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# 8-week, single-blind, randomized trial comparing risperidone versus olanzapine augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive—compulsive disorder

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**Abstract**

The aim of the present pilot study was to investigate in a single-blind manner, over a period of 8 weeks, the comparative efficacy and tolerability of risperidone versus olanzapine addition in the treatment of OCD patients who did not show a ≥35% decrease in the YBOCS score after 16-week SRI treatment (defined as resistant). The study consisted of two different phases: a 16-week open-label prospective phase to ascertain resistance to SRI treatment and an 8-week single-blind addition phase for resistant subjects only. Ninety-six subjects with DSM-IV OCD (YBOCS ≥ 16) entered the open-label prospective phase; at the end of the 16-week period, 50 (52%) were judged to be resistant and were randomized to receive risperidone (1 to 3 mg/d) or olanzapine (2.5 to 10 mg/d) addition for 8 weeks. Overall, patients in both groups responded significantly, without differences between the two treatment groups; although no differences emerged for the proportion of patients reporting at least an adverse event, the profiles of adverse experiences differed significantly, being risperidone associated with amenorrhoea and olanzapine with weight gain.


## 1. Introduction

Obsessive–compulsive disorder (OCD) has been considered for many decades a chronic, poorly responsive disorder until the introduction of Serotonin Reuptake Inhibitors (SRIs) and behavioural techniques changed dramatically its prognosis; nevertheless, many patients either do not respond to treatments, or their response is incomplete and unsatisfactory. Although the proportion of patients who may be considered treatment-resistant or intolerant is difficult to define, it may be approximately estimated to be between 40 and 50% after an adequate drug treatment trial. Moreover, even those patients who are judged to be clinical responders based on stringent response criteria (i.e., typically a greater than 25

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or 35% decline in the Yale–Brown Obsessive Compulsive Scale—YBOCS-total score) often continue to experience a significant impairment from their residual OCD symptoms (Albert et al., 2002a,b; Maina et al., 2005a,b; Denys, 2006).

This consideration prompted researchers to investigate, in recent years, pharmacological strategies for resistant patients. One of the most studied and promising treatment is, to date, low-dose antipsychotic augmentation (Maina et al., 2005b): first generation antipsychotics such as haloperidol and pimozide showed efficacy as augmentation treatments in open-label (pimozide) and double-blind studies (haloperidol)(Delgado et al, 1990; McDougle et al, 1990; McDougle et al, 1994), although concerns exist about their side effects profile. Second generation antipsychotics proved to be effective in open-label and several double-blind studies (McDougle et al, 2000; Bystritsky et al, 2004; Denys et al, 2004; Erzegovesi et al, 2005), although negative double-blind studies also exist for risperidone (Hollander et al., 2003), olanzapine (Shapira et al., 2004) and quetiapine (Fineberg et al, 2005; Carey et al, 2005). It has to be pointed out, however, that in the negative risperidone study (Hollander et al., 2003) there was a response rate of 40% with risperidone and 0% with placebo and that the failure to demonstrate a significant difference in terms of responder rates was due to the limited sample size of the trial (16 patients only). The negative olanzapine trial (Shapira et al., 2004) might have been biased by the fact that patients were randomized to olanzapine or placebo after only 8 weeks on SRI; this could have accounted for the high placebo responder rate found in that study (41%). The interpretation of results of one of the quetiapine negative study (Fineberg et al., 2005) needs also some clarifications: in that study 27.3% of quetiapine-treated patients responded compared to 10% of those given placebo and this difference did not reach statistical significance. These negative results may be explained by considering the longer duration of the study (16 weeks of augmentation, which might have given a higher placebo response rate due to more time spent on the SRI alone); another possible explanation (apparently in contradiction with the previous) is the longer duration of SRI treatment before enrolment in the double-blind phase (6 months); this might have selected a group of highly resistant subjects and lowered the response rate to quetiapine addition (27.3%, slightly lower than those reported in other quetiapine studies).

Recent meta-analyses of the randomized trials supported the use of antipsychotic augmentation as a promising strategy for treatment-resistant OCD patients, although pointed towards the need for more and larger trials, as differences might exist between different antipsychotics (Bloch et al., 2006; Ipser et al., 2006; Skapinakis et al., 2007): Bloch et al. (2006), for example, concluded that there is sufficient evidence demonstrating the efficacy of haloperidol and risperidone, while the evidence regarding the efficacy of quetiapine and olanzapine is inconclusive. A recent pooled analysis (Denys et al., 2007) and another recent meta-analysis (Fineberg et al., 2006) of existing double-blind randomized placebo-controlled studies looking at the addition of quetiapine in resistant OCD cases, however, showed evidence of efficacy of this second generation antipsychotic in resistant patients.

The heterogeneity of the studies evaluating the efficacy of antipsychotic augmentation may explain some observed differences in the response rates: differences in entry criteria or designs of the studies, in fact (e.g. length of prior ineffective SRI trial—8 vs. 12 weeks, severity of patients included in terms of YBOCS scores or comorbid conditions, tapering schedules for reaching the minimal effective dose of the antipsychotic) might have accounted for higher or lower response rates in different studies. For this reason, comparison between pharmacological agents across different placebo-controlled studies might be erroneous and head-to-head trials between antipsychotic augmentation agents are needed to show whether all antipsychotic agents are equally effective. However, there is, to date, only one randomized, double-blind, placebo-controlled crossover study that compares the efficacy of the addition of two different antipsychotics to SRIs treatment in resistant OCD (Li et al, 2005). Sixteen patients were randomly assigned to receive 2 weeks of placebo, risperidone (1 mg/d), or haloperidol (2 mg/d) after a 1-week single-blind period. The patients received the 3 treatments in different sequences in a crossover fashion with a 1-week placebo washout period between each treatment. In the completer analysis, both risperidone and haloperidol reduced YBOCS obsession scores compared with placebo. Haloperidol decreased total YBOCS score relative to placebo, but risperidone did not (only approached significance); the difference between risperidone and haloperidol was, however, not significant. This study suggests that differences might exist between different antipsychotics, although conclusions are biased by the small sample size (which limits the statistical power of the study), the crossover design and the short duration of each treatment.

To our knowledge there are no published studies comparing two different second generation antipsychotics as augmenting agents in treatment-resistant OCD. The aim of the present pilot study was to investigate in a single-blind manner, over a period of 8 weeks, the comparative efficacy and tolerability of risperidone versus olanzapine as augmenting agents in the treatment of resistant OCD patients.

## 2. Experimental procedures

### 2.1. Patients

Participants were male or female outpatients, aged 18 years or older, who met DSM-IV criteria for a primary diagnosis of OCD. All patients' diagnoses were assessed by means of the Structured Clinical Interview for DSM-IV criteria (SCID)(Spitzer et al., 1995). Other inclusion criteria were as follows:

1) obsessive–compulsive symptoms had to have been present for at least 1 year prior to study entry.
2) patients had to have a YBOCS total score $\geq$16.

A current diagnosis of major depressive disorder and/or a HAM-D score of 15 or greater, a present or previous diagnosis of schizophrenia or other psychotic disorder, or an organic brain syndrome or medical illness that would contra-indicate the use of SRI and/or risperidone or olanzapine excluded potential subjects from the study. Pregnant or nursing women and women of childbearing potential not using adequate contraceptive measures were also excluded.