Risperidone and Haloperidol Augmentation of Serotonin Reuptake Inhibitors in Refractory Obsessive-Compulsive Disorder: A Crossover Study

Xiaohua Li, M.D., Ph.D.; Roberta S. May, M.A.; Lelland C. Tolbert, Ph.D.; Warren T. Jackson, Ph.D.; James M. Flournoy, Jr., Ph.D.; and Lewis R. Baxter, Jr., M.D.

Background: Although serotonin reuptake inhibitors (SRIs) are the first-line treatment for obsessive-compulsive disorder (OCD), approximately half of patients with OCD do not respond adequately to SRI monotherapy. Patients with predominant obsessions are common in OCD and are often difficult to treat, necessitating adjunctive treatment.

Method: This was a 9-week, double-blind, placebo-controlled, crossover study comparing the benefits of 2-week adjunctive treatments with risperidone, haloperidol, and placebo in patients with OCD (DSM-IV criteria) who continued to have severe symptoms despite taking a stable dose of an SRI. Eligible patients must have been receiving a therapeutic dose of an SRI for at least 12 weeks and at the screening visit had a score ≥ 10 on items 1–5 (obsession) and a total score ≥ 16 on the Yale-Brown Obsessive Compulsive Scale (YBOCS). Data were collected from January 1999 through April 2002.

Results: Sixteen patients were enrolled and 12 completed the study. On the YBOCS, both risperidone and haloperidol significantly reduced obsession ($p < .05$) when compared with placebo. There was a tendency that haloperidol, and to a lesser degree risperidone, also reduced the compulsion and the total YBOCS scores. These results were accompanied by a reduction in the Hopkins Symptom Checklist 90-revised (SCL-90R) anxiety scale score. According to the 17-item Hamilton Rating Scale for Depression, the SCL-90R depression scale, and the Profile of Mood States, risperidone, but not haloperidol, also improved depressed mood. Neither risperidone nor haloperidol changed neurocognitive function during the 2-week treatment. All 12 patients completed the 2-week risperidone treatment, but 5 of the 12 terminated haloperidol treatment early owing to intolerable side effects.

Conclusion: Adjunctive risperidone improved obsessions and depressed mood and was well tolerated in patients with SRI-refractory OCD.

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Corresponding author and reprints: Xiaohua Li, M.D., Ph.D., UAB-Psychiatry, 213 Smolian, 1700 7th Avenue South, Birmingham, AL 35294 (e-mail: xili@uab.edu).

Obsessive-compulsive disorder (OCD) is a common psychiatric disorder, with a lifetime prevalence of 2.5%.[1] It is characterized by recurrent obsessions or compulsions that are time-consuming, associated with distress or impairment, and viewed by patients as unreasonable. More than 90% of patients with OCD have both obsessions and compulsions, although about 30% claim to be troubled mainly by obsessions, 20% by compulsions, and 50% equally by both.[2] Many patients with predominant obsessions have intrusive and frightening thoughts related to aggression, sexuality, and unacceptable urges. Patients with OCD may have a poor prognosis, with severely impaired interpersonal relationships and limited vocational attainment.[3] OCD is often comorbid with depression, anxiety, tics, and symptoms of other psychiatric disorders.[4]

In the last 2 decades, pharmacologic and behavioral treatments have improved the prognosis in OCD.[4] Clomipramine, a potent serotonin reuptake inhibitor (SRI) with weaker norepinephrine reuptake blockade, showed excellent efficacy for OCD in many clinical trials carried out in the 1980s and early 1990s.[4] Today, SRIs given at moderate-to-high doses are the first-line agents for the treatment of OCD.[5,6]

Because 40% to 60% of patients with OCD do not respond adequately to SRI monotherapy, adjunctive treatment with another agent is common.[7] Many agents, including buspirone, clonazepam, clonidine, inositol, lith-

ium, l-tryptophan, monoamine oxidase inhibitors, and trazodone, have shown little or inconsistent benefit in SRI augmentation or have the potential to cause serious adverse effects when given with an SRI.[5,8] Previously, the conventional antipsychotics were used as adjunctive treatment in severe OCD patients, especially those with comorbid psychiatric conditions. McDougle et al.[9] reported that haloperidol could be used to augment the effect of fluvoxamine in OCD patients, especially for those with motor tics or other signs of Tourette's syndrome.

Given the superior safety and tolerability of the atypical antipsychotics, it is not surprising that they have been used in many SRI augmentation studies. In 3 case series[10–12] and 1 open-label study,[13] 46 patients with refractory OCD and various psychiatric comorbidities received adjunctive risperidone at doses of 0.5 to 8 mg/day; most patients (N = 29; 63.0%) were classified as responders, and many experienced improved OCD symptoms. Only 6 (13.0%) of 46 patients discontinued risperidone because of adverse events.[12,13] In the series of 21 patients described by Saxena et al.,[12] the 5 patients with a history of obsession accompanied by horrific mental imagery experienced the strongest and fastest response to risperidone. The 5 patients with a history of tic disorders were the least likely to respond and the most likely to experience adverse events, especially akathisia.[12] Olanzapine augmentation has also been reported to benefit patients with treatment-resistant OCD, irrespective of OCD subtypes or psychiatric comorbidities.[14–17] The effects of adjunctive quetiapine have also been assessed, [18–20] and patients with various OCD symptoms and psychiatric comorbidities responded to quetiapine treatment in these studies.

These early investigations helped to dispel concerns arising from studies of conventional antipsychotics that augmentation would benefit only a subset (those with motor tics or a family history of Tourette's syndrome) of treatment-resistant patients.[9,21] They also helped allay fears, based on the experience of patients with schizophrenia and obsessive-compulsive symptoms,[22,23] that antipsychotics would exacerbate rather than improve symptoms in patients with OCD.

The primary objective of this study was to determine whether patients with treatment-refractory OCD would derive more clinical benefit from risperidone than from placebo or the conventional antipsychotic haloperidol. The study was also designed to assess whether risperidone or haloperidol changed other comorbid symptoms and cognitive function and whether the subjects could better tolerate risperidone or haloperidol.

METHOD

This was a 9-week, double-blind, placebo-controlled, crossover study. Patients who had been diagnosed with OCD and had continued to have severe symptoms while being maintained on a stable dose of an SRI received crossover adjunctive treatment with placebo, risperidone, and haloperidol in a counterbalanced order. The study was approved by the University of Alabama at Birmingham Institutional Review Board. Consent information was discussed thoroughly with the participants, and their signatures were obtained on an approved consent form before further evaluation was conducted. Data were collected from January 1999 through April 2002.

Participants

Seven men and 9 women aged 19 to 56 years with a primary diagnosis of OCD according to DSM-IV[24] criteria were enrolled in the psychiatric outpatient research clinic at the University of Alabama at Birmingham. At screening, eligible patients had been receiving a therapeutic dose of an SRI (≥ 40 mg/day of fluoxetine or paroxetine, ≥ 200 mg/day of fluvoxamine, or ≥ 100 mg/day of sertraline) for at least 12 weeks. The 12-week duration of SRI pretreatment was decided upon, because an adequate response to a therapeutic dose of SRI usually takes 4 to 6 weeks, and an additional 6 to 8 weeks of treatment ensures the therapeutic effect of an SRI. All potential subjects were administered the Yale-Brown Obsessive Compulsive Scale (YBOCS),[25,26] on which a score ≥ 10 on items 1 to 5 (obsession) and a total score ≥ 16 were required for acceptance into the study. Enrolled participants also had scores < 16 on the 17-item Hamilton Rating Scale for Depression (HAM-D-17).[27]

Subjects were excluded if they concomitantly met criteria for any other Axis I diagnosis of the DSM-IV and the Schedule for Affective Disorders and Schizophrenia-lifetime version (SADS-L).[28] Subjects were also excluded if they had a history of major motor or vocal tics or if these were evident at screening.

Medications

Throughout the 9-week trial, subjects continued to take the same SRI at the same dose they were receiving at the time of screening. After a 1-week, single-blind placebo period, each subject was randomly assigned to receive 2 weeks of placebo, risperidone (1 mg/day), or haloperidol (2 mg/day) in a crossover fashion, with a 1-week placebo washout between each treatment. The subjects received the 3 treatments in different sequences, as shown in Table 1. They were instructed to take the study medication at bedtime. If they experienced intolerable side effects while receiving one of the study medications, subjects were permitted to discontinue treatment with that agent but were allowed to remain in the trial. Concomitant medications were not permitted during the study period except for emergency relief of intolerable side effects, such as benztropine for acute dystonia. The subjects were not instructed in formal behavior therapy techniques during the trial.

Table 1. Demographic Characteristics of Treatment-Refractory OCD Patients and Medication Distribution of Adjunctive Risperidone, Haloperidol, and Placebo in a Crossover Study

Patient No.	Race	Sex	Age, y	Week 1	2	3	4	5	6	7	8	9
1	White	Male	19	P	H	H	P	R	R	P	P	P
2	White	Female	36	P	P	P	P	R	R	P	H	H
3	Black	Female	42	P	R	R	P	H	H	P	P	P
4	White	Male	36	P	P	P	P	H	H	P	R	R
5	White	Male	36	P	H	H	P	P	P	P	R	R
6	White	Female	26	P	R	R	P	P	P	P	H	H
7	White	Female	34	P	R[a]	R[a]	P[a]	P[a]	P[a]	P[a]	H[a]	H[a]
8	White	Male	26	P	H	H	P	R	R	P	P	P
9	White	Female	44	P	P	P	P	H	H	P	R	R
10	White	Female	37	P	P	P	P[a]	R[a]	R[a]	P[a]	H[a]	H[a]
11	White	Female	48	P	H	H	P	P	P	P	R	R
12	White	Male	28	P	R[a]	R[a]	P[a]	H[a]	H[a]	P[a]	P[a]	P[a]
13	White	Male	24	P	H	H	P	R	R	P	P	P
14	White	Female	20	P	P[a]	P[a]	P[a]	R[a]	R[a]	P[a]	H[a]	H[a]
15	White	Female	26	P	R	R	P	H	H	P	P	P
16	White	Male	56	P	P	P	P	H	H	P	R	R

[a]No medication was administered due to patient dropout.
Abbreviations: H = haloperidol, OCD = obsessive-compulsive disorder, P = placebo, R = risperidone.

Assessments

Psychiatric and medical histories were taken at the screening visit, and each subject received a formal evaluation with the SADS-L. A physical examination, including a neurologic examination, was conducted at the screening visit, and vital signs were measured at screening and at each visit. Laboratory tests at screening included a urine drug screen for each subject and a urine pregnancy test for each female participant.

At screening and at the end of each week, treatment efficacy was assessed using several clinician-administered measures including the YBOCS and the HAM-D-17. During each visit, participants also completed 2 self-report measures, the Hopkins Symptom Checklist 90-revised (SCL-90R)[29] and the Profile of Mood States (POMS).[30] On the SCL-90R, responses were assessed on the domains of somatization, obsession-compulsion, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoia, and psychoticism. The mood states in the POMS were categorized into the standard domains of tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. A total mood disturbance score was calculated by summing the raw scores for each mood domain and then subtracting the raw score of the vigor-activity domain. Additionally at each visit, the investigator recorded adverse events, and the Abnormal Involuntary Movement Scale (AIMS)[31] and Simpson-Angus Scale (SAS)[32] were used to evaluate abnormal movements.

At the screening visit, the intellectual functioning of each subject was assessed using the Barona Estimate of Premorbid Intelligence.[33] A battery of neuropsychological tests was performed at the end of each washout period and at the conclusion of the second week of each of the 3 treatment periods. These tests included the Stroop Neuropsychological Screening Test (SNST),[34,35] the Hopkins Verbal Learning Test-revised (HVLT-R),[36,37] and the Conners' Continuous Performance Test (CPT).[38,39]

Data Analysis

Our a priori hypotheses were that risperidone would be better than placebo in reducing obsessions and improving the patients' sense of well-being and would be better tolerated than haloperidol.

Data analysis, tabulation of descriptive statistics, and calculation of inferential statistics were performed using Microsoft Excel and the SAS (release 8.2) for Windows. The analyzed data set consisted of 12 OCD patients who received 3 treatments in a randomly assigned sequence over 9 consecutive weeks.

Each of 20 efficacy variables was analyzed as the dependent variable in statistical models: 3 YBOCS variables (obsession, compulsion, and total score), 9 SCL-90R variables (somatization, obsession-compulsion, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoia, and psychoticism), 7 POMS variables (tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, confusion-bewilderment, and total mood disturbance scores), and HAM-D-17 score. The independent variables included the screening value of the dependent variable, treatment group (placebo, risperidone, or haloperidol), period (weeks 1–3, weeks 4–6, or weeks 7–9), time (week within period), sequence (which of the 6 possible treatment sequences the patient received), and carryover effect (treatment in the previous period).

A mixed-effects model was used to evaluate each dependent variable. The fixed-effect factors included screening value, treatment, period, time, sequence, interaction of treatment-by-time, interaction of period-by-

time, and interaction of sequence-by-time. The random factor in the model was patient, with the assumption that the patient random effect and the residual error random effect were uncorrelated (a "variance components" covariance structure). Pairwise comparisons between treatments were performed based on least squares mean estimates from the model. Pairwise comparisons between treatments were only performed if the overall treatment p value was statistically significant ($p \leq .05$).

In addition, a second model was fit, including all the same assumptions and model terms as well as carryover and the carryover-by-time interaction.

RESULTS

Of the 27 screened subjects, 16 met the criteria for inclusion and 12 completed the study. Table 1 summarizes demographic variables and the distribution of study medication. The mean ± SD age of the subjects was 33.6 ± 10.4 years, ranging from 19 to 56 years. The subjects had experienced obsessive-compulsive symptoms for a mean of 9 years and had completed a mean of 4 medication trials for these symptoms. Four of the 16 subjects (patients 7, 10, 12, and 14) discontinued the study prematurely with less than 3 weeks' participation. All 4 discontinued voluntarily, of which 3 received only the first week of placebo, and none discontinued due to the lack of efficacy of their treatment or reported intolerance to the study medications. The 12 study completers were assessed for treatment efficacy weekly. Five participants terminated the haloperidol phase before completion of week 2 treatment owing to dystonia or severe lethargy; however, these subjects were able to complete the other 2 phases of the study. In these cases, data from the week 2 haloperidol treatment were collected within 1 to 2 days of haloperidol discontinuation.

Obsessive-Compulsive and Anxiety Symptoms

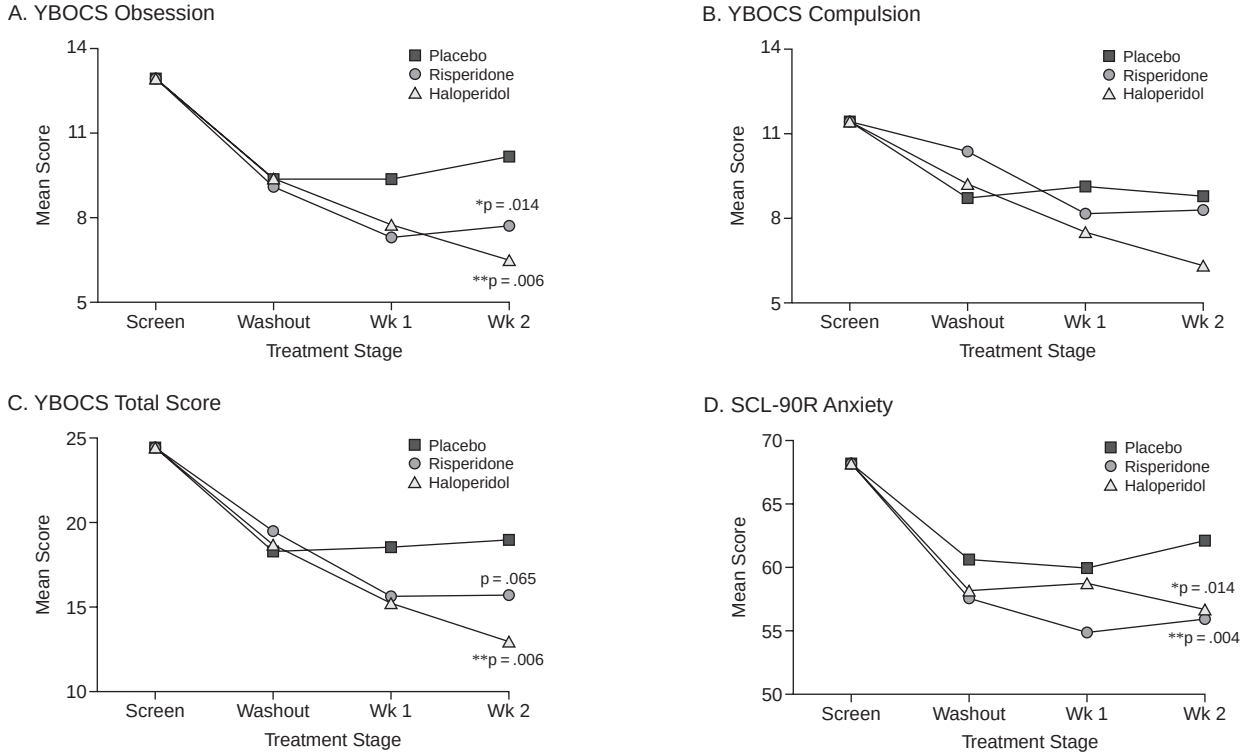
At screening, the mean ± SD obsession score on the YBOCS was 13.00 ± 1.60, the compulsion score was 11.42 ± 3.26, and the mean total score was 24.33 ± 4.27. At the end of the washout week, the mean YBOCS scores decreased, a decline that was similar among the 3 washouts from each treatment arm, and none of these scores was significantly different from the scores at screening (by paired t test). Although the placebo effect remained unchanged until the end of week 2 treatment, both risperidone and haloperidol reduced YBOCS scores at the end of week 1 and week 2 treatment, with the effects more prominent on obsession and total scores (Figures 1A–1C). When the YBOCS obsession score was analyzed using the mixed-effects model, the overall treatment effect was statistically significant ($p = .011$), which implies that at least 1 of the 3 treatments is different than the others. Therefore, pairwise comparisons were performed. When compared with placebo (mean ± SE = 9.23 ± 1.07), both risperidone (7.07 ± 1.07) and haloperidol (6.70 ± 1.08) significantly reduced obsession ($p = .014$ and $p = .006$, respectively). Although the overall treatment effect for compulsion was not statistically significant ($p = .059$), there was a tendency that haloperidol (6.64 ± 0.98), and to a lesser degree, risperidone (7.99 ± 0.96), lowered the compulsion score when compared with placebo (8.54 ± 0.96). For the total YBOCS score, the overall treatment effect demonstrated a statistically significant difference ($p = .019$). On the pairwise comparisons, risperidone showed a tendency to decrease the total score, although the difference between risperidone (15.09 ± 1.81) and placebo (17.85 ± 1.81) did not reach statistical significance ($p = .065$). Haloperidol (13.45 ± 1.83) demonstrated a stronger and significant reduction in total YBOCS score relative to placebo ($p = .006$). Not only did risperidone and haloperidol reduce obsession, but also the overall treatment effect on the SCL-90R anxiety scale was significant ($p = .008$), with both risperidone and haloperidol significantly reducing anxiety when compared with placebo ($p = .004$ and $p = .014$, respectively) (Figure 1D). When YBOCS obsession, compulsion, and total scores and SCL-90R anxiety scores were analyzed with the mixed-effect model including a carryover effect, the carryover model terms were not statistically significant.

Mood Symptoms

None of the 12 participants who completed the study met diagnostic criteria (DSM-IV) for a current major depressive episode, and the mean ± SD score on the HAM-D-17 at the screen visit was 10.67 ± 3.39 (Figure 2A). Nevertheless, compared with placebo, HAM-D-17 scores were significantly reduced with risperidone ($p = .012$) and slightly increased with haloperidol, resulting in a statistically significant difference in HAM-D-17 scores between risperidone and haloperidol treatments ($p = .004$). On the self-rated SCL-90R depression scale, the scores of risperidone treatment, but not haloperidol treatment, also separated significantly from the placebo treatment ($p = .013$) (Figure 2B).

Results of the POMS self-rating scale, a sensitive measure of short-term changes in mood and affect during outpatient drug trials,[30] are shown in Figure 3. The mean ± SD total mood disturbance score at the screening visit was 178.25 ± 37.11. The profile is further divided into 6 factors, including 5 negative mood states and 1 positive state (vigor-activity). Compared with placebo treatment, the most prominent effect of risperidone was a significant reduction in depression-dejection scores and anger-hostility scores ($p = .011$ and $p = .022$, respectively) (Figure 3). Haloperidol also significantly reduced anger-hostility scores ($p = .022$), but failed to improve depression-dejection ($p = .053$) and significantly worsened fatigue-inertia when compared with both placebo

Figure 1. The Effects of Risperidone and Haloperidol on OCD Patients as Measured With the YBOCS and the SCL-90R Anxiety Scale in a Crossover Study



*p Value significant at the level of .05 when compared with placebo from the mixed-effects model.
**p Value significant at the level of .01 when compared with placebo from the mixed-effects model.
Abbreviations: OCD = obsessive-compulsive disorder, SCL-90R = Hopkins Symptom Checklist 90-revised, YBOCS = Yale-Brown Obsessive Compulsive Scale.

and risperidone (p = .021 and p = .006, respectively). In addition, risperidone improved vigor-activity and haloperidol reduced it; although neither was significantly different from placebo, the 2 were significantly different from each other (p = .004).

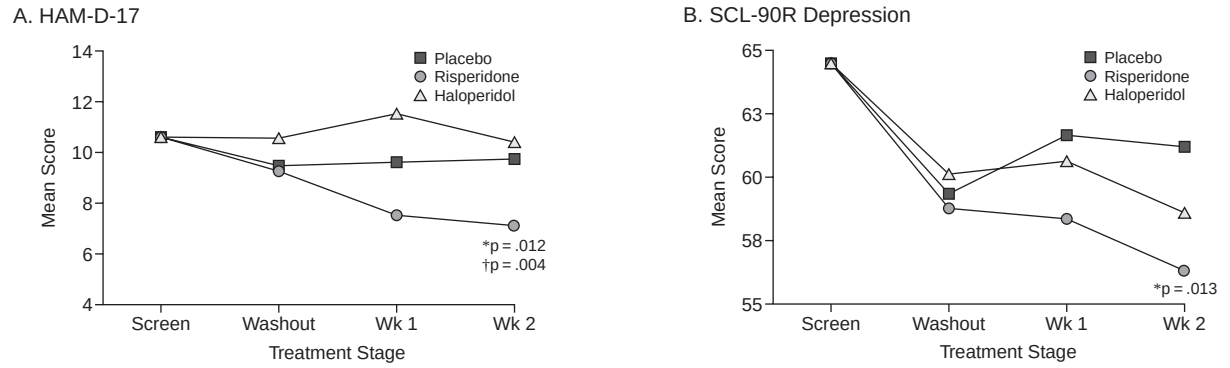
Cognitive Function

Neuropsychological tests were conducted at the end of each washout week and the end of treatment week 2 with each agent. Intellectual functioning (Barona Estimate) at the screen visit was similar among all 16 recruited subjects (including completers and noncompleters), with a mean ± SD full scale IQ score of 108.31 ± 7.71. According to the results of the SNST, HVLT-R, and CPT, neither risperidone nor haloperidol changed cognitive function from baseline, and between-group differences were not significant. For example, data at the end of week 2 treatment showed that the mean ± SD reaction times in the SNST were 103.19 ± 30.77 seconds for placebo, 105.59 ± 26.70 seconds for risperidone, and 109.82 ± 30.24 seconds for haloperidol; the mean ± SD HVLT-R total number of word completion was 28.69 ± 5.79 for placebo, 28.25 ± 4.29 for risperidone, and 29.91 ± 6.09 for haloperidol; and the mean ± SD CPT hit response times were 44.04 ± 15.99 seconds for placebo, 44.90 ± 14.34 seconds for risperidone, and 46.03 ± 9.85 seconds for haloperidol.

Safety and Tolerability

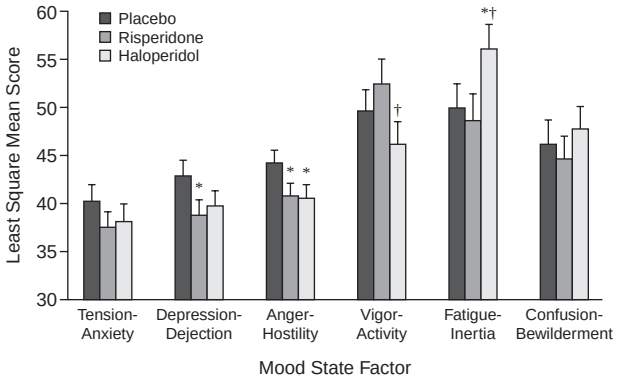
The safety and tolerability of the study medications were assessed by clinical interview, self-report, and movement evaluation instruments (AIMS and SAS). The descriptive data are summarized in Table 2. According to the AIMS and the SAS, no abnormal movements were observed during the placebo phase. No acute dystonia or other abnormal movements were observed during risperidone treatment, whereas 3 subjects experienced mild to moderate dystonia during the haloperidol phase that resulted in early termination of treatment with haloperidol. Subjects who experienced acute dystonia from haloperidol were managed with an antihistamine or benztropine until symptom-free (all within 3 days) and were maintained in the study by proceeding to the next washout phase. Other self-reported adverse events during the

Figure 2. The Effects of Risperidone and Haloperidol on OCD Patients as Measured With the HAM-D-17 and the SCL-90R Depression Scale in a Crossover Study



*p Value significant at the level of .05 when compared with placebo.
†p Value significant at the level of .01 when compared with haloperidol from the mixed-effects model.
Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, OCD = obsessive-compulsive disorder, SCL-90R = Hopkins Symptom Checklist 90-revised.

Figure 3. The Effects of Risperidone and Haloperidol on the Mood State Factors of the POMS in a Crossover Study[a]



[a]Values are the least square mean ± SE from the mixed-effect model analysis for each treatment.
*p Value significant at the level of .05 when compared with placebo.
†p Value significant at the level of .01 when compared with risperidone.
Abbreviation: POMS = Profile of Mood States.

Table 2. Adverse Events Reported in OCD Patients Receiving Crossover Treatment With Risperidone or Haloperidol

Occurrence	Risperidone (N = 12)	Haloperidol (N = 12)
Adverse event		
Acute dystonia	0	3
Lethargy	4	8
Irritability	0	4
Insomnia	0	2
Gastrointestinal distress	1	5
Action taken		
Continue medication	12	7
Discontinue medication	0	5

Abbreviation: OCD = obsessive-compulsive disorder.

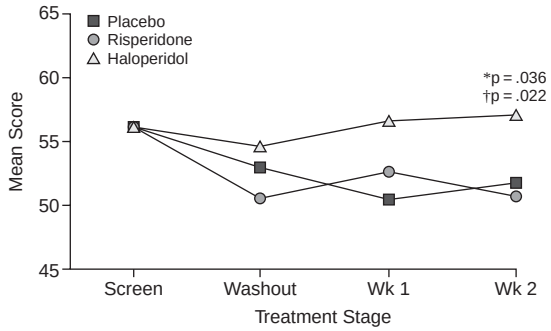
risperidone and haloperidol augmentation included lethargy, irritability, insomnia, and gastrointestinal distress (Table 2). Lethargy was the most common adverse event, reported by 4 subjects during risperidone treatment, but none of the subjects discontinued risperidone treatment. In contrast, 8 subjects reported lethargy during the haloperidol phase and 2 discontinued haloperidol treatment because of severe lethargy. One subject reported gastrointestinal distress while taking risperidone, compared with 11 on haloperidol treatment reporting irritability, insomnia, and/or gastrointestinal distress. Furthermore, the self-reported somatic symptoms on the SCL-90R somatization scale during treatment with placebo and with risperidone were not different (p = .791), while the somatic symptom scores during haloperidol treatment were significantly higher than during both placebo and risperidone treatment (p = .036 and p = .022, respectively) (Figure 4).

DISCUSSION

In this 9-week study of patients with SRI-refractory OCD, including severe obsessive symptoms, augmentation treatment with risperidone (1 mg/day) or with haloperidol (2 mg/day) was associated with rapid improvements in obsessive symptoms as assessed by the YBOCS scale. Furthermore, risperidone, but not haloperidol, significantly improved depressed mood as assessed by the HAM-D-17 scale, the SCL-90R, and the POMS. When compared with haloperidol, risperidone augmentation was generally well tolerated by OCD patients.

In a double-blind, placebo-controlled, 6-week study of patients with OCD, McDougle et al.[40] previously demonstrated that risperidone augmentation of an SRI was efficacious and well tolerated. In the present study, we used a crossover design to compare the efficacy and tolerability

Figure 4. The SCL-90R Somatization at Screening and During Crossover Treatment With Placebo, Risperidone, and Haloperidol



*p Value significant at the level of .05 when haloperidol was compared with placebo from the mixed-effects model.
†p Value significant at the level of .01 when haloperidol was compared with risperidone from the mixed-effects model.
Abbreviation: SCL-90R = Hopkins Symptom Checklist 90-revised.

of risperidone and a conventional antipsychotic (haloperidol) and sought to distinguish between effects on obsessive symptoms and on compulsive symptoms. The focus on obsession reflects the fact that this presentation of OCD is common, associated with great distress, and often difficult to treat.[2] Exclusion of patients with other Axis I disorders made it possible to focus on the benefits of risperidone augmentation in OCD with few complications from other comorbid psychiatric diseases. The decision to exclude persons with a history of or with current tic disorders was made on the basis of research suggesting that OCD with comorbid tics may be a distinct subtype of the disorder.[8,41]

The most promising finding of our study was the rapid and significant improvement in obsession (YBOCS scale) with risperidone and haloperidol. Considering that the patients had severe residual symptoms during SRI treatment, a significant reduction in obsession within 2 weeks of treatment initiation with each drug is notable. Risperidone appeared to be more effective in obsession, whereas its effect on compulsion was limited in this study, which may have been affected by the small number of subjects and shorter duration of treatment. Haloperidol appeared to be as effective as risperidone in the improvement of obsession, and its effect on compulsion was also promising. Although neither risperidone nor haloperidol demonstrated a statistically significant effect on compulsion, the trend of reducing compulsion by both drugs, especially haloperidol, warrants further investigation of their effectiveness in larger trials beyond 2 weeks of treatment duration. The larger reduction of compulsion by haloperidol may have contributed to its significant effect on the total YBOCS score. In summary, the effectiveness of both risperidone and haloperidol shown in this study supports the use of antipsychotics in the acute treatment of severe OCD that is refractory to SRI treatment.

Although none of the subjects met diagnostic criteria for major depression at study entry, OCD patients often experience depressive symptoms. In this study, risperidone, but not haloperidol, significantly reduced HAM-D-17 and SCL-90R depression scores. Our results are consistent with those of McDougle et al.,[40] that risperidone improves depressive symptoms in OCD patients, and suggest that risperidone may be superior to haloperidol in treating depressive symptoms in OCD patients.

According to 3 of the 6 POMS factors, the patients also experienced an enhanced sense of well-being during risperidone augmentation. Unlike the HAM-D-17, the depression-dejection factor in the POMS mainly rates the mood state related to the sense of personal inadequacy. The sense of self-inadequacy appears to be especially sensitive to risperidone augmentation, which suggests that risperidone enhances the sense of well-being in OCD patients. This effect of risperidone may also benefit the improvement of mood symptoms in other psychiatric disorders, such as psychotic and mood disorders, and further clinical trials are warranted to confirm this effect of risperidone. The data from the vigor-activity and fatigue-inertia factors further separated risperidone from haloperidol, in that haloperidol caused a negative outcome by decreasing vigor-activity and increasing fatigue-inertia. These negative effects of haloperidol may be a consequence of the prominent adverse events during haloperidol treatment.

An important difference between risperidone and haloperidol augmentation in OCD participants was in tolerability. The patients experienced substantially more serious adverse events such as dystonia and lethargy while receiving haloperidol, resulting in premature discontinuation of haloperidol treatment in 5 participants. None of the risperidone-treated subjects discontinued treatment because of adverse events. By weighing the benefits with the risks, the use of haloperidol in the treatment of OCD needs to be cautious. On the other hand, although risperidone is more tolerable during the short treatment, one should consider its long-term side effect profile when it is used in the treatment of OCD.

The neuropsychological tests examined the effects of placebo, risperidone, and haloperidol on cognitive functions during each treatment. The nonsignificant findings in our study suggest that short-term treatment with a low dose of risperidone or haloperidol does not have a significant impact on cognitive function in OCD patients.

One of the limitations of this study is the small number of participants. The promising effects of risperidone in obsession, anxiety, and depression, as well as the favorable side effect profile seen with risperidone in this study, warrant additional placebo-controlled research in refractory OCD patients. Another limitation factor of the study

is the short duration (2 weeks) of adjunctive treatment with risperidone and haloperidol. At present we do not know if the significant effects observed here would be maintained over a longer period of treatment. Also, it is possible that a longer duration of treatment with each drug might have resulted in a more significant reduction in compulsion. Although the doses of risperidone (1 mg) and haloperidol (2 mg) used in this study were considered relatively low in the treatment of psychosis, OCD patients may have lower tolerance to these drugs. A lower starting dose, especially with haloperidol, may result in better tolerance of the drug.

Drug names: benztropine (Cogentin and others), buspirone (BuSpar and others), clomipramine (Anafranil and others), clonazepam (Klonopin and others), clonidine (Catapres, Duraclon, and others), fluoxetine (Prozac and others), haloperidol (Haldol and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), paroxetine (Paxil and others), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft), trazodone (Desyrel and others).

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