Double-Blind, Placebo-Controlled, Pilot Trial of Paliperidone Augmentation in Serotonin Reuptake Inhibitor–Resistant Obsessive-Compulsive Disorder

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ABSTRACT

Objective: This pilot study explored the efficacy and tolerability of paliperidone augmentation of serotonin reuptake inhibitors (SRIs) in adults with treatment-resistant obsessive-compulsive disorder (OCD).

Method: Thirty-four patients aged 24–67 years (mean = 43.7 years, SD = 11.4) who met *DSM-IV* criteria for OCD and remained symptomatic following 2 or more past adequate SRI trials (including their current medication) were enrolled from May 2008 to March 2012. Participants were treated for 8 weeks in a double-blind study with either paliperidone (up to 9 mg/d) or matching placebo in addition to their SRI. Blinded raters conducted outcome assessments. The primary outcome, obsessive-compulsive symptom severity, was assessed using the Yale-Brown Obsessive Compulsive Scale (YBOCS). Secondary outcomes included the Clinical Global Impressions-Severity of Illness and -Improvement scales.

Results: Paliperidone administration resulted in significant baseline-to-posttreatment reductions in obsessive-compulsive symptoms as measured by the YBOCS ($P < .01$, $d = 0.66$), although placebo administration also resulted in medium-sized, trend-level significant YBOCS changes ($P = .05$, $d = 0.53$). In exploratory analyses examining between-group differences, tests for paliperidone superiority relative to placebo were not significant ($P = .14$, $d = 0.34$); however, a numerical trend toward significant between-group differences was found, with a reduction of 7.98 points on the YBOCS for the paliperidone group compared to a reduction of 4.02 points for the placebo group. Paliperidone was generally well tolerated and not associated with significant weight gain (mean [SD] weight: paliperidone, pretreatment 84.70 [27.08] kg, posttreatment 84.84 [18.99] kg; vs placebo, pretreatment 77.50 [25.33] kg, posttreatment 77.43 [19.90] kg; $P = .21$).

Conclusions: These results suggest that paliperidone augmentation is well tolerated and has potential efficacy in the short-term treatment of some patients with SRI-resistant OCD. Well-powered, randomized, controlled studies are necessary to more definitively address the efficacy of this treatment strategy.

Trial Registration: ClinicalTrials.gov identifier: NCT00632229

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Obsessive-compulsive disorder (OCD) is a common,[1,2] chronic, and often disabling disorder.[3] The only established first-line treatments for OCD are cognitive-behavioral therapy with exposure/response prevention (CBT) and serotonin reuptake inhibitor (SRI) medications. Few patients with OCD experience complete symptom resolution with either modality. Even after 2 consecutive adequate SRI trials, as many as 30%–40% of patients fail to derive a satisfactory response,[4,5] and, among those who are responders, most remain symptomatic. Treatment options for these SRI-resistant cases include adding CBT, switching to a different SRI medication, increasing the SRI dose, or augmenting with another agent.[6]

Among the pharmacologic augmentation strategies, adjunctive antipsychotic medications have empirical support, as well as wide-scale use in clinical practice. Approximately 33% of OCD patients classified as nonresponders to SRI medication had a positive response when an atypical antipsychotic medication was added.[7–10] Risperidone has been the most studied augmentation agent and has yielded positive findings in adults with SRI-resistant OCD.[9,10] The potential acute and long-term side effects of risperidone (and other atypical antipsychotics), however, are of concern[11] and, at times, limit their use.

Paliperidone (9-hydroxy-risperidone), a metabolite of risperidone that utilizes OROS osmotic drug-release technology, has a number of advantages over risperidone, including less hepatic excretion, lower risk of causing hepatic impairment, and a more predictable pharmacokinetic profile that may be associated with better tolerability.[12] Paliperidone may also have fewer drug-drug interactions because it is not a substrate of cytochrome P450 (CYP)1A2, CYP2A6, CYP2C9, and CYP2C19, so that an interaction with inhibitors or inducers of these isozymes is unlikely. Thus, paliperidone has potential as a safe augmentation approach in SRI-resistant OCD patients. Although paliperidone augmentation has not been tested in OCD, efficacy and tolerability have been documented in adults with schizophrenia.[13] Accordingly, this controlled, pilot study examined whether paliperidone augmentation of an SRI was efficacious relative to placebo and safe and tolerable in OCD patients who have not adequately responded to past adequate SRI treatment.

METHOD

Participants

Thirty-four adults (ages 24–67 years, mean = 43.7 years, SD = 11.4; 15 men [44.1%]) with a principal diagnosis of OCD were recruited across 3 study sites between May 2008 and March 2012 (ClinicalTrials.gov identifier: NCT00632229). Inclusion

Clinical Points

- Although atypical antipsychotic augmentation shows promise in patients with treatment-resistant obsessive-compulsive disorder (OCD), there are mixed results, and many do not experience an adequate response.
- Further investigation of augmentation strategies is needed among patients with treatment-resistant OCD.

criteria were (1) primary diagnosis of OCD confirmed by both clinical evaluation and the Structured Clinical Interview for *DSM-IV*[14] and (2) Yale-Brown Obsessive Compulsive Scale (YBOCS) total score of ≥ 19[15,16] despite at least 2 adequate SRI monotherapy trials. One trial included the SRI currently being taken by the patient provided that the duration of treatment was 12 weeks or longer (at least 8 weeks at the present dose) and that the dose was deemed adequate by the study psychiatrist according to best practice guidelines.[17] We were unable to assess the degree of response to participants' current SRI, although subjects were quite symptomatic at screening and thus it is assumed that the SRI had minimal effect. Participants were taking the following SRIs (n; mean [SD] dose): clomipramine (n = 3; 216.7 [57.7] mg), citalopram (n = 7; 55.7 [18.1] mg), desvenlafaxine (n = 1; 50 mg), escitalopram (n = 2; 15 [7.1] mg), fluoxetine (n = 5; 46 [24.1] mg), fluvoxamine (n = 7; 171.4 [80.9] mg), duloxetine (n = 2; 60 [0] mg), paroxetine (n = 3; 46.7 [11.5] mg), and sertraline (n = 4; 125 [50.0] mg). Although desvenlafaxine is not usually considered an SRI, it has known serotonergic function, which has shown benefit in OCD.[18]

Exclusion criteria included (1) history of neurosurgery, encephalitis, or significant head trauma or a significant medical condition such as heart, liver, or renal disease; (2) in women, pregnancy, having unprotected sex, breastfeeding, or being of childbearing potential without using adequate contraception; (3) being at increased risk for seizures (eg, history of seizures [other than childhood febrile seizures], use of concomitant medications known to lower the seizure threshold); and (4) lifetime comorbid psychosis, bipolar disorder, autism, or current substance abuse/dependence. Concomitant benzodiazepines were permissible. Concurrent psychotherapy (eg, CBT) was not permitted.

Most participants were white (n = 32; 94.1%), with other ethnicities including African-American (n = 1; 2.9%) and Asian-American (n = 1; 2.9%). A total of 44.1% of participants (n = 15) reported a comorbid psychiatric condition, with the most common comorbidities including depression (n = 13; 38.2%), generalized anxiety disorder (n = 7; 20.6%), and social anxiety disorder (n = 6; 17.7%).

Study Design

This 8-week, randomized, double-blind, placebo-controlled study was conducted at 3 sites (University of South Florida, University of Minnesota, and Indiana University). The institutional review board at each site provided ethical approval for the investigation. After providing written informed consent, at which time procedures and possible side effects were explained, participants completed study measures, were administered physical and neurologic examinations by a board-certified psychiatrist, received an electrocardiogram (ECG), and had laboratory values assayed (eg, complete blood count [CBC], prolactin, electrolytes, lipids, creatinine, liver function tests, thyroid indices, urine toxicology, and, for women, a pregnancy test). Following screening, participants were randomized by a computer-generated program maintained in the site research pharmacy in a 1:1 ratio to treatment with either paliperidone or a matching pill placebo over an 8-week, double-blind, treatment period.

Paliperidone and placebo were initiated at 3 mg/d by mouth by the prescribing psychiatrist in 30-minute medication management sessions. These sessions focused primarily on assessing treatment response and presence of adverse effects in a supportive, empathic environment; putative CBT ingredients (eg, symptom monitoring, exposure, and response prevention) were not included in visits. Subjects returned weekly over the first 2 weeks of the study and then every 2 weeks thereafter for a total of 8 weeks of treatment. Paliperidone and placebo doses were increased by 3 mg/d every 7 days, as tolerated. Subjects were titrated up to 9 mg/d by week 6 unless dose titration was not tolerated or not clinically indicated (eg, subject was having a positive response on lower doses). Compliance was assessed by pill counts at each visit.

Assessments were conducted by experienced, blinded raters (for efficacy measures) or board certified psychiatrists (for safety assays) at screening, at baseline, weekly for weeks 1–2, and every 2 weeks thereafter (weeks 4, 6, and 8). Prior to study onset, blinded raters completed instructional training, observed measure administrations, and completed measures under supervision. No cross-site reliability measures were utilized.

Assessments

Efficacy. The primary efficacy measure was the YBOCS,[15,16] comprising 10 items that assess obsessive-compulsive symptom severity in terms of time occupied, distress, interference, resistance, and control. The Clinical Global Impressions-Severity of Illness and -Improvement scales (CGI-S and CGI-I)[19] are single-item clinician ratings of illness severity and treatment-related improvement. The CGI-S allows the clinician to rate the global severity of symptoms with scores ranging from 1 ("no illness") to 7 ("serious illness"). On the CGI-I, clinical improvement of symptoms was rated from 1 ("very much improved") to 7 ("very much worse"). The CGI-S was rated at every study visit; the CGI-I was rated at every study visit following baseline. Depressive symptoms were rated with the 24-item version of the Hamilton Depression Rating Scale (HDRS),[20] which excluded an item for rating obsessive-compulsive symptoms.

Safety and tolerability. All adverse events reported or observed during the study were recorded, together with their severity, duration, and likelihood of being related to study

Table 1. Treatment-Emergent Adverse Events[a]

Adverse Event	Placebo, n (%)	Paliperidone, n (%)
Headache	6 (35)	4 (24)
Dizziness	4 (24)	3 (18)
Light-headedness	3 (18)	3 (18)
Blurred vision	1 (6)	3 (18)
Muscle stiffness	0 (0)	4 (24)
Somnolence	8 (47)	7 (41)
Insomnia	5 (29)	5 (29)
Agitation	2 (12)	4 (24)
Shakiness	1 (6)	1 (6)
Anxiety	1 (6)	1 (6)
Weight gain	0 (0)	0 (0)
Dry mouth	3 (18)	4 (24)
Nausea	3 (18)	0 (0)
Constipation	1 (6)	5 (29)
Increased need to urinate	1 (6)	4 (24)
Ear ringing	2 (12)	2 (12)
Diarrhea	2 (12)	1 (6)
Galactorrhea	0 (0)	2 (12)
Increased appetite	3 (18)	5 (29)
Decreased appetite	1 (6)	1 (6)

[a]No significant differences between groups were detected at the $P < .05$ level.

interventions. Extrapyramidal symptoms were evaluated at each visit with the Webster (Parkinson's) Rating Scale (WPRS).[21] Symptoms of tardive dyskinesia were assessed with the Abnormal Involuntary Movement Scale (AIMS)[19] at screening and termination. The prescribing psychiatrist monitored side effects at each visit using a modified version of the Systematic Assessment for Treatment Emergent Events.[22] Other safety measures at screening and posttreatment included 12-lead ECG, weight, vital signs, and clinical laboratory assessments (CBC, creatinine, liver function tests, thyroid indices, and urine toxicology [posttreatment only]), collected with patients in a fasting state.

Analytic Plan

To evaluate medication tolerability, adverse events were compared between the placebo and paliperidone groups via Fisher exact tests. Additionally, each item on the AIMS and WPRS was compared via analyses of covariance (ANCOVA) to evaluate for group-based changes in involuntary movements at posttreatment (while covarying for pretreatment scores).

Baseline differences among sites for outcome variables were evaluated via analysis of variance (ANOVA). Given the preliminary nature of this trial, pre-post changes in outcomes for the placebo (n = 17) and paliperidone (n = 17) conditions separately were evaluated by paired *t* tests. To evaluate between-group continuous outcomes of the pilot controlled trial, ANCOVAs were performed, in which 8-week outcome scores were predicted by treatment condition while covarying for baseline scores. Comparison of response rates (ie, a categorical outcome) for the pilot controlled trial was evaluated via a Fisher exact test by contrasting 8-week response rates with group status. Effect sizes were computed for both within- and between-group analyses to evaluate the size of treatment effects. All effect sizes for continuous variables were converted to Cohen *d* using formulae provided by Cooper et al,[23] with effect sizes of 0.2, 0.5, and 0.8 representing small, medium, and large effects, respectively.[24] Missing data were addressed via multiple imputation using PROC MI and PROC MIANALYZE in SAS 9.2[25] using 100 imputations, where the imputation model included all psychopathology outcomes (eg, the CGI-S), as well as treatment group and participant weight. Given that the YBOCS total score is a linear composite of the obsessions and compulsions subscales, these subscales were imputed first and subsequently summed to form a YBOCS total score following imputation. To evaluate treatment response on the CGI-I, scores reflecting "much improved" or "very much improved" were considered to reflect treatment responder status, while all other cases were considered nonresponders, following research precedent.[26] To evaluate treatment response on the YBOCS, a cutoff of a 35% score reduction from baseline to endpoint was used to define responder status. When evaluating responder status (ie, via the CGI-I or by YBOCS cutoffs), scores were imputed using the last-observation-carried-forward method, and missing data were considered treatment nonresponse. Degrees of freedom for multiply imputed hypothesis-testing models were adjusted on the basis of recommendations by Barnard and Rubin.[27] All variables were within recommended ranges of ± 2 with regard to skewness and kurtosis prior to data imputation.[28] Among variables used for treatment outcome analyses, the proportion of missing data was relatively small (11%). There was no adjustment for multiplicity.

RESULTS

The mean (SD) doses in the paliperidone and placebo groups were 4.94 (2.36) mg/d and 6.2 (2.6) mg/d, respectively. Expected changes in prolactin levels were seen in all subjects randomized to the paliperidone arm. No differences were detected between arms with regard to adverse effects (Table 1). There were no group differences in rates of premature discontinuation (Fisher exact $P = 1.00$): 6 participants in the paliperidone group (35%) and 6 participants in the placebo group (35%) terminated before trial completion. Reasons associated with termination in the paliperidone group included dizziness (n = 1; 5.9%), as well as multiple simultaneous side effects (n = 5; 29.4%). Reasons in the placebo group included perceived lack of efficacy (n = 2; 11.8%), undisclosed reasons within the first week of participation (n = 1; 5.9%), and loss to follow-up (n = 3; 17.7%). Mean (SD) baseline weight for the paliperidone group (84.70 [27.08] kg) was not significantly different at the end of the study (84.84 [18.99] kg), with similarly small differences seen for placebo for baseline (77.50 [25.33] kg) relative to posttreatment (74.43 [19.90] kg). No group differences in weight change were detected ($P = .21$). Among participants who had posttreatment data on the AIMS and WPRS, no group differences were observed on any individual items.

Descriptive statistics for outcomes at baseline and posttreatment can be found in Table 2. When baseline group differences were compared by site, no differences were detected at the $P < .05$ level for YBOCS scores or the

Table 2. Descriptive Statistics for Preintervention and Postintervention Outcomes

	Placebo (n = 17)			Paliperidone (n = 17)			
Measure	Baseline, Mean (SD)	Posttreatment, Mean (SD)	Within-Subjects *d*	Baseline, Mean (SD)	Posttreatment, Mean (SD)	Within-Subjects *d*	Between-Subjects *d*
YBOCS total	25.18 (4.32)	21.24 (8.16)	0.53	27.12 (5.68)	19.14 (11.13)	0.66	0.43
YBOCS obsessions	12.76 (1.95)	11.05 (3.97)	0.44	13.59 (3.36)	9.73 (5.80)	0.59	0.46
YBOCS compulsions	12.41 (3.10)	10.19 (4.74)	0.52	13.53 (2.72)	9.41 (5.48)	0.76	0.30
CGI-S	5.18 (0.73)	4.21 (1.29)	0.71	5.12 (0.99)	4.09 (1.66)	0.54	0.03
HDRS	15.88 (8.37)	13.18 (9.09)	0.28	20.31 (11.64)	14.90 (13.42)	0.37	0.08

Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness, HDRS = Hamilton Depression Rating Scale, YBOCS = Yale-Brown Obsessive Compulsive Scale.

CGI-S. Site differences, however, were detected for the HDRS ($P = .03$). Given that this was an outcome that was not a principal target of treatment and the pilot nature of this study, no further adjustments to analyses were made based on this finding.

In within-subjects comparisons for the paliperidone condition, baseline-to-posttreatment differences were observed for the YBOCS total score ($P < .01$, $d = 0.66$) as well as the YBOCS obsessions ($P < .01$, $d = 0.59$) and compulsions ($P < .01$, $d = 0.76$) subscales. Baseline-to-posttreatment differences were also observed for the CGI-S ($P < .01$, $d = 0.54$), but not for the HDRS ($P = .13$, $d = 0.37$). When within-subjects comparisons were made for the placebo arm, baseline-to-posttreatment differences were medium-sized but nonsignificant for the YBOCS total score ($P = .05$, $d = 0.53$) as well as the obsessions ($P = .06$, $d = 0.44$) and compulsions ($P = .08$, $d = 0.52$) subscales. Baseline-to-posttreatment differences were observed for the placebo condition for the CGI-S ($P < .01$, $d = 0.71$), but not for the HDRS ($P = .26$, $d = 0.28$).

In exploratory analyses examining between-group differences, superiority for paliperidone relative to placebo was not demonstrated for the YBOCS total score ($P = .14$, $d = 0.43$); however, numerically, a reduction of 7.98 points was seen for the paliperidone group and a reduction of 3.94 points was observed for the placebo group. Significant effects were also not demonstrated for the YBOCS obsessions ($P = .07$, $d = 0.46$) or compulsions ($P = .35$, $d = 0.30$) subscales, the CGI-S ($P = .90$, $d = 0.03$), or the HDRS ($P = .77$, $d = 0.08$) or with regard to treatment response rate on the CGI-I ($P = .44$, odds ratio [OR] = 2.55; 95% CI for OR, 0.52–12.55) or the YBOCS ($P = 1.00$, OR = 1.31; 95% CI for OR, 0.31–5.53). In considering response rates on the CGI-I, 35% (6/17) in the paliperidone treatment condition experienced treatment response compared to 18% (3/17) of those in the placebo condition. When considering response rate on the YBOCS, 35% (6/17) in the paliperidone treatment condition experienced treatment response compared to 29% (5/17) in the placebo condition.

DISCUSSION

This preliminary trial, to the best of our knowledge, represents the first controlled trial of paliperidone augmentation of adults with SRI-resistant OCD. Within-subject analyses demonstrated a significant baseline-to-posttreatment change for the paliperidone-treated subjects, although placebo administration also resulted in a medium-sized effect on YBOCS scores. While between-group differences were not statistically different, the effect size of $d = 0.43$ for the YBOCS total score is promising; the active treatment arm experienced a mean YBOCS reduction of approximately 8 points, compared to approximately 4 points in the placebo control. Thus, while paliperidone administration resulted in the reduction of clinical symptoms, when considering the similar effects observed in the control condition, further study is warranted to test its potential efficacy in SRI-resistant adults with OCD.

Of specific interest is the nature of the nonsignificant between-group effects. These may reflect limited statistical power or, alternatively, a lack of clarity regarding the most appropriate OCD patient subgroup best served by antipsychotic augmentation. Evidence suggests that antipsychotic augmentation is modestly effective in a specific subset of OCD patients, namely those who are SRI nonresponders (versus SRI responders who remain symptomatic),[9] but who have not failed multiple medication trials. Indeed, McDougle and colleagues,[10] who published the most promising antipsychotic augmentation study to date, found a 50% response rate across patients who had failed varying numbers of SRI trials. Yet, many of those in the McDougle study[10] who responded to risperidone augmentation had 1 or zero past SRI trials, while other studies that included more treatment-refractory patients had a less robust response.[29] Thus, a sample that combines patients with differing illness presentations or treatment histories may obscure the potential efficacy of paliperidone augmentation.

Paliperidone was reasonably well tolerated. The placebo group achieved higher end-point dosages than the paliperidone arm, although typically did not achieve the maximum dose. We suspect that several factors contributed to not meeting the full dose in many cases across study arms, including clinician perceptions that low-dose atypical augmentation approaches are effective,[9,10] side effects, and participant anxiety about medications. No between-group differences in weight gain were noted over the 8-week study duration, and no significant changes in QTc intervals on ECG were noted at posttreatment. Paliperidone augmentation was associated with muscle stiffness in 4 subjects, constipation in 5 subjects, and galactorrhea in 2 subjects, although adverse effects with paliperidone did not statistically differ from placebo. The availability of a tolerable medication

with a favorable safety profile may represent an attractive alternative given side effect concerns associated with other atypical antipsychotics.

Several limitations warrant comment. First, because this was a preliminary study with a principal goal of evaluating the feasibility of paliperidone administration in this population, the sample size was modest and analyses were potentially underpowered to detect between-group differences on OCD symptom measures. Second, it was not possible to determine participants' response to their current SRI, as they entered the study after starting it. Future studies should prospectively treat patients with an SRI and examine paliperidone augmentation for partial responders and nonresponders to determine if there is differential benefit, as was found by Erzegovesi and colleagues.[9] Third, although subjects were all on adequate SRI doses for at least 12 weeks, potential confounds include variation in types of medications sampled and duration of SRI treatment. Fourth, although participants were recruited across 3 unique sites, there was little racial/ethnic and socioeconomic variability among participants. Fifth, beyond within-site supervision and regular between-site conference calls, no formal assessment of rater integrity was conducted. Finally, our assessment battery was limited to measures of obsessive-compulsive symptom severity and safety assays. We highlight the need to assay other dimensions of psychopathology (eg, general anxiety) and functioning in future studies to comprehensively examine the utility of paliperidone augmentation. Despite these limitations, this report provides support for further study of paliperidone augmentation of SRI treatment in adults with OCD. Areas that warrant further exploration based on these preliminary data include examination of paliperidone augmentation in a fully powered trial over a longer duration, as well as the efficacy of paliperidone on alternative outcomes (eg, anxiety).

Drug names: citalopram (Celexa and others), clomipramine (Anafranil and others), desvenlafaxine (Pristiq), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), paliperidone (Invega), paroxetine (Paxil, Pexeva, and others), risperidone (Risperdal and others), sertraline (Zoloft and others).

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REFERENCES

1. Adam Y, Meinlschmidt G, Gloster AT, et al. Obsessive-compulsive disorder in the community: 12-month prevalence, comorbidity and impairment. *Soc Psychiatry Psychiatr Epidemiol*. 2012;47(3):339–349.
2. Ruscio AM, Stein DJ, Chiu WT, et al. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. *Mol Psychiatry*. 2010;15(1):53–63.
3. Rasmussen SA, Eisen JL. The epidemiology and clinical features of obsessive compulsive disorder. *Psychiatr Clin North Am*. 1992;15(4):743–758.
4. Pigott TA, Seay SM. A review of the efficacy of selective serotonin reuptake inhibitors in obsessive-compulsive disorder. *J Clin Psychiatry*. 1999;60(2):101–106.
5. Ackerman DL, Greenland S. Multivariate meta-analysis of controlled drug studies for obsessive-compulsive disorder. *J Clin Psychopharmacol*. 2002;22(3):309–317.
6. Fineberg NA, Brown A, Reghunandanan S, et al. Evidence-based pharmacotherapy of obsessive-compulsive disorder. *Int J Neuropsychopharmacol*. 2012;15(8):1173–1191.
7. Bloch MH, Landeros-Weisenberger A, Kelmendi B, et al. A systematic review: antipsychotic augmentation with treatment refractory obsessive-compulsive disorder. *Mol Psychiatry*. 2006;11(7):622–632.
8. Dold M, Aigner M, Lanzenberger R, et al. Antipsychotic augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder: a meta-analysis of double-blind, randomized, placebo-controlled trials. *Int J Neuropsychopharmacol*. 2012:1–18.
9. Erzegovesi S, Guglielmo E, Siliprandi F, et al. Low-dose risperidone augmentation of fluvoxamine treatment in obsessive-compulsive disorder: a double-blind, placebo-controlled study. *Eur Neuropsychopharmacol*. 2005;15(1):69–74.
10. McDougle CJ, Epperson CN, Pelton GH, et al. A double-blind, placebo-controlled study of risperidone addition in serotonin reuptake inhibitor-refractory obsessive-compulsive disorder. *Arch Gen Psychiatry*. 2000;57(8):794–801.
11. Keith S. Use of long-acting risperidone in psychiatric disorders: focus on efficacy, safety and cost-effectiveness. *Expert Rev Neurother*. 2009;9(1):9–31.
12. Wang SM, Han C, Lee SJ, et al. Paliperidone: a review of clinical trial data and clinical implications. *Clin Drug Investig*. 2012;32(8):497–512.
13. Chwieduk CM, Keating GM. Paliperidone extended release: a review of its use in the management of schizophrenia. *Drugs*. 2010;70(10):1295–1317.
14. First MB, Spitzer RL, Gibbon M, et al. *Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version-(SCID-CV)*. Washington, DC: American Psychiatric Press, Inc; 1996.
15. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale, 1: development, use, and reliability. *Arch Gen Psychiatry*. 1989;46(11):1006–1011.
16. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale. 2: validity. *Arch Gen Psychiatry*. 1989;46(11):1012–1016.
17. Koran LM, Hanna GL, Hollander E, et al; American Psychiatric Association. Practice Guideline for the Treatment of Patients With Obsessive-Compulsive Disorder. *Am J Psychiatry*. 2007;164(suppl):5–53.
18. Denys D, Fineberg N, Carey PD, et al. Quetiapine addition in obsessive-compulsive disorder: is treatment outcome affected by type and dose of serotonin reuptake inhibitors? *Biol Psychiatry*. 2007;61(3):412–414.
19. Guy W. *ECDEU Assessment Manual for Psychopharmacology. Revised Edition*. US Department of Health, Education, and Welfare publication (ADM) 76-338. Rockville, MD: National Institute of Mental Health; 1976.
20. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56–62.
21. Webster DD. Critical analysis of the disability in Parkinson's disease.

Mod Treat. 1968;5(2):257–282.
22. Levine J, Schooler NR. SAFTEE: a technique for the systematic assessment of side effects in clinical trials. *Psychopharmacol Bull*. 1986;22(2):343–381.
23. Cooper H, Hedges LV, Valentine JC. *The Handbook of Research Synthesis and Meta-Analysis*. New York, NY: Russell Sage Foundation Publications; 2009.
24. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. Hillsdale, NJ: Lawrence Earlbaum Associates; 1988.
25. SAS Institute. *SAS/STAT User's Guide (version 9.2)*. Cary, NC: SAS Institute, Inc; 2008.
26. Storch EA, Lewin AB, De Nadai AS, et al. Defining treatment response and remission in obsessive-compulsive disorder: a signal detection analysis of the Children's Yale-Brown Obsessive Compulsive Scale. *J Am Acad Child Adolesc Psychiatry*. 2010;49(7):708–717.
27. Barnard J, Rubin DB. Miscellanea: small-sample degrees of freedom with multiple imputation. *Biometrika*. 1999;86(4):948–955.
28. Cameron A. Kurtosis. In: Lewis-Beck M, Bryman A, Liao T, eds. *Encyclopedia of Social Science Research Methods*. New York, NY: Sage Publications, Inc; 2004.
29. Hollander E, Baldini Rossi N, Sood E, et al. Risperidone augmentation in treatment-resistant obsessive-compulsive disorder: a double-blind, placebo-controlled study. *Int J Neuropsychopharmacol*. 2003;6(4):397–401.