ANTIPSYCHOTICS IN TREATMENT-RESISTANT OBSESSIVE-COMPULSIVE DISORDER: WHICH ANTIPSYCHOTIC, WHICH DOSE AND HOW LONG ANTIPSYCHOTIC ADDITION SHOULD BE MAINTAINED

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Abstract

Objectives: Treatment-resistant Obsessive-Compulsive Disorder (OCD) patients are defined as those who undergo adequate trials of first-line therapies without achieving a satisfactory response. First line treatments for OCD include both serotonin reuptake inhibitors (SRIs) and cognitive behavior therapy (CBT). Because of the high number of OCD patients not responding to first-line treatments (40-60%) and considering the even greater prevalence rate of residual symptoms and significant impairment shown in patients previously described as "clinical responders", the question of the proper treatment of resistant OCD is a clinically meaningful and a practical issue for psychiatrists. Antipsychotic augmentation proved to be an effective strategy for resistant OCD. However, there are unresolved questions concerning which antipsychotic is effective (or more effective) and how antipsychotics should be used in terms of doses and duration of treatment. The purpose of this study is to systematically review available studies on antipsychotic augmentation for treatment-resistant OCD, in order to guide the practical choice.

Materials and methods: We searched on PubMed, Psychnet and Cochrane Libraries from inception to January 2016. Articles published in English and related to the use of antipsychotics in OCD were considered. We evaluated meta-analyses, systematic reviews and randomized controlled trials of adult patients with treatment-resistant OCD.

Results: Antipsychotic augmentation is an evidence-based option for treatment-resistant OCD, with a response rate of approximately 50% within the first 4-to-6 weeks. Aripiprazole (10-15 mg/day) and risperidone (0.5-2 mg/day) are effective, olanzapine (10 mg/day) is possibly effective. Haloperidol addition is also a viable option, particularly in patients with comorbid tic disorders. Given results of studies performed to date quetiapine should be regarded as non-effective. Preliminary results from open label studies suggest that antipsychotic augmentation, once effective, should be maintained in order to maintain remission.

Conclusions: Not all antipsychotics are effective as add-on treatments in resistant OCD. Characteristics of patients and side effects generally associated with each different antipsychotic may guide the practical choice. Further research is required concerning the comparative effectiveness among antipsychotics, the optimal target dose and the ideal duration of antipsychotic addition. In our opinion, antipsychotic augmentation in patients who responded to this treatment should be maintained in order to prevent relapses. However, clinicians must remember patients' exposure to the common and serious adverse effects associated with long-term antipsychotic administration, especially metabolic disturbances.

Key words: Obsessive-Compulsive Disorder (OCD), antipsychotic, augmentation, treatment, treatment-resistant OCD

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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]. The severity of the disorder (in terms of severity of obsessive-compulsive symptoms or the severity of the associated depressive symptomatology) and the age of the patient might guide clinicians in the choice of the first approach: for an adult patient affected by a severe OCD, pharmacotherapy with an SSRI is generally considered a correct first-line approach. Analyzing the relative efficacy between different SRIs, no significant difference could be identified between citalopram, fluoxetine, fluvoxamine, paroxetine and sertraline, according to a Cochrane review depicting 17 RCTs [16]. Equally, the SSRI escitalopram improved OCD symptoms without any significant difference as compared to paroxetine [17]. Nevertheless, 40-60% of OCD patients do not respond satisfactorily to the initial SRI monotherapy [18-20]. Additionally, those patients who are defined as "clinical responders" according to stringent response criteria (i.e., typically a greater than 25 or 35% decline in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) rating) often fail to show later on a complete remission of their symptoms and/or continue to experience significant impairment from their residual symptoms in terms of reduced quality of life [21].

Because of the high number of OCD patients not responding to first-line treatments, the question of the proper treatment of resistant OCD is a clinically meaningful and practical issue for psychiatrists.

Definition of and practical steps to be implemented for treatment-resistant OCD

Patients who undergo adequate trials of first-line therapies without achieving a satisfactory response are defined as treatment-resistant OCD patients. Clinical response is usually defined as a reduction in the Y-BOCS score ≥ 35% or ≥ 25% with respect to baseline [22]. More specifically, stages of response to treatment have been recently proposed, according to an international expert consensus: treatment 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 and CGI at least 3; non response as less than 25% Y-BOCS reduction and CGI 4. Furthermore, remission is achieved if the person no longer meets syndromal criteria for the disorder and has no more than minimal symptoms (Y-BOCS ≤ 12) and CGI 1 or 2 for at least one week; recovery is obtained if the person no longer meets syndromal criteria for the disorder and has no more than minimal symptoms (Y-BOCS ≤ 12) and CGI 1 or 2 for at least one year [23].

Practically, several issues must be considered and questions have to be addressed, before confirming a condition of treatment-resistance of OCD:

1. clinicians should correctly make the diagnosis of OCD. Particularly, other symptoms should not be inappropriately 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. clinicians should check that the patient has been exposed to an adequate pharmacological trial (SRIs) in terms of appropriate doses and for at least 12 weeks. Guidelines provide minimum target and maximum doses to be used in OCD (see for example those of the APA Guidelines, illustrated in Table I); a meta-analysis confirmed that moderate-high dosages are more effective in treating OCD and thus should be prescribed before defining a patient as resistant [24];
3. the potential presence of medical or psychiatric comorbidities that could affect treatment response should be assessed (e.g., paradigmatic the case of OCD comorbid with bipolar disorder, where treatment with high doses of SRIs could worsen

Table I. Doses of serotonin reuptake inhibitors (SRIs) in the treatment of obsessive-compulsive disorder according to American Psychiatry Association guidelines (2007) [7].

Compound SRI	Starting dose and incremental dose (mg/day)*	Usual target dose (mg/day)	Usual maximum dose (mg/day)	Occasionally prescribed maximum dose (mg/day)†
Citalopram	20	40-60	80	120
Clomipramine	25	100-250	250	__ ‡
Escitalopram	10	20	40	60
Fluoxetine	20	40-60	80	120
Fluvoxamine	50	200	300	450
Paroxetine	20	40-60	60	100
Sertraline §	50	200	200	400

* Some patients may need to start at half this dose or less to minimize undesired side effects such as nausea or to accomodate anxiety about taking medications; † These doses are sometimes used for rapid metabolizers or for patients with no or mild side effects and inadeguate therapeutic response after 8 weeks or more at the usual maximum dose; ‡ Combined plasma levels of clomipramine plus desmethylclomipramine 12 hours after the dose should be kept below 500 mg/mL to minimize risk of seizures and cardiac conduction delay; § Sertraline, along among the selective serotonin reuptake inhibitors, is better absorbed with food.

both bipolar disorder – mixed episodes, rapid cycling, switch – and OCD) [25 26];

4. clinicians may also keep in mind that the first available strategy could be just waiting for the treatment to produce a full response, since 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 strategy, however, should be strictly reserved to patients who showed at least a partial response during the initial months of treatment [27 28];
5. finally, 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 [29-31]. Indeed, the family may have a potential role 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 [32 33], contribute to the maintenance of patient's symptoms as well [34].

Antipsychotic augmentation in treatment-resistant OCD

Several therapeutic options are available for treatment resistant OCD; however, only two strategies are considered, to date, evidence-based treatments for resistant OCD based on placebo-controlled randomized trials: antipsychotic augmentation of SRIs and cognitive-behavior therapy addition. This latter option proved to be effective in several open-label studies (see for an example of its use in a naturalistic setting resembling that of a clinical practice the study by Albert et al.) [35] and at least one well-performed controlled (stress management training as the inactive/placebo psychological treatment arm) randomized trial [36].

Antipsychotic augmentation of SRIs is an evidence-based treatment for resistant OCD; its efficacy has been confirmed by several randomized, double-blind and placebo-controlled trials and by several meta-analyses.

Atypical antipsychotic medications are approved only for the treatment of Schizophrenia, Bipolar Disorder and Major Depression under drug-specific circumstances. However, their use is rapidly increasing and their off-label prescription is, at least partially, responsible for their widespread use [37-41]. It has been estimated that, among adults, off-label prescriptions represent 40 to 75% of all antipsychotic prescriptions [41].

Antipsychotic drugs are generally recommended as a class for several diagnoses including treatment-resistant OCD, although they are not all the same in their efficacy, reflecting the differences in pharmacokinetic and pharmacodynamic profiles of each drug. In fact, there are still some unresolved questions concerning which atypical antipsychotic could be more effective as an evidence-based treatment for treatment-resistant OCD. Moreover, no advice is provided on how to use a specific antipsychotic for this specific disorder, in terms of doses and duration of treatment.

The purpose of this paper is to systematically review available studies on antipsychotic augmentation for treatment-resistant OCD, focusing on efficacy and comparative effectiveness (where possible) of antip-

sychotics, in order to provide a guidance for clinicians on which antipsychotic (and at which dose) should be preferred in resistant OCD.

Materials and methods

We searched on PubMed, Psychnet and Cochrane Libraries from inception to January 2016. Articles published in English and related to the use of antipsychotics in OCD were evaluated. The keyword "antipsychotic" was combined using the boolean AND with "obsessive-compulsive disorder". An additional search was performed combining OCD with "aripiprazole", "olanzapine", "quetiapine", "paliperidone", "risperidone", "ziprasidone" via the Boolean AND. Finally, a manual search for reference lists from articles selected in the previous search and for any relevant reviews was done. Search results were limited to open-label trials and randomized controlled trials of adult patients with treatment resistant OCD.

Results

Is antipsychotic augmentation an evidence-based treatment for resistant OCD?

The use of antipsychotic addition to SRIs in resistant OCD is supported by several randomized, double-blind, placebo-controlled studies; review and meta-analytical studies also confirm that augmentation of SRIs with antipsychotic drugs can be considered a valid treatment option in resistant OCD [42-52].

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; Dold et al. calculated an overall response rate to antipsychotic addition (all RCTs, including those where antipsychotics proved to be ineffective) of approximately 30% [52]; however, studies in which the active compound (antipsychotic) differentiated from placebo (positive studies) found response rates around 50% [43]. When response to antipsychotic addition occurs, it is evident within the first 4-6 weeks [43 50]. According to these results, it may be advisable to change strategy when antipsychotic addition after 6 weeks results ineffective. However, not all antipsychotics have been studied in double-blind conditions and differences in efficacy exist between antipsychotics.

Which antipsychotics proved effective in resistant OCD in double-blind, placebo-controlled studies?

Efficacy: first generation antipsychotics

Two studies investigated augmentation of SRIs with typical antipsychotics (haloperidol and pimozide) [53 54]; only haloperidol proved to be effective in a double-blind, placebo-controlled study, particularly in patients with comorbid tic disorders [54 55]. However, the side effect profile of haloperidol, with dose-dependent extrapyramidal symptoms, limits the potential benefit

Table II. Efficacy of antipsychotic augmentation in treatment-resistant OCD: double-blind, placebo-controlled studies.

Antipsychotic	Authors	Sample (N)	Trial duration (weeks)
Aripiprazole	Muscatello et al., 2011 [66] Sayyah et al., 2012 [67]	40 39	16 12
Haloperidol	McDougle et al., 1994 [54]	34	4
Olanzapine	Bystritsky et al., 2004 [68] Shapira et al., 2004 [69]	26 44	6 6
Paliperidone	Storch et al., 2013 [70]	34	8
Quetiapine	Atmaca et al., 2002 *[57] Denys et al., 2004 [58] Carey et al., 2005 [59] Fineberg et al., 2005 [81] Kordon et al., 2008 [60] Diniz et al., 2011 #[61]	27 40 42 21 40 54	8 8 6 16 12 12
Risperidone	McDougle et al., 2000 [62] Hollander et al., 2003 [63] Erzegovesi et al., 2005 [64] Simpson et al., 2013 [65]	36 16 20 60	6 8 6 8

* Single-blind, placebo-controlled study; # Double-blind placebo and clomipramine controlled study.

of this strategy; by comparison, the atypical antipsychotics are associated with fewer extrapyramidal symptoms, though they are known to be associated with a higher risk of metabolic adverse effects [56].

Efficacy: second generation/atypical antipsychotics

Concerning the efficacy of second-generation antipsychotic augmentation of SRIs in treatment-resistant OCD, there are six RCTs regarding the addition of quetiapine [57-61 81], four risperidone [62-65], two aripiprazole [66 67], two olanzapine [68 69] and one paliperidone [70]. Results of double-blind, placebo-controlled studies (together with doses used in each study) are summarized in Table II.

Aripiprazole and risperidone both differentiated from placebo in all studies and may be considered effective. No evidence could be identified for the efficacy of adjunctive quetiapine (no difference in response between quetiapine and placebo in four of the five double-blind studies) and olanzapine (one positive study [68] and one negative [69]). However, the negative study with olanzapine [69] was biased by the fact that the Authors included patients not responding to only 8 weeks of SRI 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 [71]. We then think that olanzapine may be a valid alternative to aripiprazole and risperidone as an augmentation strategy in resistant patients. The paliperidone negative study [70] suffered from the same bias: treatment resistance 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. 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), and placebo administration also resulted in medium size, trend-level significant YBOCS changes (-4.02 points). Our conclusion is that 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.

Comparative effectiveness

Concerning comparative effectiveness of antipsychotics in OCD, we could retrieve only four studies [71-74]. Results of these studies are summarized in Table III. The first one compared risperidone and haloperidol addition with a crossover design: each patient received a 2-week trial of adjunctive risperidone, haloperidol and placebo [72]; both risperidone and haloperidol significantly reduced obsessions

Dose (mg/die)	Mean dose (mg/die)	Minimal length of SRI treatment before enrollment in the study	Results
15 (fixed-dose) 10 (fixed-dose)	15 (fixed-dose) 10 (fixed-dose)	12 12	Aripiprazole > Placebo Aripiprazole > Placebo
2-10	6.2 ± 3.0	12	Haloperidol > Placebo
5-20 5-10	11.2 ± 6.5 6.1 ± 2.1	12 8	Olanzapine > Placebo Olanzapine = Plabebo (patients in both arms improved)
3-9	4.94	8	Paliperidone = Placebo (patients in both arms improved)
50-200 100-300 25-300 50-400 400-600 50-200	91 ± 41 200 168.8 ± 120.8 215 ± 124 - 142 ± 65	12 8 12 12 12 8	Quetiapine > Placebo Quetiapine > Placebo Quetiapine = Placebo Quetiapine = Placebo Quetiapine = Placebo Quetiapine < Placebo
1-6 0.5-3 0.5 (fixed-dose) 0.25-4	2.2 ± 0.7 2.25 ± 0.86 0.5 (fixed-dose) 1.9 ± 1.1	12 12 12 12	Risperidone > Placebo Risperidone > Placebo Risperidone > Placebo Risperidone > Placebo

Table III. Comparative efficacy of antipsychotic augmentation in treatment-resistant OCD.

Authors	Study design	Antipsychotics	Sample (N)
Li et al., 2005 [72]	Double-blind	Risperidone *vs* Haloperidol	16
Maina et al., 2008 [71]	Single-blind	Risperidone *vs* Olanzapine	50
Selvi et al., 2011 [73]	Single-blind	Risperidone *vs* Aripiprazole	41
Shoja Shafti et al., 2015 [74]	Double-blind	Aripiprazole *vs* Quetiapine	44

Hal: Haloperidol; Risp: Risperidone.

when compared with placebo, and there was a tendency for haloperidol, and to a lesser degree for risperidone, of reducing compulsion and YBOCS total score. However, 40% of patients terminated haloperidol treatment early owing to intolerable side effects, versus none in the risperidone phase. Maina and colleagues (2008) directly compared, in a single-blind study, risperidone and olanzapine addition to SRIs in resistant OCD patients: the two compounds resulted equally effective in improving obsessive-compulsive symptoms [71]. Selvi and coworkers (2011), in a single-blind study, compared aripiprazole and risperidone 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%) [73]. Shoja Shafti and Kaviani (2015), finally, compared in a double-blind study the efficacy and safety of aripiprazole versus quetiapine. They found a statistically significant difference in response rates with quetiapine (54.5%) compared to aripiprazole (27.3%) [74].

Which antipsychotic dose should be used?

Dose ranges of antipsychotics and mean final doses used in double-blind studies on antipsychotic addition in resistant OCD are reported in Table II. Concerning antipsychotics that differentiated from placebo, aripiprazole appeared effective at a dose of 10 and 15 mg/day, olanzapine at a mean dose of 11 mg/day, risperidone at a dose comprised between 0.5 and 2 mg/day. Haloperidol proved effective at a mean final dose of 6 mg/day, but with significant side effects.

How long antipsychotic addition should be maintained?

Trial duration of double-blind studies on antipsychotic augmentation in treatment-resistant OCD (Tab. II) has been comprised between 6 and 12 weeks, with the exceptions of 4 weeks in the haloperidol study [54] and 16 weeks in the aripiprazole one [66]. We could not find double-blind maintenance studies on antipsychotic augmentation in OCD.

A recent single-blind study compared risperidone to CBT augmentation during a six-month maintenance phase. Foa and colleagues (2015) followed-up 40 patients with resistant OCD who responded (Y-BOCS decrease ≥ 25%) to 8-week adjunctive risperidone or CBT (single-blind, placebo-controlled acute study) [65]; responders continued the augmentation strategy they received acutely over further six months. Response was maintained in both groups. Since CBT patients improved more during acute treatment than risperidone patients, CBT yielded superior outcomes six months later [75]. Nevertheless, since risperidone preserved his efficacy, this study may support the need of sustaining antipsychotic augmentation in patients who acutely responded to this treatment.

However, exactly how long adjunctive antipsychotic treatment should be maintained remains an unanswered question. Only a study examined relapse rates after antipsychotic discontinuation; this study 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 [76]. Although retrospective, this study provides additional evidence that antipsychotic augmentation has to be maintained for patients who respond to this strategy.

Discussion and Conclusions

The purpose of this paper was to systematically review available studies on antipsychotic augmentation

Trial duration (weeks)	Dose (mg/die)	Minimal length of SRI treatment before enrollment in the study	Results
2	Risperidone: 1 Haloperidol: 2	2	Obsessions: Hal = Risp > Placebo Compulsions: Hal = Risp = Placebo Total YBOCS: Hal > Risp = Placebo
8	Risperidone: 1-3 Olanzapine: 2.5-10	16	Risperidone = Olanzapine
8	Risperidone: 3 Aripiprazole: 15	12	Risperidone > Aripiprazole
12	Aripiprazole: 10 Quetiapine: 300	12	Quetiapine > Aripiprazole

for treatment-resistant OCD, focusing on efficacy and comparative effectiveness (where possible) of antipsychotics, in order to provide a guidance for clinicians on which antipsychotic (and at which dose) should be preferred in resistant OCD.

The currently available evidence suggests that antipsychotic augmentation of SRIs is an evidence-based treatment option for OCD patients not responding to at least 12 weeks at a medium-to-high SRI dose.

Vulink and colleagues examined the efficacy of the combination of SRIs and antipsychotic from beginning of treatment in non-refractory OCD patients, supporting that the combination of quetiapine (300-450 mg) and citalopram (60 mg) was more effective than citalopram alone in reducing OCD symptoms in treatment-naive or medication-free OCD patients [77]. In our opinion, however, given the adverse effect profile of long-term antipsychotic use and the lack of additional evidence of the efficacy of this combination *ab initio*, antipsychotic augmentation should be reserved for resistant patients. The use of antipsychotics in monotherapy either in drug-naïve or resistant patients has never been studied under double-blind conditions.

Clinicians should expect a response rate of approximately 50% in 4-to-6 weeks after antipsychotic addition, given that the choice of the *right* antipsychotic is restricted to aripiprazole, risperidone, and olanzapine. Our conclusions is supported by two positive double-blind studies for aripiprazole (none negative), four for risperidone (none negative) and one for olanzapine (one negative study, but biased – see results). 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, as meta-analytic studies support this conclusion (patients with tics: NNT 2.3 *vs* patients without tics: NNT 5.9) but also say that results are biased by the inclusion of the haloperidol study results [43]. Quetiapine should be regarded as non-effective in OCD, given results of studies performed to date (no difference in response between quetiapine and placebo in four of the five double-blind studies).

Data emerging from comparative studies to guide clinicians in the choice between aripiprazole, olanzapine and risperidone are still preliminary and conclusions can't be drawn; characteristics of patients (e.g. BMI at baseline) and side effects generally associated with each different antipsychotic may guide the practical choice.

The characteristic feature of second-generation antipsychotics 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 of antipsychotic augmentation in resistant 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 [78]. 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 [47]. A recent metaregression analysis suggested that differences in antipsychotic effectiveness could be due to differences in dopamine binding affinities, with increasing D2 and D3 dopamine receptor binding affinities associated with greater effectiveness (greater YBOCS reduction and higher response rates) [49].

An alternative evidence-based strategy for resistant OCD is CBT addition to pharmacotherapy, when CBT is available [79]. We could find only one acute study which directly compared pharmacological (risperidone) and psychological (intensive CBT) augmentation in adult

patients with resistant OCD [65]. This comparative study suggests that intensive CBT is more effective than risperidone addition to SRIs: response rates were 80% and 23% at week 8, respectively; this randomized clinical study concluded that patients with OCD receiving SRIs who continue to have clinically significant symptoms should be offered CBT before antipsychotics given its superior efficacy and less negative adverse effect profile, although clinician should remember that intensive CBT was offered in that study (15 exposure sessions, daily homework – at least 1 hour of self-directed exposures daily, and between-session telephone check-ins, at least 2 sessions outside the clinic to promote generalization to daily life) [65]. Given the strength of the evidence for antipsychotic addition, we do suggest this option especially in patients who showed a partial but unsatisfactory response.

Further research is still required concerning the optimal target dose of antipsychotic to be prescribed in resistant patients; the available evidence suggests to use the following doses: aripiprazole 10-15 mg/day, olanzapine 10 mg/day, risperidone 0.5-2 mg/day. Haloperidol proved effective at a mean final dose of 6 mg/day, but with significant side effects; in clinical practice we advise to use it, e.g. when tic disorder is comorbid, at lower dosages, and augment up to 6 mg/day if response is not evident at lower dosages. Further research is also still required regarding the ideal duration of add-on treatment, its long tolerability and the evaluation of predictors of response. The available evidence points to the need of maintaining antipsychotic addition over the long-term in order to prevent relapses. 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 [80]. Patients with OCD on antipsychotic treatment may be particularly at risk for metabolic syndrome and should be carefully monitored for metabolic abnormalities and cardiovascular complications: a recent study of our research group showed that metabolic syndrome was present in 21.2% of a sample of 104 OCD patients; metabolic syndrome was associated with the duration of the exposure (lifetime) to antipsychotics [56]. These results add strength to the indication of restricting the use of antipsychotic augmentation in resistant patients, when CBT is not available or feasible, or is ineffective. We strongly advice not using antipsychotic addition to SRIs in drug-naïve, never treated patient.

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.

Take home messages for psychiatric care

- Augmentation of SRIs with antipsychotics is an evidence-based strategy in resistant OCD
- The overall response rate to antipsychotic addition is around 50%
- Among atypical antipsychotics, risperidone and aripiprazole may be considered the most effective in resistant OCD
- Further studies are required on the optimal dose and the ideal duration of antipsychotic add-on treatment

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