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BRIEF REPORT

Risperidone augmentation in treatment-resistant obsessive–compulsive disorder: a double-blind, placebo-controlled study

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Abstract

This double-blind, placebo-controlled trial was performed to determine the efficacy and tolerability of 8 wk of risperidone augmentation of serotonin reuptake inhibitor (SRI) treatment in adult subjects with treatment-resistant obsessive–compulsive disorder (OCD) (failure of at least two SRI trials). Sixteen adult treatment-resistant OCD patients were randomly assigned to augmentation with 8 wk of either risperidone ($n=10$) (0.5–3.0 mg/d) or placebo ($n=6$) following at least 12 wk of SRI treatment. Four patients on risperidone (40%) and none (0%) on placebo were responders with both a Clinical Global Impression – Improvement (CGI-I) score of 1 or 2 and a Yale–Brown Obsessive–Compulsive Scale (Y-BOCS) decrease $\geqslant$25%. Risperidone was generally well tolerated: there were 3 dropouts, 1 on risperidone and 2 on placebo. Better Y-BOCS insight score at baseline significantly correlated with a greater CGI-I score at endpoint on risperidone augmentation. Risperidone may be an effective and well-tolerated augmentation strategy in treatment-resistant OCD subjects, but larger sample size studies are required to demonstrate this.

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Introduction

The addition of typical and atypical antipsychotics in patients with obsessive–compulsive disorder (OCD) resistant to serotonin reuptake inhibitors (SRIs) has been proposed as a useful augmentation strategy (Koran et al., 2000; McDougle, 1997; McDougle et al., 1994; Mohr et al., 2002; Ramasubbu et al., 2000; Stein and Hollander 1992). However, the more favourable side-effects profile of the atypical antipsychotics and their broader clinical coverage (i.e. tic-related and non-tic-related) have suggested their first-line choice in treatment-resistant OCD patients.

Risperidone augmentation has been shown to be effective in some treatment-resistant OCD patients. In a trial by McDougle et al. (2000), treatment response to risperidone augmentation was unrelated to plasma levels of risperidone or SRIs, or to the presence of comorbid tic disorder or schizotypal personality disorder. However, subjects who had failed two or more trials prior to the addition of risperidone were much less likely to respond to risperidone augmentation than those who had failed only one trial. No other clinical feature predicted response to risperidone augmentation. While generally well-tolerated in this patient group, adverse events during risperidone augmentation included akathisia and extrapyramidal symptoms (EPS) in some, but not all, studies, especially at doses above 2 mg/d (Pfanner et al., 2000; Saxena et al., 1996). Poor insight may be a predictor of poor response to many (Catapano et al., 2001; Erzegovesi et al., 2001; Hantouche et al., 2000) but not all SRIs (Eisen et al., 2001), although its value as a predictor of response to risperidone augmentation has not been systematically studied.

We conducted an 8-wk randomized, double-blind, parallel design study of risperidone vs. placebo augmentation of SRIs in patients with treatment-resistant OCD, testing two hypotheses: (1) risperidone will be more effective than placebo augmentation of SRIs in treatment-resistant OCD patients (failure of at least

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two SRI trials), and (2) risperidone will not differ from placebo in dropout rates due to adverse events. In addition, we hypothesize that the degree of insight will be predictive of response to risperidone augmentation.

Methods

Sixteen outpatients with treatment-resistant OCD were enrolled in a randomized, double-blind, parallel design study approved by the Institutional Review Board (IRB) of Mt. Sinai School of Medicine. All subjects suffered from DSM-IV OCD for at least 2 yr, and for each subject, OCD was the predominant clinical problem, causing the most distress and dysfunction, via Structured Clinical Interview for DSM-IV Diagnosis (SCID). No subjects suffered from major medical illness or past or present schizophrenia, schizoaffective disorder, or bipolar disorder.

Subjects were treatment-resistant, defined as non-response [Clinical Global Impression – Improvement (CGI-I) score of 3, minimally improved, or worse] to at least two SRI trials (including venlafaxine) of adequate dose and duration. In order to be eligible for the present study, subjects were required to be currently taking SRI medication for at least 12 wk at a minimum daily dose of 125 mg clomipramine, 40 mg fluoxetine, 150 mg fluvoxamine, 100 mg sertraline, 30 mg paroxetine, 40 mg citalopram or 150 mg venlafaxine. However, 15 of the 16 subjects were taking a daily dose greater than the minimum required. The actual minimum daily doses in the 16 subjects were 200 mg clomipramine, 60 mg fluoxetine, 150 mg fluvoxamine, 150 mg sertraline, 60 mg citalopram, and 325 mg venlafaxine. None of the subjects were taking paroxetine at the time of augmentation.

Ten subjects were randomized to risperidone augmentation for the 8-wk trial: 6 males and 4 females; mean age 36.8 yr ($\pm$10.4 yr); mean duration of OCD 19.3$\pm$12.4 yr; mean baseline CGI – Severity (CGI-S) score of 5.33 ($\pm$0.87); mean baseline Global Assessment of Functioning (GAF) (SCID) score of 50.89 ($\pm$8.37); mean baseline total Hamilton Depression 17-item score of 12.50 ($\pm$9.59); mean baseline Y-BOCS total score of 29.20 ($\pm$5.73), with a mean baseline Y-BOCS obsession score of 15.20 ($\pm$2.57) and compulsion score of 14.00 ($\pm$3.86). Eight out of 10 patients had a family history of psychiatric illness determined by the intake interview (3 OCD, 4 mood disorders, 1 psychotic disorder); 4 out of 10 had lifetime (not current) alcohol abuse on SCID; current health status of each patient was determined through clinical medical and neurological visit, general blood examination comprehensive of red and white cell assessment, liver, kidney and thyroid parameters, electrolytes; 6 out of 10 had previously undergone cognitive behavioural therapy (CBT). No other drug or non-drug treatment was allowed during the trial.

Six patients were randomized to placebo augmentation: 3 males and 3 females; mean age 43.2$\pm$15.8 yr; mean OCD duration 26.0$\pm$21.1 yr; mean baseline CGI-S score of 5.50 ($\pm$0.84); mean baseline GAF (SCID) score of 48.25 ($\pm$9.95); mean baseline total Hamilton Depression 17-item score of 20.33 ($\pm$10.86); mean baseline Y-BOCS total score of 29.33 ($\pm$2.80), with a mean baseline Y-BOCS obsession score of 15.17 ($\pm$2.32) and compulsion score of 14.17 ($\pm$1.17). Four out of 6 patients had a positive family psychiatric history (2 OCD, 2 mood disorders); 2 out of 6 had respectively lifetime (not current) alcohol and cannabis abuse; 4 out of 6 had previously received CBT.

Risperidone or matched placebo tablets were initiated at 0.5 mg/d and gradually increased by 0.5 mg every 7 d over the first 6 wk until patients either reached the maximum dose of 3 mg/d, or experienced therapeutic effects or side-effects. Although raters were blind to drug condition but not to side-effects status, side-effects of mild severity were experienced in approx. one-third of patients treated with both risperidone and placebo, and dosage was adjusted accordingly in both groups. Patients were rated by a psychiatrist specializing in the treatment of OCD at baseline and every 2 wk over the course of the study on severity of obsessive–compulsive symptoms (10-item Y-BOCS), obsession and compulsion-related insight (item 11 of Y-BOCS) (Goodman et al., 1989a,b), and depression severity (Hamilton Depression Rating Scale) (HDRS; Hamilton, 1960). Subjects were rated as responders or non-responders to risperidone or placebo augmentation based on a 25% reduction in the total Y-BOCS score and CGI-I score of 1 (very much improved) or 2 (much improved).

Group differences were examined using Fisher's exact test for dichotomous variables (due to small sample sizes) and *t* test for continuous variables. Analyses were performed on an intent-to-treat basis with the last observation carried forward. Repeated-measures analyses of variance (MANOVA) creating simple contrast with baseline values were used to assess mean Y-BOCS total and HDRS change from baseline. All significance tests were performed at an α-level of 0.05.

Results

Four (40%) out of 10 risperidone-treated patients responded according to the a-priori criteria (CGI-I of 1 or 2 plus $\geqslant$25% reduction from baseline on Y-BOCS total

Table 1. Baseline and endpoint severity information

	Risperidone ($n=10$)	Placebo ($n=6$)	p
Baseline Y-BOCS			
Total	29.20 ($\pm$5.73)	29.33 ($\pm$2.80)	ns
Obsession	15.20 ($\pm$2.57)	15.17 ($\pm$2.32)	ns
Compulsion	14.00 ($\pm$3.86)	14.17 ($\pm$1.17)	ns
Insight	2.00 ($\pm$0.94)	2.33 ($\pm$0.52)	ns
Baseline CGI (severity of illness)	5.33 ($\pm$0.87)	5.50 ($\pm$0.84)	ns
Baseline HDRS total	12.50 ($\pm$9.59)	20.33 ($\pm$10.86)	ns
Baseline GAF (SCID)	50.89 ($\pm$8.37)	48.25 ($\pm$9.95)	ns
Mean endpoint dose risperidone/placebo (mg/d)	2.25 ($\pm$0.86)	2.75 ($\pm$0.50)	ns
Completers/dropouts	9/1	4/2	ns
Responders/non-responders[a]	4/6	0/6	ns
Baseline Y-BOCS total	29.20$\pm$5.73	29.33$\pm$2.80	ns
Endpoint Y-BOCS total	23.10$\pm$8.33	28.00$\pm$7.31	ns
Mean Y-BOCS total reduction	6.10 ($\pm$8.18)	1.33 ($\pm$3.14)	ns
Mean Y-BOCS total % reduction	19.04 ($\pm$29.07)	4.62 ($\pm$9.97)	ns

[a] Response = CGI-I score of 1 or 2 plus Y-BOCS total $\geqslant$25% reduction.
ns, Non-significant difference.

score), while none of the 6 placebo-treated patients were categorized as responders. The results did not achieve statistical significance ($p=0.115$), but were limited by the small sample size (Table 1). Results were similar looking at Y-BOCS obsession and compulsion subscores separately. Four patients on risperidone had $\geqslant$25% reduction on Y-BOCS compulsion score vs. none on placebo, and 3 on risperidone had $\geqslant$25% reduction on Y-BOCS obsession score vs. none on placebo.

Augmentation dosage equivalents did not significantly differ between risperidone (2.25$\pm$0.86 mg/d) and placebo (2.75$\pm$0.50 mg equiv./d) groups, as well as between risperidone responders and non-responders (2.25$\pm$0.96 and 2.25$\pm$0.88 mg/d). All 3 subjects currently on fluvoxamine in the risperidone group (2 on a daily dose of 250 mg, 1 on a daily dose of 300 mg) were responders. One of the 3 subjects currently on fluoxetine in the risperidone group (daily dose of 60 mg) was a responder, while the 2 remaining subjects (daily doses of 80 mg) were non-responders to risperidone augmentation. Of the remaining non-responders to risperidone augmentation, 2 were on clomipramine (200, 250 mg), 1 was on citalopram (80 mg), and 1 was on sertraline (150 mg).

Mean total Y-BOCS scores decreased from 29.20$\pm$5.73 to 23.10$\pm$8.33 (19.04% reduction) on risperidone, although this did not significantly differ from placebo, where total Y-BOCS scores decreased from 29.33$\pm$2.80 to 28.00$\pm$7.31 (4.62% reduction) ($t=1.35$; d.f. = 14; $p=0.198$). Change in total HDRS scores did not significantly differ on risperidone vs. placebo ($t=0.76$; d.f. = 14; $p=0.461$).

There were 3 dropouts in the study: 1 on risperidone (week 3) and 2 on placebo (weeks 6 and 7), all due to unsatisfactory clinical response. Risperidone augmentation was generally well-tolerated, although 4 out of 10 risperidone-treated patients experienced at least one side-effect, including sedation ($n=3$), dizziness ($n=1$), and dry mouth ($n=2$). Two out of 6 patients receiving placebo experienced side-effects (dry mouth and sexual dysfunction). No changes were noted in blood pressure or heart rate, and no EPS were reported or observed.

No difference was found in mean change of the OCD insight score (Y-BOCS item 11) from baseline to endpoint between risperidone (0.40$\pm$0.52) and placebo (0.33$\pm$0.52) ($t=0.25$; d.f. = 14; $p=0.806$). However, the 4 subjects who responded to risperidone augmentation all had 'good' baseline insight scores (mean 1.00$\pm$0.00), while the 6 subjects who did not respond had poorer baseline insight scores (mean 2.67$\pm$0.52) ($t=6.33$; d.f. = 8; $p<0.001$). There was a significant positive correlation between baseline Y-BOCS insight score (higher scores indicating lower insight) and CGI-I at week 8 (higher scores indicating poorer outcome) in the risperidone-treated group ($r=0.727$, $n=10$, $p=0.017$), but not in the placebo group ($r=0.0$, $n=6$, $p=1.0$).

Discussion

In this study, 40% (4/10) of SRI-resistant OCD patients responded to risperidone augmentation and 0% (0/6) to placebo. While promising, the findings did not reach statistical significance due to the small sample size. The response rate found in the present study (40% on risperidone vs. 0% on placebo) is consistent with the previous literature suggesting that approx. 30–50% of OCD patients resistant to treatment with SRIs may respond to augmentation with an atypical antipsychotic (Koran et al., 2000; McDougle et al., 2000; Mohr et al., 2002) compared to 0% with placebo augmentation (McDougle et al., 2000).

Risperidone was well tolerated in this augmentation trial, and there was no significant difference in dropout rates due to adverse events with risperidone augmentation vs. placebo. Follow-up of the 4 responder subjects after an additional 3 months demonstrated maintenance of clinical improvement and no additional EPS or reported weight gain side-effects on a mean daily risperidone dosage of 2.6 ± 0.4 mg/d.

Better OCD-related insight at baseline significantly correlated with greater CGI-I at endpoint on risperidone. Several studies have demonstrated the predictive value of insight to SRI response (Catapano et al., 2001; Erzegovesi et al., 2001; Hantouche et al., 2000), but this is the first controlled study to report that insight in treatment-resistant OCD patients may have predictive value for risperidone augmentation response. The finding that better insight in OCD at baseline was correlated with better risperidone outcome at week 8 was counter-intuitive for response to an 'antipsychotic' medication, but consistent with the more ill patients doing less well with treatment. However, it is important to note that in the present study insight was measured by one single item on the Y-BOCS (item 11). Future studies should assess the relationship between degree of insight and augmentation response using a specific rating scale for insight, such as the Brown Assessment of Beliefs Scale (BABS), and should clarify whether 'insight' can be considered to be a clinical symptom of OCD, or can be linked to a neuropsychological substrate identified by functional imaging studies. Perhaps, patients with better insight had lower striatal activity on FDG–PET at baseline, which was associated with more robust response to risperidone augmentation (Buchsbaum et al., unpublished observations).

The lack of information regarding previous CBT trials is a limitation of the present study. Both risperidone and placebo groups had similar rates of previous CBT: 6 out of 10 (60%) in the risperidone group, 4 out of 6 (66%) in the placebo group. Unfortunately, systematic data with regards to length of the CBT trial and whether or not there was transient response to CBT was not elicited. Future augmentation trials should examine the relationship between CBT non-response or short-term response and response to augmentation with an atypical antipsychotic.

The small group size represents a major limitation of this study. Based on the response rate for this study, there is an effect size of $w = 0.88$ for Pearson χ^2 test (Cohen, 1988). With this very large effect size, we would have a power of 0.99 with a total sample of 25.

This study was also limited by a short trial duration. Controlled studies in larger samples are needed to replicate these preliminary findings to confirm tolerability over long-term treatment. Further, optimal duration of risperidone augmentation needs to be established, as well as how and when this treatment can be discontinued without the risk of OCD relapse.

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