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# Treatment-Resistant Obsessive-Compulsive Disorder (OCD): Focus on Antipsychotic Augmentation to SRIs

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## Abstract

**Introduction:** Obsessive-Compulsive Disorder (OCD) is a common psychiatric illness with 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 common and the evaluation of next-step treatment strategies is highly relevant. Antipsychotic augmentation is the most studied pharmacological strategy. The purpose of this review is to provide guidance regarding the choice of antipsychotic medication on the basis of current evidence.

**Material and Methods:** We carried out a search on MEDLINE/PUBMED database, selecting meta-analyses, systematic reviews and randomized controlled studies written in English on antipsychotic augmentation of treatment resistant OCD. We also considered open-label studies and case series, written in English. We reviewed the available evidence for antipsychotic use in treatment-resistant-OCD.

**Results:** Antipsychotic addition to SRI treatment is supported by a positive number of double-blind studies although differences between them seem to exist. Fourteen double blind, randomized, placebo controlled trials investigating quetiapine (N=5), risperidone (N=3), olanzapine (N=2), aripiprazole (N=2), haloperidol (N=1), paliperidone (N=1) were identified. Significant efficacy was identifiable for risperidone and aripiprazole but not for quetiapine and olanzapine. Results regarding haloperidol and paliperidone were inconsistent.

**Discussion:** Overall, about 50% of SRI-resistant-OCD patients benefited from augmentation strategy with antipsychotic. Risperidone and aripiprazole can be considered as the agents of first choice and should be preferred to the others antipsychotic. In our opinion, olanzapine may be a valid alternative to risperidone. Further trials are required to optimize pharmacological treatment for SRI-resistant-OCD.

**Keywords:** Obsessive-Compulsive Disorder (OCD); Treatment-resistant OCD; Augmentation; Antipsychotic

## Introduction

Obsessive-Compulsive Disorder (OCD) is a heterogeneous disorder of unknown etiology, characterized by the presence of recurrent or persistent, upsetting, worries, images, or urges, which are experienced as intrusive and senseless (obsessions), and excessive repetitive behaviors or mental acts (compulsions), performed in response to these obsessions (DSM-5, APA, 2013).

### Diagnosis

The diagnosis is made by clinical interview, with a specific and detailed focus on OCD. To warrant DSM-5 diagnosis, the patient must have obsessions, compulsions or both. Obsessions are defined by (1) and (2):

a) Recurrent and persistent thoughts, urges, or images that are experienced, at some time during the disturbance, as intrusive and unwanted, and that in most individuals cause marked anxiety or distress;

b) The individual attempts to ignore or suppress such thoughts, urges, or images, or to neutralize them with some other thought or action.

Compulsions are defined by (1) and (2):

a) Repetitive behaviors or mental acts that the individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly;

b) The behaviors or mental acts are aimed at preventing or reducing anxiety or distress, or preventing some dreaded event or situation; however, these behaviors or mental acts are not connected in a realistic way with what they are designed to neutralize or prevent, or are clearly excessive.

The obsessions or compulsions are time-consuming (e.g., take more than 1 hour per day) or cause clinically significant distress or impairment in social, occupations, or other important areas of functioning. The obsessive-compulsive symptoms are not




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attributable to the physiological effects of a substance or another medical condition. The disturbance is not better explained by the symptoms of another mental disorder (DSM-5, APA 2013). The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) is regarded as the gold standard measure of obsessive-compulsive symptom severity and is used in most treatment trials [1].

### Prevalence and impact

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 [2]. The disorder has no sex differences in distribution with the exception that in children the disorder is more common in boys than in girls [3] OCD has a significant impact on human and social functioning, quality of life, family relationships, and socio-economic status [4-7].The World Health Organization listed this disorder among the 10 most disabling illnesses [8], while the National Comorbidity Survey-Replication study indicated that OCD is the anxiety disorder with the highest percentage (50.6%) of serious cases [9]. 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 [10].

### Treatment approaches

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 [11-15]. 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) [16-19]. 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 [20] Equally, the SSRI escitalopram improved OCD symptoms without any significant difference as compared to paroxetine [19].

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 between these two approaches: 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 SRI therapy and an even greater proportion of patients fail to experience complete remission of their symptoms after a first trial [21-23] 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 Y-BOCS rating) continue to experience significant impairment from their residual OCD symptoms [24] Because of the high number of patients with Obsessive-Compulsive Disorder (OCD) not responding satisfactorily to the initial SRI monotherapy, the evaluation of additional treatment options is highly relevant. Augmentation of ongoing serotoninergic treatment with an antipsychotic for treatment-resistant OCD patients is one of the most studied and well documented strategies. However, differences between antipsychotics in their efficacy in treatment-resistant OCD seem to exist, reflecting the differences in pharmacodynamic characteristics of each drug.

The purpose of this paper is to review available data on antipsychotic augmentation in treatment-resistant OCD.

## 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 ≥35% or ≥25% with respect to baseline [25]. 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. Furthermore, recovery is defined as a complete and objective disappearance of symptoms, corresponding to YBOCS value of 8 or below; remission can indicate a response that reduces symptoms to a minimal level, i.e. YBOCS score of 16 or less, being this value the minimum threshold one for a patient to be included in a clinical trial [26,27].

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

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, in mental retardation or in organic mental disorders; obsessive concerns 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 [28] as illustrated in Table 1.
3. Clinicians have to assess the potential presence of medical or psychiatric comorbidity that could affect treatment response (e.g., 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) [29,30].
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

**Table 1:** Doses of Serotonin Reuptake Inhibitors (SRIs) in the treatment of obsessive-compulsive disorder in according to American Psychiatry Association guidelines (2007).

| Compound 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, along among the selective serotonin reuptake inhibitors, is better absorbed with food.

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 [31,32].

5. Finally, 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 [33,34], contribute to the maintenance of patient's symptoms as well [35]. 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 [36-38].

Once all these questions have been addressed and a condition of treatment-resistance of OCD is confirmed, several therapeutic options are available. In this review we will focus our attention on antipsychotic augmentation, as this strategy is the only one confirmed by several double-blind randomized controlled trials and by several meta-analyses. Another possibility is to add cognitive-behavior therapy; this option proved to be effective in several open-label studies [39] and at least one well-performed controlled (stress management training as the inactive/placebo psychological treatment arm) randomized trial [40].

## Antipsychotic Augmentation

Following the hypothesis of dopaminergic hyper-activation in OCD [41,42], 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 [43] most studies were aimed at determining whether the co-administration of SRIs and antipsychotics is effective in patients unresponsive to SRIs alone [44].

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 [45-50]. In summary, the evidence based on the meta-analytic calculations suggests an efficacy of this pharmacological strategy measured by both the response rates (criterion: Y-BOCS reduction ≥ 35%) and the changes in Y-BOCS total score; about one-third of OCD patients responded to this therapeutic option [50]. However, not all antipsychotics have been studied in double-blind conditions and differences in efficacy exist between antipsychotics.

### Which antipsychotic?

#### First generation antipsychotics (FGAs)

Early studies added typical antipsychotics (haloperidol and pimozide) to SRIs [51,52], only haloperidol (mean dose 6.2±3.0 mg/die; maximal dose=10 mg/die), however, among the typical antipsychotics, proved to be effective in a double-blind, placebo-controlled study, particularly for patients with comorbid tic disorders [53]. The side effect profile of haloperidol, with dose-dependent extra-pyramidal symptoms, limits the potential benefit of this strategy in resistant OCD patients.

#### Second generation antipsychotics (SGAs)

Atypical antipsychotics may be better tolerated in the short-term, although concerns exist regarding long-term metabolic side effects [54].

Recently, Dold and colleagues published a new meta-analysis of results of all double-blind studies on antipsychotic augmentation of SRIs in treatment-resistant OCD [50]. Concerning atypical antipsychotics, this meta-analysis included five RCTs regarding the addition of quetiapine (178 patients) [19,55-58], three risperidone (72 patients) [59-61], two olanzapine (70 patients) [62,63] and one aripiprazole (40 patients) [64]. The authors conclude that

antipsychotic augmentation, overall, significantly improve obsessive-compulsive symptoms. Significant efficacy was identifiable, however, only for risperidone, but not for quetiapine and olanzapine. However, the negative study with olanzapine [63] 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 to both compounds, suggesting equivalent efficacy [65] We then think that olanzapine may be a valid alternative to risperidone as an augmentation strategy in resistant patients.

Concerning aripiprazole, Dold et al. [50] conclude that results are preliminary on the basis of the only placebo-controlled study available, which was in favor of aripiprazole. Since then, aripiprazole proved to be effective in another study, which compared aripiprazole (10 mg/day fixed-dose for 12 weeks) and placebo in 39 treatment resistant patients with OCD: a significant difference emerged, in favor of aripiprazole, in the mean reduction of the Y-BOCS total score [66]. The evidence supporting the use of aripiprazole in the treatment of resistant OCD is increasing and, in our opinion, this compound could be considered a valid augmentation strategy.

A very recent study compared paliperidone addition (3-9 mg/die, mean final dose=4.94 mg/die) to placebo addition in 39 patients [67]; treatment resistance, however, was defined as an entry YBOCS total score of 19 or greater despite at least two adequate SRI monotherapy trials, one of which included the SRI currently being taken by the patient provided that the duration of treatment was only 8 weeks at a medium-to-high dose. This study was a negative one, as paliperidone did not differentiate from placebo: paliperidone administration resulted in significant baseline to post-treatment reductions in obsessive-compulsive symptoms (-7.98 points in YBOCS score), although placebo administration also resulted in medium size, trend-level significant YBOCS changes (-4.02 points). Paliperidone may have a potential efficacy in treating OCD patients resistant to SRIs, although further studies are needed. Future studies might benefit from including patients whose resistance to treatments is prospectively evaluated in a trial lasting a minimum of 12 weeks at the maximum dose.

Table 2 summarizes results of controlled studies investigating antipsychotic augmentation.

Concerning response rate, Dold et al. [50] calculated an overall response rate to antipsychotic addition (all RCTs, including those with antipsychotics proved to be ineffective) of approximately 30%; however, if we consider results of studies in which the active compound (antipsychotic) differentiated from placebo (positive studies), response rates were around 50%. When response to antipsychotic addition occurs, moreover, it is evident within the first 4-6 weeks [46]. According to these results, it may be advisable to change strategy when antipsychotic addition after 6 weeks results ineffective.

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 [65,68] Maina et al [65] directly compared 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 et al. [68] 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%). This might suggest that a greater affinity at D2 receptors is needed for an antipsychotic to be effective in resistant OCD.

## For how long?

Another unresolved question is how long clinicians should maintain the antipsychotic in combination with the serotoninergic 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 [69] 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 [70]. In a recent study we enrolled 104 patients with OCD. Metabolic syndrome was present in 21.2% of the sample. Abdominal obesity was present in 36.5%, hypertension in 42.3%, high triglycerides in 23.1%, low high-density lipoprotein cholesterol levels in 22.1% and fasting hyperglycemia in 4.8% of the sample. Metabolic syndrome was associated with the duration of the exposure (lifetime) to antipsychotics. Patients with OCD on antipsychotic treatment are then particularly at risk for metabolic syndrome and should be carefully monitored for metabolic abnormalities and cardiovascular complications [71]. 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 [72-76].

Some evidence exists in favor of the combination of SRIs and antipsychotic from beginning of treatment, in non-refractory OCD patients [77]. 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.

## Neurobiological interpretation

The characteristic feature of second-generation antipsychotic is a combination of antagonism at the dopamine-D2 receptor and at the serotonin-5-HT2a receptor. Which receptor-binding, in addition to the serotonin reuptake inhibition induced by SSRIs, primarily causes the therapeutic effects in OCD appears to be unclear at the present. Haloperidol and risperidone are characterized by a markedly more potent affinity to the D2-receptor than quetiapine and olanzapine.

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

| Compound | Authors | Patients included | Duration treatment (weeks) | Dose (mg/day) | Medium dose (mg/day) | Results |
|---|---|---|---|---|---|---|
| *Haloperidol* | McDougle et al [52] | 34 | 4 | 2-10 | 6.2 ± 3.0 | Haloperidol > Placebo |
| *Risperidone* | McDougle et al [59] | 36 | 6 | 1-6 | 2.2 ± 0.7 | Risperidone > Placebo |
| | Hollander et al. [60] | 16 | 8 | 0.5-3 | 2.25 ± 0.86 | Risperidone > Placebo |
| | Erzegovesi et al.[61] | 39 | 6 | 0.5 (fixed-dose) | 0.5 (fixed-dose) | Risperidone > Placebo |
| *Olanzapine* | Bystritsky et al.[62] | 26 | 6 | 5-20 | 11.2 ± 6.5 | Olanzapine > Placebo |
| | Shapira et al.[63] | 44 | 6 | 5-10 | 6.1 ± 2.1 | Olanzapine = Placebo |
| *Quetiapine* | Atmaca et al.[79] | 27 | 8 | 50-200 | 91 ± 41 | Quetiapine > Placebo |
| | Denys et al. [41] | 40 | 8 | 200-300 | 300 | Quetiapine > Placebo |
| | Fineberg et al.[19] | 21 | 16 | 50-400 | 215 ± 124 | Quetiapine = Placebo |
| | Carey et al. [56] | 42 | 6 | 25-300 | 168.8 ± 120.8 | Quetiapine = Placebo |
| | Kordon et al. [57] | 40 | 12 | 400-600 | - | Quetiapine = Placebo |
| | Diniz et al. [58] | 54 | 12 | ≤200 | - | Quetiapine < Placebo |
| *Aripiprazole* | Muscatello et al. [64] | 40 | 16 | 15 (fixed-dose) | 15 (fixed-dose) | Aripiprazole > Placebo |
| | Sayyah et al. [66] | 39 | 12 | 10 (fixed-dose) | 10 (fixed-dose) | Aripiprazole > Placebo |
| *Paliperidone* | Storch et al.[67] | 34 | 8 | 3-9 | 4.94 | Paliperidone = Placebo |

* single-blind, placebo-controlled.

Because haloperidol and risperidone were superior to quetiapine and olanzapine in the meta-analytic calculations, it may be conjectured that the pharmacological effects in OCD are primarily caused by the D2-receptor blockade of the antipsychotic [50]. This assumption is supported by a positive open-label augmentation study with the selective, potent D2 and D3-receptor blocker amisulpride in SRI-resistant-OCD [78]. Because amisulpride has no relevant affinity for serotonergic receptors, this result tends to confirm an involvement of the D2 antagonism in the mechanism of action of antipsychotic in OCD [50]. Further studies are needed to confirm this possible mechanism of action.

## Conclusion

In conclusion, the currently available evidence suggests that antipsychotic addition to SRIs in patients not responding to at least 12 weeks at a medium-to-high SRI dose is effective. Given the strength of the evidence we do suggest this option especially in patients who showed a partial but unsatisfactory response. An alternative strategy, evidence-based, is CBT addition to pharmacotherapy, when available.

Approximately 50% of patients will respond to antipsychotic addition, given that the choice of the "right" antipsychotic is restricted to risperidone, olanzapine, aripiprazole. Haloperidol addition is also a viable option, particularly in patients with comorbid tic disorders. Whether resistant patients with comorbid tic disorders respond better to all antipsychotics is still to be determined. Quetiapine should be regarded as non-effective in OCD, given results of studies performed to date.

Further research is still required regarding the optimal dose of several antipsychotics, the ideal duration of add-on treatment, its long tolerability and the evaluation of predictors of response. Further investigations should also assess which SRIs are the most suitable for an antipsychotic augmentation strategy. Moreover, additional work is required to understand the psychobiological mechanisms underlying the efficacy of antipsychotic addition in resistant OCD.

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