Neurobiology and Effectiveness of Antipsychotic Drugs in Resistant Obsessive-Compulsive Disorder: A Systematic Review

Déborah Ducasse1* and Guillaume Fond1,2

1INSERM U1061, Université Montpellier 1, service universitaire de psychiatrie adulte, CHU Montpellier, avenue Charles Flahaut, France
2INSERM U955, University Paris-East, Fondamental Fondation, Fondation de Coopération Scientifique, AP-HP, Groupe Hospitalier Mondor, 40, Rue de Mesly, Creteil, F-94000, France

Abstract

Forty to sixty percent of the patients with Obsessive Compulsive Disorder (OCD) is resistant to well conducted treatment with Selective Serotonin Reuptake Inhibitors (SSRIs) over period of 8 weeks. Data concerning the effectiveness of the addition of antipsychotics in this indication is controversial.

Keywords: Antipsychotic; Obsessive compulsive disorder; First generation; Second generation; Treatment; Resistant

Aims of the Study

To synthesize in a comprehensive review, the mechanistic hypotheses of antipsychotic potential activity in OCD and to summarize clinical trials on the effectiveness of antipsychotic drugs in OCD, in monotherapy or in combination with SSRIs.

A systematic review of the literature was conducted using PRISMA criteria. The paradigm search was "obsessive compulsive disorder and antipsychotic agents". Medline, Cochrane and Web of science databases were explored without date or language restriction. Case reports, open label studies and randomized double-blind controlled trials were included in the qualitative review.

Unlike the classical serotonergic hypothesis, OCD may result from striatal dopaminergic hyperactivity, modulated in some patients by an underlying serotonergic hypo activity. In the treatment of resistant OCD, most studies report the effectiveness of first-generation antipsychotic (haloperidol, amisulpride) and some second-generation antipsychotics (risperidone, olanzapine, aripiprazole, quetiapine) in combination with an SSRI. Moreover, in case reports, recrudescence or onset of OCD symptoms in patients with schizophrenia have been described in a switch from first generation antipsychotic medication to olanzapine, risperidone, aripiprazole or clozapine, but not within a switch to amisulpride or quetiapine.

These preliminary results on the use of antipsychotic medication in OCD deserve further investigation for potential guideline updates.

Obsessive-Compulsive Disorder (OCD) is "the presence of recurrent ego-dystonic and intrusive thoughts or images (obsessions), with ritualized behaviors (compulsions) performed in order to neutralize obsessive thoughts" [1]. The lifetime prevalence of OCD in France in 2006 was 2 to 3%, its prevalence over a period of 6 months was 1 to 2% and the sex ratio is 1 [2]. In the USA, in 2005, OCD was recognized as a fairly common psychological disorder with reported lifetime prevalence between 1.6 and 3.3%, and 1 year prevalence between 1.0 and 2.1% [3]. In 2012, the first line pharmacological treatment according to the guidelines of the Haute Autorité de Santé (HAS) (the French equivalent of the Food and Drug Administration in the USA) is in 2012 the administration of Selective Serotonin Reuptake Inhibitors (SSRIs) in monotherapy: fluoxetine (20-60 mg/day), fluvoxamine (100 to 300 mg/day), paroxetine (20 to 60 mg/day), sertraline (50 to 200 mg/ day), escitalopram (10-20 mg/day) [2].

"Resistant OCD" may be defined as OCD whose symptoms persist after treatment by SSRIs in high doses for at least 8 weeks [2]. The SSRI response-rate is only 40% to 60% of patients [4]. Whereas resistant OCD is typically explained by serotonin mechanisms, another neurobiological mechanisms are involved [5]. For example, in some patients, dopaminergic hyperactivity modulated by an underlying serotonergic hypo activity has been suggested [6].

Antipsychotics have been suggested as second-line treatment in resistant OCD with a controversial effectiveness [7]. At first sight, risperidone's effectiveness in resistant OCD [8] seems paradoxical: if OCD is conceived as a serotonin deficiency, the coprescription of a 5-HT antagonist with a SSRI should worsen OCD symptomatology. Moreover, low doses of risperidone (<3 mg/d) have found to be the best effective where the anti-5-HT2A activity is optimal with a very low anti-D2 activity [9,10]. Finally, some second-generation antipsychotics have been involved in de novo OCD genesis in psychotic patients [11].

The study's objective is to synthesize the mechanistic hypotheses on OCD treatments' activity and to review the literature on the effectiveness of antipsychotic drugs in OCD according to their pharmacological profiles, in monotherapy or in combination with SSRIs.

A systematic review of the literature was conducted using the PRISMA criteria (Preferred Reporting Items for Systematic reviews and Meta-Analysis). The research paradigm was "obsessive compulsive disorder and antipsychotic agents". Search criteria were specified in advance, without date or language limitations. Research databases Medline (1966-2012), Cochrane (all items) and Web of Science (1975-2012) have been explored. Additional items were added after analysis of bibliographic references. Case reports, open-labeled and randomized double-blind controlled trials were included in the qualitative review. The last search was conducted on the 16th of December 2012.

*Corresponding author: Dr. Deborah Ducasse, INSERM U1061, Université Montpellier 1, service universitaire de psychiatrie adulte, CHU Montpellier, avenue Charles Flahaut, F-34000, France, Tel: +33632601595; E-mail: deborah.ducasse@orange.fr

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Overall, 672 articles have been found, of which, after reading the abstracts, 38 corresponded to the subject of our study. 17 articles have been added by examining the complete references.

**Different monoaminergic models proposed in OCD**

**Serotonin model and its limitations**

The OCD symptoms have been suggested to be typically linked to a dysfunction of the brain serotonergic system [12]. This hypothesis stems from the observation of a positive response in clomipramine-treated OCD patients. Clomipramine is a tricyclic antidepressant which has, among other properties, a non-selective serotonin reuptake inhibitor [6].

Pirot [12] hypothesized a hypoactivity of serotoninergic projections associated with a secondary hypersensitivity of postsynaptic 5-HT receptors in the orbitofrontal cortex, the anterior cingulate cortex and the caudate nucleus [12]. In OCD, these three structures, which are network-organized, may have an abnormally high activity that would be potentially normalized by pharmacological treatments or cognitive-behavioral psychotherapy [12]. Chronic administration of serotoninergic antidepressants may induce a gradual desensitization of the presynaptic autoreceptor 5-HT1B/D and 5-HT1A by down-regulation. The reduction of these feedback systems activity may induce increased levels of synaptic serotonin and desensitization of postsynaptic receptors, which may be associated with clinical remission of obsessive-compulsive symptoms [12]. Chronic administration of fluoxetine or clomipramine has been found to abolish human exacerbation of obsessive-compulsive symptoms induced by m-CPP (non-selective agonist of 5-HT1A, 1B/D, 1C and 2C receptors) [12]. Another indicator is that remission of OCD symptoms often require high doses of SSRIs (e.g fluvoxamine 300 mg/day, fluoxetine 60 mg/ day) with delayed action time (8 weeks versus 2-3 weeks for depression) [2]: 5-HT1B/1D autoreceptors of the orbitofrontal cortex may be desensitized more slowly (8 weeks) than those in other structures such as the hippocampus (3 weeks) and would need higher doses to be desensitized [12]. However, the therapeutic effectiveness of SSRIs is incomplete, with a response-rate of only 40 to 60% [4]. In addition, studies have shown reduced levels of plasma serotonin in only some OCD patients [6]. So, a dysregulation of serotonin function does not seem sufficient to explain the complete physiopathology of OCD.

**Dopaminergic model**

The increased frequency of OCD induced by direct (apomorphine, bromocriptine) or indirect (cocaine, amphetamine) dopaminergic agonists has suggested the involvement of dopaminergic pathways in this disease [13]. Anatomo-clinical studies [14], and imaging by Tomography by Emission of Positron (PET) [6,9] have suggested the involvement of specific brain regions in OCD, especially a dysfunction of the presynaptic autoreceptor 5-HT1B/D and 5-HT1A by down-regulation. The reduction of these feedback systems activity may induce increased levels of synaptic serotonin and desensitization of postsynaptic receptors, which may be associated with clinical remission of obsessive-compulsive symptoms [12]. Chronic administration of fluoxetine or clomipramine has been found to abolish human exacerbation of obsessive-compulsive symptoms induced by m-CPP (non-selective agonist of 5-HT1A, 1B/D, 1C and 2C receptors) [12]. Another indicator is that remission of OCD symptoms often require high doses of SSRIs (e.g fluvoxamine 300 mg/day, fluoxetine 60 mg/ day) with delayed action time (8 weeks versus 2-3 weeks for depression) [2]: 5-HT1B/1D autoreceptors of the orbitofrontal cortex may be desensitized more slowly (8 weeks) than those in other structures such as the hippocampus (3 weeks) and would need higher doses to be desensitized [12]. However, the therapeutic effectiveness of SSRIs is incomplete, with a response-rate of only 40 to 60% [4]. In addition, studies have shown reduced levels of plasma serotonin in only some OCD patients [6]. So, a dysregulation of serotonin function does not seem sufficient to explain the complete physiopathology of OCD.

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The activity of these brain structures, including the striatal dopaminergic pathway, may be modulated by the serotoninergic system. Indeed, neurons in the midbrain raphe nuclei project to the ventromedial part of the striatum, involved in the maintenance of an inhibitory tone of dopaminergic transmission which regulates the balance between the direct and indirect dopaminergic pathways described above [6].

Further noteworthy finding is that ritanserin and amperozide, two 5-HT2A receptors antagonists, both increase the striatal dopaminergic transmission and the prefrontal cortex activity by blocking the serotoninergic inhibition [17,18]. Methergoline, a non-selective 5HT1A/5HT2A antagonist, worsens the obsessive-compulsive symptoms of OCD patients responding to clomipramine [19].

**Classification of antipsychotic according to their potential efficacy (or iatrogenicity) in resistant OCD**

**Potentially effective antipsychotic drugs**

**First-generation antipsychotics:** Only one double-blind randomized controlled trial has shown the effectiveness of first-generation antipsychotics in patients with resistant OCD: McDougle et al. [20] tested the effectiveness of haloperidol (10 mg/d) in addition to fluvoxamine (fixed dose 300 mg/day) in 34 patients with resistant OCD throughout 7 weeks of treatment. The response was defined as a decrease of at least 35% of the Y-BOCS score at 4 weeks. Seven (41%) of the 17 patients in the group receiving haloperidol were responders against none in the placebo group (p<0.008). The treatment was generally well tolerated regarding extrapyramidal symptoms (with an anticholinergic correction immediately prescribed), but 9 (53%) patients suffered from akathisia. In patients with resistant OCD, middle-dosed haloperidol seemed then to be poorly tolerated.

**Second-generation antipsychotics (table 1):** Most clinical trials focused on the effectiveness of second-generation antipsychotics (risperidone, olanzapine, aripiprazole, quetiapine) in addition to SRI in
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#### Antipsychotic

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Author &amp; year</th>
<th>Study design and population</th>
<th>Dose of antipsychotic</th>
<th>Dose of SRI</th>
<th>Major findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>McDougle et al. 2000 [41]</td>
<td>N=36 RCT</td>
<td>mean: 2,2±0,7 mg/d (1 to 6 mg/d)</td>
<td>CLOM (250 mg/d) FLUO (80 mg/d) FLUV (300 mg/d) PARO (60 mg/d) SERT (200 mg/d)</td>
<td>9 patients (50%) responders with risperidone 0 patients responders with placebo: (X²=8.0, p&lt;0.005) Important decrease of Y-BOCS score in the risperidone group (31.8%, 27.4±5.4 to 18.7±8.3) (F=14.61, p&lt;0.001)</td>
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<td></td>
<td>Hollander et al. 2003 [8]</td>
<td>N=16 RCT</td>
<td>2,3±0,9 mg/d (0,5 à 3 mg/d)</td>
<td>CITA (80 mg/d) CLOM (200 mg/d) FLUO (60 mg/d) FLUV (150 mg/d) SERT (150 mg/d) VENL (325 mg/d)</td>
<td>4 patients (40%) responders with risperidone 0 patients responders with placebo (no significative difference)</td>
</tr>
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<td></td>
<td>Erzegovesi et al. 2005 [35]</td>
<td>N=20 RCT</td>
<td>0,5 mg/d</td>
<td>FLUV ( 300 mg/d)</td>
<td>5 patients (50%) responders with risperidone 2 patients (20%) with placebo</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Koran et al. 2000 [38]</td>
<td>N=10 OLT</td>
<td>10 mg / d</td>
<td>FLUO (60 mg/d)</td>
<td>3 patients (30%) have been responders, with a decrease of Y-BOCS scores: 68%, 30% and 29%</td>
</tr>
<tr>
<td></td>
<td>Bogetto et al. 2000 [5]</td>
<td>N=33 OLT</td>
<td>5 mg / d</td>
<td>FLUV (300 mg/d)</td>
<td>10 patients (43,5%) responders. Significative decrease of Y-BOCS score: 29,4%; 26,8±3,0 to 18,9±5,9 (p&lt;0,0005)</td>
</tr>
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<td></td>
<td>D'Amico et al. 2003 [31]</td>
<td>N=21 OLT</td>
<td>10 mg / d</td>
<td>PARO (60 mg/d)</td>
<td>7 patients (38,9%) responders. Significative decrease of Y-BOCS score: 25.8%, 27.1±4 to 20.1±3,9 (p&lt;0,001)</td>
</tr>
<tr>
<td></td>
<td>Bystritsky et al. 2004 [29]</td>
<td>N=26 RCT</td>
<td>mean: 11,2±6,5 mg/d</td>
<td>CLOM (200-250mg/d) FLUO (60 mg/d) PARO (80 mg/d) SERT (200 mg/d)</td>
<td>6 patients (46%) responders with olanzapine 0 patients responders with placebo: (X²=8.0, p&lt;0.005) Important decrease of Y-BOCS score in the risperidone group (31.8%, 27.4±5.4 to 18.7±8.3) (F=14.61, p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>Shapira et al. 2004 [47]</td>
<td>N=44 RCT</td>
<td>mean: 6,1±2,1 mg/d</td>
<td>FLUO (40 mg/d)</td>
<td>9 patients (41%) responders in olanzapine group and 9 patients (41%) responders in placebo group: 0 patients responders with placebo (no significative difference)</td>
</tr>
<tr>
<td></td>
<td>Maina et al. 2008 [39]</td>
<td>N=50 OLT</td>
<td>Risperidone (1 - 3 mg/d) Olanzapine (2,5 - 10 mg/d)</td>
<td>CITA (20 mg/d) CLOM (100 mg/d) FLUO (40 mg/d) PARO (40 mg/d) SERT (50 mg/d)</td>
<td>no statistical difference between the olanzapine and the risperidone groups</td>
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<tr>
<td>Quetiapine</td>
<td>Denys et al. 2002 [33]</td>
<td>N=10 OLT</td>
<td>200 mg/d</td>
<td>CLOM (250 mg/d) FLUO (80 mg/d) FLUV (300 mg/d) PARO (60 mg/d) SERT (225 mg/d) VENL (300 mg/d)</td>
<td>Response in 7 patients (70%), 3 (30%) of these have been a full response</td>
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<td></td>
<td>Atmaca et al. 2002 [48]</td>
<td>N=27 RCT</td>
<td>50-200 mg/d</td>
<td>CLOM (37,5-300 mg/d) FLUO (50-300 mg/d) FLUV (20-80 mg/d)</td>
<td>Response in 10 patients (71,4%) in quetiapine group None of placebo group patients showed improvement (p&lt;0,0001)</td>
</tr>
<tr>
<td></td>
<td>Denys et al. 2004 [33]</td>
<td>N=40 RCT</td>
<td>300 mg/d</td>
<td>CITA (20-60 mg/d) CLOM (75 mg/d) FLUO (20-60 mg/d) FLUV (50-200mg/d) IMIP (150 mg/d) PARO (20-60 mg/d) VENL (300 mg/d)</td>
<td>8 patients (40%) responders in quetiapine group 2 patients (10%) responders in placebo group: X²=4,8, df=1, p=0,028 Mean of decrease of Y-BOCS score in quetiapine group: 9,0±7,0 Mean of decrease of Y-BOCS score in placebo group: 1,8±3,4 (F=16.99, df=1,38, p&lt;0,001)</td>
</tr>
<tr>
<td></td>
<td>Fineberg et al. 2005 [36]</td>
<td>N=21 RCT</td>
<td>mean: 215±124 mg/d</td>
<td>CITA (60-80 mg/d) PARO (40-60 mg/d) SERT (75-200mg/d)</td>
<td>3 patients (27%) responders in quetiapine group 1 patient (10%) responders in placebo group Mean of decrease of Y-BOCS score in quetiapine group: 3,4 (14%) Mean of decrease of Y-BOCS score in placebo group: 1,4 (6%). (NS, F=1)</td>
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</table>
the treatment of resistant OCD [5,8,30-46]. The designs of these studies are heterogeneous as regard the duration of the antipsychotic treatment (8 to 12 weeks), the severity of the patients included (Y-BOCS scores), the presence of comorbidities (including tics and schizotypal personality disorder, not systematically evaluated). A recent meta-analysis [42] on ten randomized controlled studies (haloperidol [20], risperidone [8,35,41], olanzapine [30,47] and quetiapine [33,36,48,49] conclude to a global response rate ratio of 3.3; 95% CI [1.40-7.84] [42].

A retrospective study conducted by Maina et al. [39] in 2003, aimed to assess the impact of the cessation of antipsychotics in patients who had presented a resistant OCD and whose symptoms were persistent. The severity of the patients included (the Y-BOCS scores), the response criteria (decrease of 25% or 35% of the Y-BOCS) and the observation is therefore in accordance with the hypothesis of a striatal hyperdopaminergy in the physiopathology of OCD.

Shapira et al. [47] have suggested that risperidone, unlike olanzapine, has an alpha-2 antagonist activity that is associated with an increased serotonergic transmission [51]. Some studies reported no significant differences between olanzapine, quetiapine and placebo [47]. In addition, risperidone has anti 5-HT2 activity in the medial prefrontal cortex, but not in the orbitofrontal cortex, which is involved in OCD [52]. However, comparative studies on this subject are missing for olanzapine and quetiapine [47].

Only two studies [32,43] were found reporting the efficacy of aripiprazole in the treatment of OCD. This treatment seems promising and may represent a treatment of choice due to its acceptability/ tolerability profile.

**Potentially ineffective or iatrogenic antipsychotic drugs:** Clozapine, risperidone, olanzapine and aripiprazole have been cited in case reports as potential inducers of OCD symptoms [7,11,13,28,53]. The onset of OCD appeared mostly after a switch from a first-generation antipsychotic medication to dopaminergic hyperactivity due to the increase of postsynaptic receptors [50]. This observation is therefore in accordance with the hypothesis of a striatal hyperdopaminery in the physiopathology of OCD.
to a second generation antipsychotic. It is suggested then, according to the previous hypothesis, that the anti-5HT2A antagonism of SGAs may increase the dopaminergic transmission and thus may reactivate previously suppressed OCD symptoms [6]. Clozapine is the most frequently cited antipsychotic in case reports: this may be due to the high prescription frequency or to the disease’s mean severity (given that clozapine is indicated in resistant schizophrenia) [54], but this may be due also to the lower anti-dopaminergic power of clozapine compared to other antipsychotics. Whatever the explanation, clozapine does not seem to be recommended in OCD treatment [55].

Conclusion

While the serotoninergic hypothesis has prevailed for several decades and SSRIs remain the standard treatment for OCD, another model based on striatal hyperdopaminergia regulated by serotonergic neurons may explain the resistance to SSRI in a large proportion of OCD patients. The current guidelines do not recommend the routine use of antipsychotics in the OCD treatment yet, but preliminary results presented in this review seem to favor the prescription of haloperidol, amisulpiride, quetiapine or aripiprazole in moderate doses, in addition with SSRIs or as first-line monotherapy. Further investigations are justified to clearly establish guidelines in this direction. However, further studies are necessary to update these guidelines.

Acknowledgement

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34. Denys D, van Megen H, Westenberg H (2002) Quetiapine addition to serotonin


