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

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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.

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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 serotonergic 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-HT 1A, 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 cortico-striato-thalamo-cortical circuitry. Thus, treatment's success is associated with a normalization of the metabolic activity. OCD may result in a functional imbalance between direct and indirect projections from the orbitofrontal cortex to the basal ganglia, and may be associated with a striatal dopaminergic hyperactivity [12]. The etiologies of this hyperdopaminergic activity in OCD are unclear to date. A polymorphism allele TAQIA2 [15] and a decreased activity of Catecholamine-O-Methyl Transferase (COMT) (involved in the dopamine degradation) have been discussed [15,16].

The activity of these brain structures, including the striatal dopaminergic pathway, may be modulated by the serotonergic system. Indeed, neurons in the midbrain raphe nuclei project to the ventromedial part of the striatum, involved in the maintainance of an inhibitor 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 serotonergic 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

Metin et al. [21] tested the effectiveness of amisulpride (200-600 mg/day, mean dose 325 ± 106 mg/day) in addition to SSRIs or mixed sertonine-norepinephrine reuptake inhibitors (sertraline: 100 to 200 mg/d, paroxetine 30 to 40 mg/d, fluoxetine 40 to 60 mg/d, venlafaxine: 150 to 225 mg/d) in 20 patients with resistant OCD throughout 12 weeks of treatment. It was an open label study. Overall, 19 (95%) of the 20 patients were responders (Y-BOCS improvement >35% at 12 weeks) with a good tolerance of the drugs. The effectiveness of amisulpride in medium doses (200-600 mg/days) may be explained by the fact that higher doses of amisupride reduce dopaminergic transmission by blocking post-synaptic D2/D3 receptors, whereas low doses enhance dopaminergic transmission by selective blockade of pre-synaptic D2/D3 dopamine receptors [21]. This leads to the suggestion that haloperidol and amisulpride both improve OCD symptoms because of their absence of anti-5-HT2A activity [21].

Other open studies or case reports have reported the effectiveness of first-generation antipsychotics alone or in combination with SSRIs in patients with resistant OCD [22-27].

Li et al. [28] conducted a double-blind cross-over randomized controlled trial versus placebo, in order to compare the effectiveness of haloperidol (2 mg/day) and risperidone (1 mg/day) in addition to SSRI, in 60 patients with resistant OCD. When compared with the placebo, haloperidol resulted in a significant decrease in Y-BOCS scores whereas risperidone did not. The difference between risperidone and haloperidol was not statistically significant [28]. Since chloropromazine's equivalents were twice higher for haloperidol than for risperidone. Therefore it was not possible to conclude in this study that haloperidol had a superior effectiveness when compared to risperidone [29].

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

Antipsychotic	Author & year	Study design and population	Dose of antipsychotic	Dose of SRI	Major findings
Risperidone	McDougle et al. 2000 [41]	N=36 RCT	mean: 2,2+/-0,7 mg/d (1 to 6 mg/j)	CLOM (250 mg/d) FLUO (80 mg/d) FLUV (300 mg/d) PARO (60 mg/d) SERT (200 mg/d)	9 patients (50%) responders with risperidone 0 patients responders with placebo:(X2=8.0, p<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<0,001)
	Hollander et al. 2003 [8]	N=16 RCT	2,3+/-0,9 mg/d (0,5 à 3 mg/d)	CITA (60 mg/d) CLOM (200 mg/d) FLUO (60 mg/d) FLUV (150 mg/d) SERT (150 mg/d) VENL (325 mg/d)	4 patients (40%) responders with risperidone 0 patients responders with placebo (no significative difference)
	Erzegovesi et al. 2005 [35]	N=20 RCT	0,5 mg/d	FLUV (300 mg/d)	5 patients (50%) responders with risperidone 2 patients (20%) with placebo
Olanzapine	Koran et al. 2000 [38]	N=10 OLT	10 mg / d	FLUO (60 mg/d)	3 patients (30%) have been responders, with a decrease of Y-BOCS scores: 68%, 30% and 29%
	Bogetto et al. 2000 [5]	N=33 OLT	5 mg / d	FLUV (300 mg/d)	10 patients (43,5%) responders. Significative decrease of Y-BOCS score: 29,4%; 26,8+/-3,0 to18,9+/-5,9 (p<0,0005)
	D'Amico et al. 2003 [31]	N=21 OLT	10 mg / d	PARO (60 mg/d)	7 patients (38,9%) responders. Significative decrease of Y-BOCS score: 25,8%; 27,1+/-4 to 20,1+/-3,9 (p<0,001)
	Bystritsky et al. 2004 [29]	N=26 RCT	mean: 11,2+/-6,5 mg/d maximum: 20 mg/d	CLOM (200-250mg/d) FLUO (60 mg/d) PARO (80 mg/d) SERT (200 mg/d)	6 patients (46%) responders with olanzapine 0 patients responders with placebo: response risk difference=0,46, 95% CI [0,19-0,73], p=0,01 Mean of decrease of Y-BOCS score in olanzapine group: 4,2 (SD=7,9) Mean of increase of Y-BOCS score in placebo group: 0,54 (SD=1,31) (F=4,85, df=2,23, p=0,01)
	Shapira et al. 2004 [47]	N=44 RCT	mean: 6,1+/-2,1 mg/d maximum: 10 mg/d	FLUO (40 mg/d)	9 patients (41%) responders in olanzapine group and 9 patients (41%) responders in placebo group 5 patients (23%) in olanzapine group and 4 patients (18%) in placebo group: decrease of most than 35% of Y-BOCS score Mean of decrease of Y-BOCS score in olanzapine group: 5,1+/-4,9. Mean of decrease of Y-BOCS score in placebo group: 3,8+/-3,8. (F=11,64, p<0,0001)
Risperidone Olanzapine	Maina et al. 2008 [39]	N=50 OLT	Rispéridone (1 - 3 mg/d) Olanzapine (2,5 - 10 mg/d)	CITA (20 mg/d) CLOM (100 mg/d) FLUO (40 mg/d) FLUV (100 mg/d) PARO (40 mg/d) SERT (50 mg/d)	no stastistical difference between the olanzapine and the risperidone groups
Quetiapine	Denys et al. 2002 [33]	N=10 OLT	200 mg/d	CLOM (250 mg/d) FLUO (80 mg/d) FLUV (300 mg/d) PARO (60 mg/d) SERT (225 mg/d) VENL (300 mg/d)	Response in 7 patients (70%), 3 (30%) of these have been a full response
	Atmaca et al. 2002 [48]	N=27 RCT	50-200 mg/d	CLOM (37,5-300 mg/d) FLUV (50-300 mg/d) FLUO (20-80 mg/d)	Response in 10 patients (71,4%) in quetiapine group None of placebo group patients showed improvement (p<0,0001)
	Denys et al. 2004 [33]	N=40 RCT	300 mg/d	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)	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<0,001)
	Fineberg et al. 2005 [36]	N=21 RCT	mean: 215+/-124 mg/d maximum: 400 mg/d	CITA (60-80 mg/d) PARO (40-60 mg/d) SERT (75-200mg/d)	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)

	Carey et al. 2005 [49]	N=42 RCT	mean: 169+/-121 mg/d maximum: 300 mg/d	CITA (60 mg/d) CLOM (250 mg/d) FLUO (60 mg/d) FLUV (300 mg/d) PARO (60 mg/d) SERT (200 mg/d)	8 patients (40%) responders in quetiapine group 10 patients (47,6%) responders in placebo group Mean of decrease of Y-BOCS score in quetiapine group: 7,10+/-7,2 (26,9%) Mean of decrease of Y-BOCS score in placebo group: 7,19+/-8,4 (26%) (F=0,19, p=0,636)
	Kordon et al. 2008 [44]	N=40 RCT	400-600 mg/d	CITA (40 mg/d) CLOM (175 mg/d) FLUO (40 mg/d) FLUV (200 mg/d) PARO (40 mg/d) SERT (100 mg/d)	no stastistical difference between the quetiapine and the placebo groups
Rispéridone Olanzapine Quetipiapine	Matsunaga et al. 2009 [40]	N=90 OLT	Risperidone (1-5 mg/d) Quetiapine (25-100 mg/d) Olanzapine (1-10 mg/d)	FLUO (250 mg/d) PARO (50 mg/d)	Significant superior improvement in antipsychotic group (p<0,01)
Aripiprazole	Delle Chiaie et al. 2011 [31]	N=20 OLT	5 - 20 mg/d (mean 12,62 mg/d)	CLOM (112,5-150 mg/d) FLUV (300 mg/d) PARO (40-60 mg/d)	16 (80%) patients have had a total response 2 (10%) patients have had a partial response 2 (10%) patients have had no response
	Muscatello et al. 2011 [45]	N=40 RCT	15 mg/d	FLUV (200-300 mg/d) FLUO (40-60 mg/d) CITA (40-60 mg/d) PARO (40-60 mg/d) CLOM (220-225 mg/d)	11 patients (68,7%) responders in aripiprazole group Mean of decrease of Y-BOCS score in aripiprazole group: 28,5% Mean of decrease of Y-BOCS score in placebo group: 0,6% (p<0,0001)
	Sayyah et al. 2012 [46]	N=39 RCT	10 mg/d	FLUO (70-80 mg/d) FLUV (200-300 mg/d) SERT (150-200 mg/d) CITA (60-80 mg/d)	8 patients (53%) responders in aripiprazole group 3 patients (17,6%) responders in placebo group Mean of decrease of Y-BOCS score in aripiprazole group: 29,5% Mean of decrease of Y-BOCS score in placebo group: 4,1% (p=0,0001)
Clozapine	McDougle et al. 1995 [55]	N=12 OLT	300 - 600 mg/d	Only clozapine medication	0 responders
Aripiprazole Risperidone	Selvi et al. 2011 [43]	N=34 OLT	Aripiprazole: 15 mg/d Rispéridone: 3 mg/d	FLUO (60 mg/d) PARO (60 mg/d) SERT (200 mg/d)	8 patients (50%) responders with aripiprazole 13 patients (72,2%) responders with rispéridone t(32) = 2,630, p<0,05

N: Number of randomized patients, RCT: randomized controlled trial, OLT: open label trial, CR: case report, CITA (citalopram), CLOM (clomipramine), FLUO (fluoxetine), FLUV (fluvoxamine), IMIP (imipramine), PARO (paroxetine), SERT (sertraline), VENL (venlafaxine).

Table 1: Clinical trials evaluating the addition of a second-generation antipsychotic treatment to a Serotonin Reuptake Inhibitor (SRI) in patients with resistant Obsessive-Compulsive Disorder (OCD). The response criteria, according to the studies, was defined as a decrease of 25 to 35% of the Y-BOCS score at 6 or 8 weeks.

the treatment of resistant OCD [5,8,30-46]. The designs of these studies are heteregenous as regard the duration of the antipsychotic treatment (8 to 12 weeks), the severity of the patients included (Y-BOCS scores), the response criteria (decrease of 25% or 35% of the Y-BOCS) and 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 3.31; 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 improved by antipsychotic drugs (haloperidol, pimozide, risperidone or olanzapine). Among the 18 patients included, 15 (83.3%) had a recurrence of their OCD (an increase of at least 35% of the Y-BOCS score), and most of the increased symptoms occurred within 8 weeks after treatment discontinuation. This study suggests the need to pursue long term antipsychotic treatment or to program a very progressive withdrawal from the antipsychotics. Therefore it is hypothesized that terminating an anti-dopaminergic medication leads to dopaminergic hyperactivity due to the increase of postsynaptic receptors [50]. This 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

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 recommanded 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, amisulpride, quetiapine or aripiprazole in moderate doses, in addition with SSRIs or as firt-line monotherapy. Further investigations are justified to clearly establish guidelines in this direction. However, further studies are necessary to update these guidelines.

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