsessive efficacy (to be used in patients refractory to conventional therapies) are duloxetine (Dell'Osso et al. 2008), mirtazapine (Koran et al. 2001, Koran et al. 2005), and agomelatine (Fornaro 2011). All these compounds are off-label therapies and should be considered in very refractory cases, until their efficacy in drug-naïve or resistant OCD patients is confirmed in methodologically sound studies.

The use of mega-doses of SRIs is another alternative

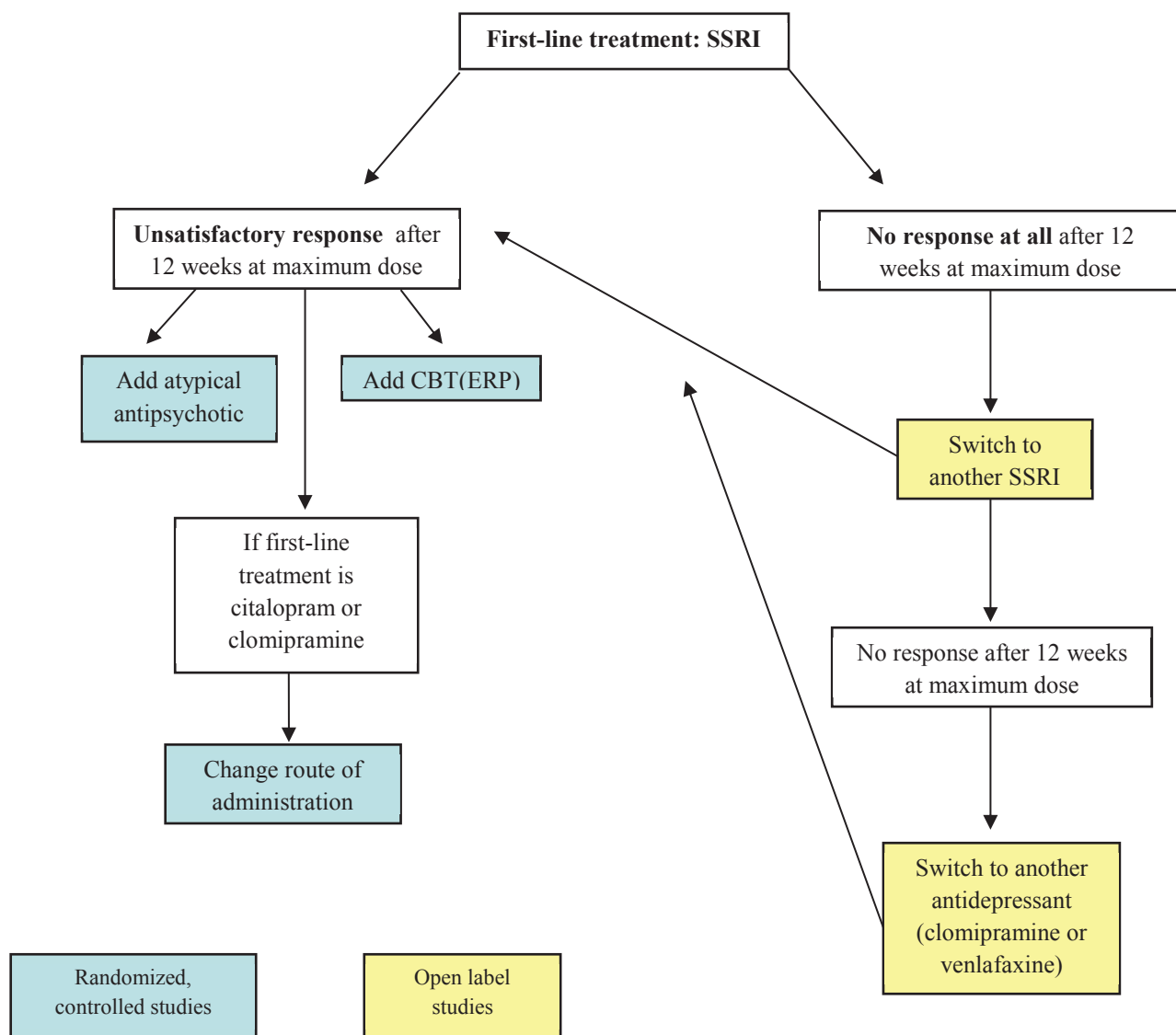
for the treatment of resistant patients. This strategy is not supported by double-blind, placebo-controlled studies, but results of open label studies with sertraline at a dose of 250-400 mg/die (Ninan et al. 2006), escitalopram up to 50 mg/day (Rabinowitz et al. 2008), citalopram up to 120 mg/day and fluoxetine up to 100 mg/day (Pampaloni et al. 2010) are promising.

## 5. Conclusions

Several questions regarding the strategies to be implemented in case of unsatisfactory response to drug treatment in OCD remain unresolved and need to be addressed by future research.

Is switching from one SSRI to a second classmate effective? Or should we switch to clomipramine, given the broader neurotransmitter action of this compound? In case of unsatisfactory response to a first drug, should we switch to CBT or should we switch to another drug? What if a patient has failed two previous SSRIs? Would venlafaxine be a preferential approach

**Figure 1.** Algorithm for the management of treatment-resistant OCD patients



with respect to clomipramine or another SSRI in this highly resistant patient sample? What is the role of non-serotonergic drugs in the treatment of OCD? What about antipsychotics in terms of duration of treatment, doses, better choice of the compound?

However, based on this review of published papers on treatment-resistant OCD, we suggest the following algorithm for the management of subjects not adequately responding to a first trial with a SSRI given at correct dosage and for at least 12 weeks (**figure 1**).

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