Neuropsychopharmacology (2006) 31, 2505–2513

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Effects of Risperidone Augmentation in Patients with Treatment-Resistant Depression: Results of Open-Label Treatment Followed by Double-Blind Continuation

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Approximately one-third of persons with depression do not respond to antidepressant monotherapy. Studies suggest that atypical antipsychotic augmentation may benefit these patients. We investigated the longer-term efficacy of risperidone augmentation of serotonin-selective reuptake inhibitor treatment for resistant depression. In 57 in- and outpatient centers in three countries, we conducted a three-phase study with 4–6 weeks of open-label citalopram monotherapy, 4–6 weeks of open-label risperidone augmentation, and a 24-week double-blind, placebo-controlled discontinuation phase. A total of 489 patients with major depressive disorder and 1–3 documented treatment failures entered the citalopram monotherapy phase (20–60 mg/day). Patients with <50% reduction in HAM-D-17 scores entered the risperidone augmentation phase (0.25–2.0 mg/day). Patients with HAM-D-17 $\leqslant$ 7 or CGI-S $\leqslant$ 2 were randomized to risperidone or placebo augmentation. The primary outcome was time to relapse during the double-blind phase. During citalopram monotherapy, 434 patients had <50% HAM-D-17 reduction; 299 (68.9%) were fully nonresponsive (<25% reduction) and 135 were partially nonresponsive (25–49% reduction). Of the 386 nonresponders who entered the augmentation phase, 243 remitted and 241 entered the double-blind phase. Median time to relapse was 102 days with risperidone augmentation and 85 days with placebo (NS); relapse rates were 53.3 and 54.6%, respectively. In a *post hoc* analysis of patients fully nonresponsive to citalopram monotherapy, median time to relapse was 97 days with risperidone augmentation and 56 with placebo ($p = 0.05$); relapse rates were 56.1 and 64.1%, respectively ($p \leqslant 0.05$). Open-label risperidone augmentation substantially enhanced response in treatment-resistant patients, but the longer-term benefits of augmentation were not demonstrated in this study.
Neuropsychopharmacology (2006) **31,** 2505–2513. doi:10.1038/sj.npp.1301113; published online 7 June 2006

Keywords: resistant depression; risperidone augmentation; citalopram

INTRODUCTION

Major depressive disorder is a common, chronic, and recurrent illness, affecting more than 320 million people worldwide (Weissman *et al*, 1996). It is characterized by increased medical morbidity and mortality (Tranter *et al*, 2002), functional impairment, reduced quality of life, substantial health-care costs, and an increased risk of suicide (Greden, 2001). The major factor contributing to this profound health burden is the extraordinarily high rates of relapse and recurrence associated with major depressive disorder (Robins and Regier, 1991). The results of longitudinal studies suggest that complete resolution of symptoms provides greater protection against relapse (Solomon *et al*, 2004; Fava *et al*, 2004). Therefore, the psychiatric community has identified complete symptom resolution and relapse prevention as the primary treatment goals for patients with major depressive disorder (American Psychiatric Association, 2000).

Although initial antidepressant therapy significantly reduces symptoms of depression in many patients, only 50–60% of patients with major depressive disorder respond to treatment (Nierenberg and DeCecco, 2001). Moreover, between 30 and 40% of persons who suffer from major depressive disorder never achieve symptom resolution with standard antidepressant therapy (Amsterdam and Hornig-Rohan, 1996; Nierenberg and Amsterdam, 1990). This has

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Received 17 June 2005; revised 27 April 2006; accepted 2 May 2006
Online publication: 10 May 2006 at http://www.acnp.org/citations/Npp051006050388/default.pdf

stimulated a comprehensive search for more effective treatment alternatives (Keller, 2005). However, the term 'treatment-resistant depression' is used inconsistently in the literature as well as in protocols for randomized clinical studies. Definitions have varied widely as treatment-resistant depression encompasses a broad continuum of severity and complexity. In fact, proposed staging criteria for treatment-resistant depression range from failure to respond to an adequate trial (dose and duration) of a single antidepressant to failure to respond to multiple classes of antidepressants, as well as electroconvulsive therapy (Thase and Rush, 1995, 1997; Ananth, 1998).

Currently, there is no evidence-based algorithm to guide treatment for patients whose depression has been poorly responsive to one or more standard therapies. There is a general consensus, however, that potential options include (1) augmentation with psychotherapy (De Jonghe *et al*, 2004), (2) switching classes of medication (McGrath *et al*, 1993), (3) supplementation with a second antidepressant of a different class (Bodkin *et al*, 1997; Gomez Gomez and Teixido Perramon, 2000), (4) somatic therapy such as rapid transcranial magnetic stimulation, electroconvulsive therapy, or vagal-nerve stimulation (Figiel *et al*, 1998; Rush *et al*, 2000; Wahlund and von Rosen, 2003), and (5) augmentation strategies with agents usually not considered as classical antidepressants, such as lithium (Fava, 2001) or thyroid hormone (Joffe *et al*, 1993). One augmentation strategy that has recently been explored is supplementation of antidepressants with atypical antipsychotic medications (Ostroff and Nelson, 1999; Shelton *et al*, 2001; Adson *et al*, 2004; Papakostas *et al*, 2004).

At this time, only one large-scale trial evaluating atypical antipsychotic augmentation in treatment-resistant depression has been published, and there are no large double-blind data regarding the benefits of any type of continued augmentation treatment for patients with resistant depression (Shelton *et al*, 2005). These gaps in knowledge served as the impetus for this 9-month international study designed to evaluate the effect of long-term augmentation treatment with risperidone in patients with confirmed treatment-resistant depression. We sought to determine whether short-term open-label risperidone augmentation of a serotonin-selective reuptake inhibitor (SSRI) reduces depressive symptomatology in treatment-resistant patients and whether continuation treatment with risperidone augmentation provides greater maintenance of effect than a return to antidepressant monotherapy. Our primary hypothesis was that continuation augmentation treatment with risperidone would reduce relapse rates more than placebo treatment.

METHODS

Augmentation with Risperidone in Resistant Depression (ARISe-RD) is a large international study conducted at 57 sites in the USA, Canada, France, and the UK from June 2002 to January 2004. It was approved by the institutional review board/ethics committee for each site and written informed consent was obtained from each subject. This 9-month prospective study included three phases: (1) 4–6 weeks of open-label citalopram monotherapy to confirm nonresponse to a standard SSRI; (2) 4–6 weeks of open-label risperidone treatment to evaluate the augmentation effects relative to SSRI monotherapy and to identify patients with symptom resolution; and (3) a 24-week double-blind discontinuation phase to assess the effect of augmentation with risperidone *vs* placebo in the prevention of relapse. Subjects who met criteria for relapse in this third phase were offered open-label risperidone augmentation for the duration of the trial.

Patient Population

Subjects were in- or outpatients, aged 18–85 years, meeting Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) diagnostic criteria for major depressive disorder, single or recurrent episode, with or without psychotic features, and with a Hamilton Rating Scale for Depression (Hamilton, 1960) (HAM-D-17) total score $\geqslant 20$. The diagnoses were made at each site by experienced clinicians based on a comprehensive assessment of the patient. However, a structured diagnostic interview was not performed. Subjects were required to have a history of resistance to standard antidepressant therapy, defined as failure to respond to at least one but not more than three adequate antidepressant trials during the current episode (at least 6 weeks at a dose of antidepressant medication within the ranges approved by the Food and Drug Administration for the treatment of depression). Comorbid anxiety disorders other than obsessive–compulsive disorder were not grounds for exclusion. All other DSM-IV axis 1 diagnoses, including dementia and bipolar disorder (type I or II) as well as a lifetime diagnosis of DSM IV borderline personality disorder, were exclusion criteria.

All subjects received a complete medical history, physical examination, laboratory evaluation, including chemistry panel, liver panel, complete blood count, urine analysis, and urine pregnancy test (for women), toxicology screening, and electrocardiography. Subjects who were medically healthy and those who had stable medical conditions were eligible to participate in the study.

Study Design

The design of this three-phase study is shown in Figure 1.

Open-label citalopram monotherapy: In the open-label citalopram monotherapy phase, flexible dosing was initiated at 20 mg/day. The citalopram dose was increased based on clinical efficacy and side effects. The clinicians were requested to try to achieve a target dose of 60 mg/day for patients aged 18–54 years and 40 mg/day for those aged 55–85 years. The citalopram monotherapy treatment period was 6 weeks (or 4 weeks for patients who were unchanged or worse at that point). Patients who were nonresponders ($<50\%$ reduction in HAM-D-17 total scores) at the end of citalopram monotherapy were eligible to enter the risperidone augmentation phase of the study.

Open-label risperidone augmentation: The open-label risperidone augmentation phase was 4–6 weeks in duration (at the discretion of the investigator, patients who demonstrated clinical improvement but had not yet achieved symptom resolution could be treated for 6 weeks). Patients who achieved symptom resolution, defined as a HAM-D-17

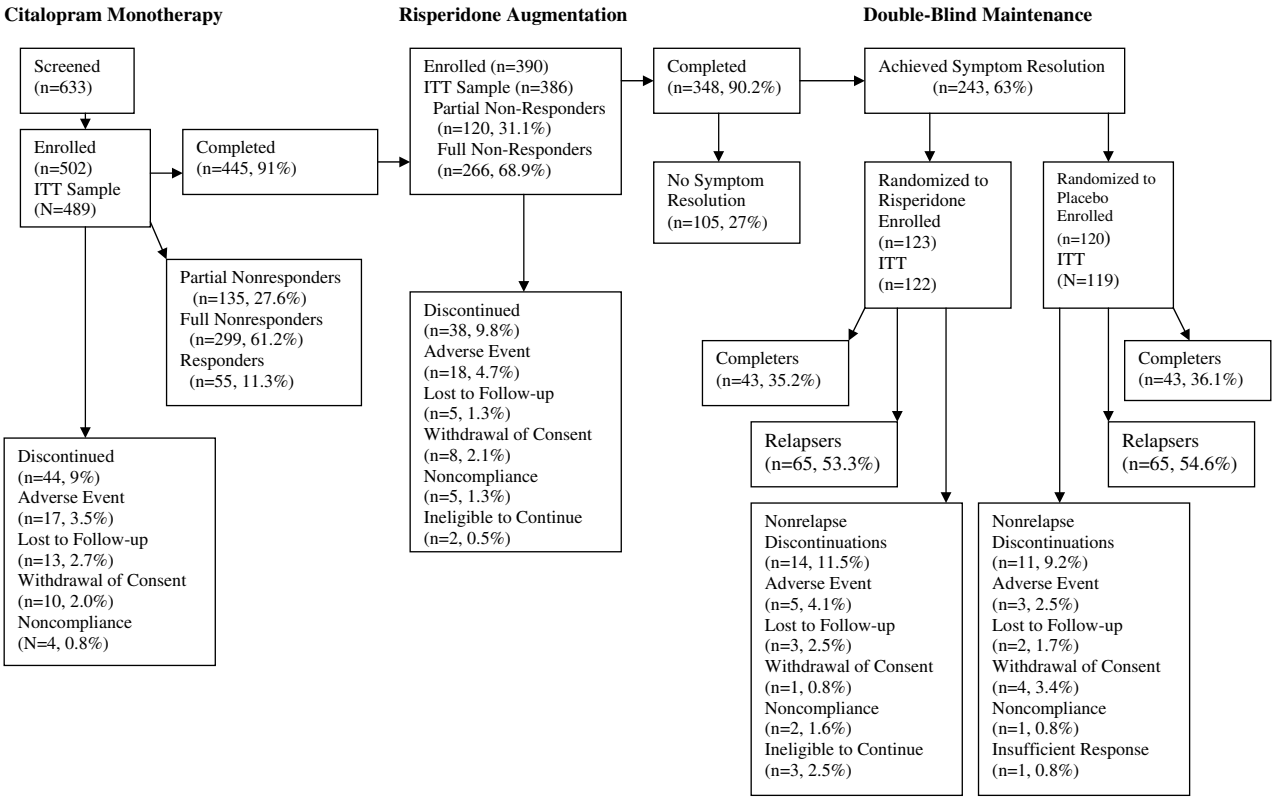

Figure 1 Study design and patient flow.

score $\leqslant 7$ or Clinical Global Impressions-Severity (CGI-S) score of 1 (not ill) or 2 (borderline ill) (Guy, 1976), with risperidone augmentation were eligible to enter the double-blind continuation phase. Citalopram was continued at the same dose achieved at the end of the monotherapy period. The risperidone augmentation dose was initiated at 0.5 mg/day and targeted to 1 mg/day (0.5–2.0 mg/day permitted) for patients aged 18–54 years and initiated at 0.25 mg/day and targeted to 0.5 mg/day (0.25 or 1 mg/day permitted) for patients aged 55–85 years.

Double-blind continuation phase: In the 24-week double-blind phase, patients were randomized to continue on risperidone plus citalopram or to receive placebo plus citalopram. The primary outcome was time to relapse, defined as any one or more of these four criteria: (1) CGI-Change (CGI-C) score of 6 (much worse) or 7 (very much worse); (2) HAM-D-17 total score $\geqslant 16$; (3) discontinuation owing to lack of therapeutic effect; or (4) deliberate self-injury or suicidal intent. Patients who met relapse criteria during the double-blind treatment phase of the study were eligible to receive open-label risperidone and continue assessments for the remainder of the 24-week study period. At the end of the 24-week double-blind study period, patients were either tapered off study medication over 2 weeks or continued in a 3-month aftercare program.

Additional psychotropic medications were excluded during the entire study, with the exception of lorazepam or an equivalent benzodiazepine for agitation or restlessness during the citalopram monotherapy phase. Zolpidem, zaleplon, or zopiclone could be used to treat the symptoms of insomnia during any phase of the study.

Outcome Measures

Efficacy assessments included clinician-rated scales designed to measure symptoms of depression and overall clinical status. The Montgomery–Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), a 10-item scale that assesses a range of depressive symptoms, was the primary outcome measure used to assess depression severity. The HAM-D-17 evaluates depressed mood as well as the neurovegetative and cognitive symptoms of depression. In this study, the HAM-D-17 was employed as a screening tool to determine subject eligibility for the three phases of the study and as one relapse criterion during the double-blind discontinuation phase. The MADRS and HAM-D-17 were completed during the open-label citalopram monotherapy phase (baseline, weeks 2, 4, and 6), the open-label risperidone augmentation phase (baseline, day 4, weeks 1, 2, 4, and 6), and the double-blind phase (baseline, weeks 2, 4, 8, 12, 16, 20, and 24). The CGI-S scale measures global severity of illness at a given point in time, whereas the CGI-C measures the change in the patient's clinical status. The CGI-S ratings were obtained during the open-label citalopram monotherapy (baseline, end point), the risperidone augmentation phase (baseline, day 4, weeks 1, 2, 4, and 6), and the double-blind phase (baseline, weeks 8, 16, and 24). CGI-C ratings were obtained during the double-blind phase (weeks 2, 4, 8, 12, 16, 20, and 24). Other scales assessing anxiety, quality of life, sexual functioning, resource utilization, and cognition were also administered. Their results will be presented elsewhere.

Safety assessments included reports of spontaneous adverse events collected at every visit. Vital signs, electrocardiograms (ECGs), and laboratory test results were obtained at scheduled visits. The Abnormal Involuntary Movement Scale (AIMS; for dyskinesia and dystonia) (Guy, 1976), the Simpson–Angus Rating Scale (SAS; for parkinsonism) (Simpson and Angus, 1970), and the Barnes Akathisia Scale (BAS) (Barnes, 1989) were completed at regular intervals to measure movement disorders.

Randomization and Blinding

A statistician independent of the study generated randomization sequences. The randomization was noncentralized and stratified by site, age (18–54 and 55–85 years), and presence of psychotic features. The blinded treatment codes were assigned using an automated interactive voice response system. The integrity of the double blind was maintained through database lock.

Statistical Methods

A power analysis was based on an estimated relapse rate of 35% in the risperidone group and 55% in the placebo group, indicating that the number of observed relapses required to have a 90% chance of detecting a constant hazard ratio of 0.54 was approximately 110, at the 5% significance level with a two-sided test. Thus, it was estimated that a total of approximately 234 subjects, 117 in each group with 1:1 randomization ratio, would yield adequate statistical power to detect differences in the double-blind phase. Assuming that approximately 10% of the subjects would not complete the study owing to reasons other than relapse, the total number of planned subjects was increased to 260.

The safety population consisted of all enrolled subjects who had received at least one dose of study medication. The efficacy population for each phase consisted of all enrolled subjects who had received at least one post-baseline efficacy assessment. The last available evaluation for each patient defined the end-point analyses (last observation carried forward). Analysis of covariance, with treatment and center as independent factors and baseline score as covariate, was used to compare treatments on continuous variables. Categorical variables were evaluated using the Cochran–Mantel–Haenzel test stratifying by site. Time to relapse was compared between groups using Kaplan–Meier survival curves. A *post hoc* analysis using linear rank tests (weighted log-rank test) was performed because of a violation of the proportional hazards assumptions of the preplanned survival analysis (Kaplan–Meier survival curves intersected). Further *post hoc* analyses were performed assessing the subgroup of patients whom we considered fully nonresponsive ($<25\%$ improvement) to open-label citalopram monotherapy (Fava and Davidson, 1996). A Cox regression model was used to assess the impact of level of response (full or partial) to citalopram monotherapy on subsequent relapse in the double-blind phase. Uncorrected *t*-statistics was used to compare adverse events in the two patient groups.

RESULTS

Patient Flow and Baseline Characteristics

Of the 633 patients who gave their written informed consent and were screened, 489 entered the citalopram monotherapy phase of the study. Of the 144 patients who did not enter this phase, 54% did not meet entry criteria, 23% withdrew consent, 10% were lost to follow-up, and 13% were withdrawn for a variety of unspecified administrative reasons. Baseline characteristics are shown in Table 1. Subjects were predominantly female and white with a mean ($\pm$SD) age of 46.3 ± 12.6 years. The mean duration of illness was 16.2 ± 12.7 years and duration of the current episode was 2.0 ± 4.2 years. Sixty-five percent of subjects were treated with two or more antidepressants within the current episode. Two percent of subjects had psychotic features. Baseline HAM-D-17 (25.1 ± 3.5) and MADRS (31.8 ± 5.0) scores reflect substantial symptom severity. The citalopram monotherapy phase was completed by 445 (91.0%) of the patients. Reasons for discontinuation are shown in Figure 1. Four hundred and thirty-four (88.8%) patients were nonresponders to open-label citalopram monotherapy ($<50\%$ reduction in HAM-D-17 scores at end point); 299 (68.9%) were fully nonresponsive ($<25\%$ HAM-D-17 score reduction); and 135 (31.1%) were partially nonresponsive (25–49% HAM-D-17 score reduction).

Three hundred and eighty-six patients entered the open-label risperidone augmentation phase. Their clinical and demographic characteristics were similar to those at study baseline (Table 1). This phase was completed by 348 (90.2%) patients; reasons for discontinuation are shown in Figure 1. With risperidone augmentation, 243 (63.0%) achieved symptom resolution (HAM-D-17 score $\leqslant 7$ or CGI-S score of 1 or 2). Of the 241 patients who entered the double-blind placebo-controlled continuation phase, 63.1% had been fully nonresponsive to open-label citalopram and 36.9% had been partially nonresponsive. Discontinuations for reasons other than relapse are shown in Figure 1. Overall, clinical and demographic characteristics of subjects entering the double-blind phase were similar to those at study entry (Table 1).

Mean ($\pm$SD) modal doses were 46.0 ± 15.8 mg/day of citalopram during the citalopram monotherapy phase; 52.6 ± 11.1 mg/day of citalopram and 1.1 ± 0.6 mg/day of risperidone during the open-label risperidone augmentation phase; and 53.1 ± 10.5 mg/day of citalopram and 1.2 ± 0.6 mg/day of risperidone during the double-blind continuation phase.

Efficacy Outcome Measures

Open-label citalopram monotherapy and risperidone augmentation: Mean MADRS total scores were significantly reduced at each time point and at end point during the citalopram monotherapy phase. The left side of Figure 2 shows the MADRS change score for all patients and for the 88.8% of citalopram nonresponders who were eligible to enter the risperidone augmentation phase. The right side of Figure 2 shows that the MADRS total scores were significantly reduced from day 4 to end point in the 386 patients who entered the risperidone augmentation phase;

Table 1 Demographic and Baseline Characteristics of Patients Entering Each Study Phase (Safety Population)

			Double-blind	
	Open-label citalopram monotherapy (*N* = 500)	**Open-label risperidone augmentation (*N* = 388)**	**Risperidone augmentation (*N* = 122)**	**Placebo augmentation (*N* = 119)**
	***N* (%)**	***N* (%)**	***N* (%)**	***N* (%)**
Age (years) (mean ± SD)	46.3 ± 12.6	47.0 ± 12.6	47.8 ± 11.4	48.4 ± 12.0
Patients < 65 years of age	464 (92.8%)	360 (92.8%)	113 (92.6%)	111 (93.3%)
Women	345 (69.0%)	265 (68.3%)	87 (71.3%)*	67 (56.3%)
Race				
White	448 (89.6%)	350 (90.2%)	114 (93.4%)	105 (88.2%)
Hispanic	25 (5.0%)	18 (4.6%)	6 (4.9%)	(4.2%)
Black	14 (2.9%)	11 (2.8%)	1 (0.8%)	4 (3.4%)
Oriental	5 (1.0%)	4 (1.0%)	1 (0.8%)	2 (1.7%)
Other	8 (1.6%)	5 (1.3%)	0	3 (2.5%)
Age at onset of major depression (mean ± SD)	35.9 ± 12.9	30.6 ± 14.1	29.9 ± 12.6	30.8 ± 14.0
Duration of illness (years) (mean ± SD)	16.2 ± 12.7	16.5 ± 12.7	17.9 ± 12.3	17.6 ± 13.9
Patients diagnosed as MDD without psychotic features	480 (98.2%)	379 (98.2%)	121 (99.2%)	115 (96.6%)
Number of depressive episodes in the last 12 months				
One	430 (87.9%)	338 (87.6%)	105 (86.1%)	103 (86.6%)
Two	45 (9.2%)	38 (9.8%)	13 (10.7%)	13 (10.9%)
> Two	13 (2.6%)	10 (2.6%)	4 (3.3%)	3 (2.5%)
Current episode				
Mean duration (years) (mean ± SD)	2.0 ± 4.2	2.0 ± 3.6	2.0 ± 3.7	2.0 ± 3.8
Number (%) of patients with an episode duration > 1 year	229 (44.8%)	174 (45.1%)	54 (44.3%)	51 (43.9%)
Previous antidepressant treatment (current episode)				
One antidepressant	161 (32.9%)	119 (30.8%)	35 (28.7%)	36 (30.3%)
Two or more antidepressants	320 (65.4%)	261 (67.6%)	85 (69.7%)	83 (69.8%)
Missing	8 (1.6%)	6 (1.6%)	2 (1.6%)	0 (0)
Number of hospitalizations for depression since onset				
None	352 (72.0%)	281 (72.8%)	81 (66.4%)	90 (75.6%)
One	75 (15.3%)	60 (15.5%)	23 (18.9%)	14 (11.8%)
> One	61 (12.5%)	45 (11.7%)	18 (14.8%)	15 (12.6%)

*$p < 0.05$ *vs* placebo.

mean (± SD) scores were reduced from 27.7 ± 7.2 at baseline to 13.2 ± 10.1 at end point ($p < 0.001$). Mean MADRS and HAM-D 17 scores are shown in Table 2.

Double-blind placebo-controlled risperidone augmentation: The Kaplan–Meier median time to relapse was 102 days with continued risperidone augmentation and 85 days with placebo augmentation ($p = 0.52$, log-rank) (Figure 3). The rate of relapse was 53.3% in the risperidone augmentation group and 54.6% in the placebo augmentation group. As reported above, an alternative *post hoc* statistical method using linear rank tests (weighted log-rank test) was used to compare survival curves in order to regain the originally defined statistical power level. This analysis suggested a difference in time to relapse in favor of risperidone-treated patients ($p < 0.05$). Investigators reported that significant increases in HAM-D-17 and CGI-C scores were the most common criteria for relapse in both the risperidone and placebo augmentation groups (overall, 90.0 and 87.7%,

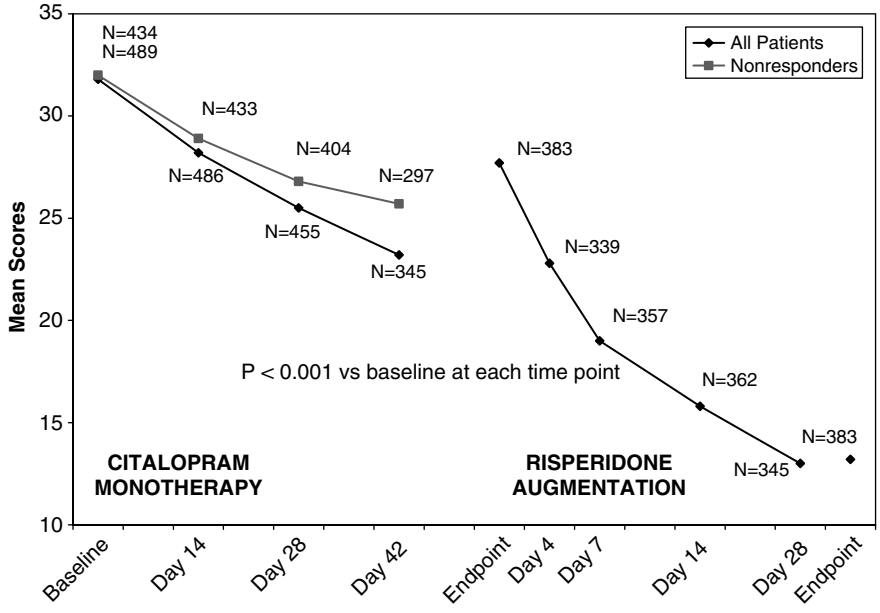

Figure 2 MADRS total scores during citalopram monotherapy and risperidone augmentation.

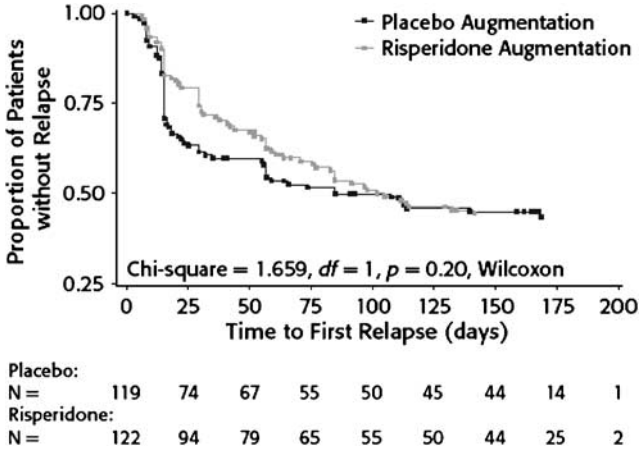

Figure 3 Kaplan–Meier estimates of the time to relapse in the total patient group.

respectively). Mean MADRS and HAM-D 17 scores are shown in Table 2.

An additional *post hoc* subgroup analysis was performed on the data of the 152 patients who were fully nonresponsive to citalopram monotherapy (<25% reduction in HAM-D-17 total score). In these patients, the Kaplan–Meier median time to relapse was 97 days with risperidone augmentation and 56 days with placebo augmentation ($p = 0.05$, Wilcoxon; Figure 4). The relapse rate was 56% in the risperidone group and 64% in the placebo group ($p = 0.05$). Among the 89 patients who were partially nonresponsive to citalopram (25–<50% reduction in HAM-D-17 total score), there was no difference in the Kaplan–Meier estimate in time to relapse ($p = 0.54$, Wilcoxon). A regression analysis explored the impact of full *vs* partial nonresponse to open-label citalopram on subsequent relapse during the double-blind phase. Results of the Cox regression model revealed a hazard ratio of 1.6

Table 2 Mean Depression Rating Scale Scores

			Double-blind	
	Open-label citalopram monotherapy (*N* = 489)	**Open-label risperidone augmentation (*N* = 383)**	**Risperidone augmentation (*N* = 122)**	**Placebo augmentation (*N* = 119)**
MADRS total				
Baseline score	31.8 ± 5.0	27.7 ± 7.2	6.8 ± 4.7	8.1 ± 4.6
End-point change	−6.3 ± 8.7*	−14.5 ± 9.6*	11.2 ± 12.6†	10.4 ± 11.2†
HAM-D 17 total				
Baseline score	25.1 ± 3.5	21.4 ± 5.2	6.0 ± 3.0	6.3 ± 2.9
End-point change	−5.3 ± 6.4*	−11.1 ± 6.9*	7.6 ± 8.8†	7.9 ± 8.1†

*$p < 0.01$, †$p < 0.001$ change score *vs* baseline.

($p = 0.014$), suggesting that patients who were fully nonresponsive to citalopram were much more likely to relapse during the double-blind phase than those who were partial nonresponders.

Among the 130 patients who fulfilled relapse criteria during the double-blind phase, 110 (84.6%) elected to resume open-label treatment with risperidone. Overall, 50% again met the criteria for symptom resolution; results did not differ significantly as a function of treatment condition during the double-blind phase (risperidone, 45%; placebo, 54%; $p = 0.34$ by χ^2).

Safety Outcome Measures

Adverse event rates are presented in Table 3 for all three phases of the study. The types and frequency of adverse events reported are consistent with previous reports in the literature and were usually judged to be mild in severity. There were no clinically significant changes in mean SAS, BAS, or AIMS scores in any study phase and no significant between-group differences in the double-blind period. No clinically meaningful changes in vital signs or ECGs were noted during the study. The only potentially clinically meaningful laboratory abnormality was the mean ($\pm$SD) prolactin level at end point: 35.4 ± 53.4 ng/ml in the risperidone group *vs* 6.6 ± 21.0 ng/ml in the placebo group ($p < 0.001$). Galactorrhea was reported in 2.5% of risperidone-treated patients but none of the placebo-treated subjects. The proportion of patients who gained 7% or more of their body weight from baseline to end point of each phase was 1.3% in citalopram monotherapy; 3.1% in risperidone augmentation; and 8.3 and 2.6% in the risperidone augmentation and placebo augmentation groups, respectively. The mean weight change during the double-blind phase was 1.3 ± 3.8 kg with risperidone augmentation and -0.5 ± 2.9 kg with placebo augmentation.

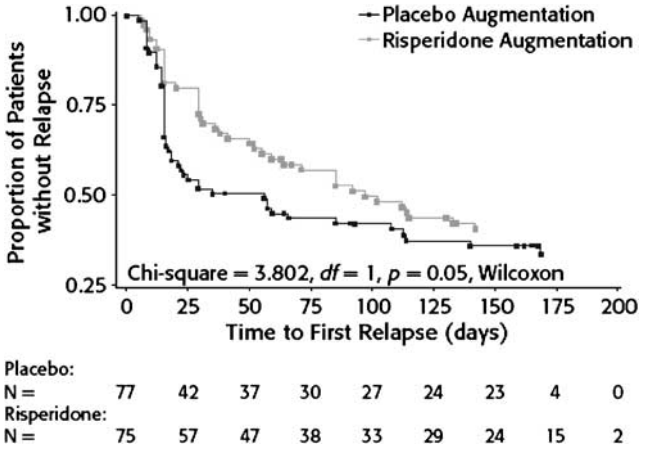

Figure 4 Kaplan–Meier estimates of the time to relapse in the fully resistant patients.

DISCUSSION

This is one of two large placebo-controlled studies of treatment augmentation with an atypical antipsychotic in patients with treatment-resistant depression that have been published (Shelton *et al*, 2005), and the only controlled study to date investigating the efficacy of atypical antipsychotic augmentation for continuation treatment of resistant depression. The primary finding from the open-label phase of this study suggests that risperidone augmentation is associated with symptom resolution for a significant number of patients who were nonresponsive to a prospective adequate trial with citalopram. The rapid reduction in MADRS scores (Figure 2) during this

Table 3 Most Commonly Reported Adverse Events (5% or More of Patients in Any Group; Safety Population)

			Double-blind		
	Open-label citalopram monotherapy ($N = 500$)	Open-label risperidone augmentation ($N = 388$)	Risperidone augmentation ($N = 122$)	Placebo augmentation ($N = 119$)	Exact prob.[a]
Adverse event	***N* (%)**	***N* (%)**	***N* (%)**	***N* (%)**	
Headache	97 (19.4)	45 (11.6)	14 (11.5)	7 (5.9)	0.17015
Nausea	55 (11.0)	19 (4.9)	4 (3.3)	4 (3.4)	1.00000
Dry mouth	45 (9.0)	49 (12.6)	2 (1.6)	3 (2.5)	0.68099
Insomnia	40 (8.0)	11 (2.8)	4 (3.3)	7 (5.9)	0.37153
Somnolence	35 (7.0)	32 (8.2)	3 (2.5)	4 (3.4)	0.71970
Diarrhea	33 (6.6)	19 (4.9)	5 (4.1)	4 (3.4)	1.00000
Dizziness	27 (5.4)	33 (8.5)	7 (5.7)	3 (2.5)	0.33372
Constipation	19 (3.8)	19 (4.9)	4 (3.3)	4 (3.4)	1.00000
Fatigue	16 (3.2)	10 (2.6)	6 (4.9)	9 (7.6)	0.43512
Tremor	11 (2.2)	30 (7.7)	4 (3.3)	2 (1.7)	0.68369
Weight increase	10 (2.0)	24 (6.2)	9 (7.4)	5 (4.2)	0.41033
Appetite increase	9 (1.8)	22 (5.7)	2 (1.6)	3 (2.5)	1.00000

[a]For comparisons of risperidone *vs* placebo during the double-blind discontinuation phase.

augmentation phase is similar to that seen in previous smaller studies of atypical antipsychotic augmentation of SSRI-resistant depression (Ostroff and Nelson, 1999; Shelton *et al*, 2001, 2005; Adson *et al*, 2004; Papakostas *et al*, 2004). The precipitous decline in MADRS scores with risperidone augmentation is not what one would anticipate if this merely reflected an increased exposure to a few more weeks of antidepressant monotherapy (Rapaport *et al*, 2004). These open-label observations do require confirmation with double-blind placebo-controlled trials.

An important finding from the double-blind phase of the study is that continuation of augmentation with risperidone does not seem to confer significant additional benefit beyond short-term treatment (Figure 3). Consistent with observed rates of relapse, there was also a worsening in mean depression rating scale scores in both groups (Table 2). However, for patients who respond partially to citalopram treatment, brief periods of augmentation may be sufficient to enable them to overcome an impasse in response to SSRI treatment. Such findings are analogous to the use of short-term corticosteroid augmentation therapy in asthma, Crohn's disease, and ulcerative colitis.

Another clinically important, albeit exploratory, observation from this study is that 110 of 130 patients who relapsed during the double-blind discontinuation phase elected to enter an open-label stabilization retrieved-dropout component of the study. This suggests that the patients believed that they benefited from risperidone augmentation. Approximately 50% of these patients remitted with flexible-dose open-label augmentation therapy.

Secondary analyses suggest that among the patients who were fully nonresponsive to citalopram monotherapy, risperidone augmentation was associated with a statistically and potentially clinically meaningful delay in the time to relapse (Figure 4). The percentage advantage over placebo treatment is similar to that reported by Robert and Montgomery (1995) in patients randomized to continuation treatment with citalopram. As previously noted, this observation requires further evaluation in a well-controlled prospectively designed study.

Data from our longer-term trial of an atypical antipsychotic augmentation of an SSRI in treatment-resistant depression indicate that risperidone augmentation is generally safe and well tolerated (Table 3). There were no unexpected adverse events reported and those reported were similar in the two augmentation groups. Treatment with risperidone augmentation was associated with serum prolactin elevations, but few reports of clinically associated adverse events were evident. A small number of subjects had a greater than 7% increase in body weight over the course of the study. Finally, ratings of motor side effects were low throughout the trial, suggesting minimal risk of movement disorders. It is important to note that the doses of risperidone used in this study were significantly lower than those typically used for the treatment of schizophrenia or bipolar mania.

One limitation of the study design is the open-label nature of the lead-in phases. The citalopram monotherapy nonresponse rate in this study was higher than that suggested in previously published reports (Einarson, 2004; Thase *et al*, 2001). Although rater or patient bias may have influenced the open-label results, an alternative explanation may be the chronicity and severity of illness of these patients resulting in this low rate of response. Moreover, according to our definition of initial nonresponse during the citalopram monotherapy phase, patients who were partially as well as fully nonresponsive to citalopram were included. Although this only represents a small subset of subjects, this may have influenced findings in the double-blind phase of this study. A second limitation is that a structured diagnostic interview was not part of the initial assessment of subjects. This may have resulted in less uniformity in diagnosis. However, entry into this study required a clinical assessment by an experienced clinician. A third possible criticism of this study is the relatively brief initial period of citalopram monotherapy. We had to balance ethical concerns about the continued exposure of patients with resistant depression to a monotherapy that was clearly not benefiting them with ideal scientific rigor. We felt that a 4- to 6-week initial phase was a reasonable trial for patients who had not previously responded to an average of two other medication trials.

This study is the first large augmentation continuation trial in treatment-resistant depression and may suggest the need to consider alternative designs. Treatment-resistant depression tends to have a complex waxing and waning course. A single-event definition of relapse may not adequately model 'true' relapse for patients who suffer a recurrent illness with fluctuating symptoms. It may well be that a measurement that captures 'total days well' may be a more clinically meaningful outcome to employ for studies of patients with resistant major depression. Another design feature that might allow a more clinically relevant approach to investigating efficacy during the continuation phase of therapy would be the use of a flexible-dose strategy during the double-blind phase. Only subjects who meet relapse criteria despite assertive manipulation of the double-blind compound would be classified as having a relapse. This approach would more closely approximate what usually occurs in clinical practice.

In conclusion, treatment-resistant depression is a common challenge that clinicians and patients must face. In this large international multicenter study, two-thirds of the patients responded rapidly and robustly to open-label risperidone augmentation. This supports previously published open-label studies investigating augmentation with a number of atypical antipsychotic medications (Shelton *et al*, 2001; Adson *et al*, 2004; Papakostas *et al*, 2004). A recent double-blind study of olanzapine augmentation in acutely ill patients showed a rapid but less robust response (Shelton *et al*, 2005), demonstrating the need for replication of the risperidone findings in a prospective double-blind placebo-controlled clinical trial. A second important finding from this trial is that some patients may benefit from a brief period of augmentation, as 50% of the patients who entered the placebo arm of the double-blind phase remained relapse-free. This suggests that treatment-resistant depression is a heterogeneous entity and that a variety of different treatment approaches may be needed to ensure that a patient receives the most appropriate care. Our secondary analysis revealed that patients who were least responsive to citalopram monotherapy may be those most likely to benefit from continuation therapy with risperidone. This *post hoc* finding bears replication but may serve as a potential

indicator of which subgroup of patients with treatment-resistant depression requires longer-term augmentation therapy. In general, results of the present study demonstrate that risperidone augmentation of citalopram is a reasonable and safe strategy that is helpful for some patients with treatment-resistant major depressive disorder.

ACKNOWLEDGEMENTS

This research was funded by Medical Affairs, Janssen Pharmaceutica, LP. MH 61757-A2, 1R21 AT002751-01, 1R01 MH73765-01A1, Cedars-Sinai GCRC Grant RR00425 and The Polier Endowed Chair for Schizophrenia and Related Disorders were supported MHR.

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