# RISPERIDONE AUGMENTATION FOR MAJOR DEPRESSIVE DISORDER SUBOPTIMALLY RESPONSIVE TO ANTIDEPRESSANT TREATMENT: A RANDOMIZED, DOUBLE-BLIND, PROSPECTIVE, PLACEBO-CONTROLLED TRIAL

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## ABSTRACT

**Background:** Based on its effects on neurotransmitters involved in depression, risperidone may further improve clinical response in patients with a suboptimal response to antidepressant medication, although this strategy has not been systematically evaluated.

**Methods:** In a double-blind trial, outpatients with major depressive disorder suboptimally responsive to ≥8 weeks of antidepressant therapy were randomized to risperidone (n=137) or placebo (n=131) augmentation for 6 weeks. At the day 29 (week 4) visit, the dose of study medication could be increased from 1 to 2 mg. The primary endpoint was change from baseline to week 4 (last observation carried forward, LOCF) in the least squares mean (± standard error) 17-item Hamilton Rating Scale for Depression (HRSD-17) total score. HRSD-17 and other efficacy endpoints were also assessed at week 6 LOCF. Adverse events were summarized.

**Results:** Both groups exhibited improvement from baseline to week 4 LOCF in HRSD-17; however, the reduction in HRSD-17 was greater with risperidone vs. placebo (-8.80 ± 0.63 vs. -7.07 ± 0.62, p=0.027). Week 6 LOCF analyses found greater reduction in HRSD-17 with risperidone compared with placebo (-10.5 ± 0.68 vs. -8.06 ± 0.68, p=0.004) and greater percentages of remitters (19.7% vs. 9.5%, respectively; p=0.016) and responders (40.9% vs. 28.6%, respectively; p=0.017). Improvement in measures of quality-of-life, disability, and overall functioning were observed in both groups, with risperidone producing significantly greater effects. The most frequently reported adverse events in both groups were headache, somnolence, and dry mouth.

**Conclusions:** Augmentation of antidepressant therapy with placebo or risperidone produced improvement in symptoms of depression, disability, functioning and quality of life, with risperidone producing a greater effect on clinical responses.

## INTRODUCTION

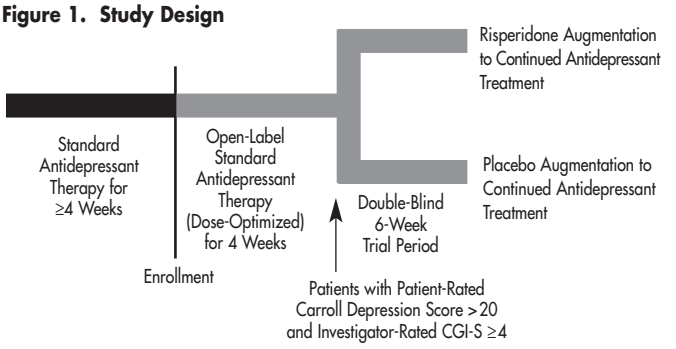
Studies suggest that approximately 50% of depressed patients have no response or only a partial response at best to initial antidepressant monotherapy, with most taking a selective serotonin reuptake inhibitor (SSRI).[1-3] In those with an insufficient response to antidepressant therapy pharmacologic strategies include switching within[3-6] or between antidepressant classes,[3,7-10] the combined use of 2 antidepressants,[7,11-18] or "augmentation" of the antidepressant regimen with a non-antidepressant agent such as thyroid hormone,[19] s-adenosyl-l-methionine (SAMe),[20] lithium,[21] or an atypical antipsychotic agent.[22-24]

Atypical antipsychotic augmentation of an antidepressant regimen is a strategy that is gaining clinical support on the basis of the synergy that can be achieved through combining agents that affect different neurotransmitters involved in depression. Evidence from open-label data indicate therapeutic advantages with atypical antipsychotic agent augmentation in patients with SSRI-resistant major depressive disease.[22-27] On the basis of these reports, we conducted a large, prospective, multicenter, double-blind, randomized, placebo-controlled clinical study to evaluate the efficacy of risperidone augmentation to standard antidepressant therapy in patients with major depressive disorder suboptimally responsive to antidepressant treatment.

# METHODS

## STUDY DESIGN

**Figure 1. Study Design**




- A prospective, multicenter, double-blind, randomized, placebo-controlled, 2-phase study was designed with a 4-week open-label period followed by a 6-week double-blind treatment phase. (Figure 1)

## PATIENTS

- Patients between 18 and 65 years of age with a DSM-IV diagnosis of major depressive disorder (MDD) who exhibited a suboptimal response to at least 4 weeks of treatment with standard antidepressant therapy immediately prior to study participation were enrolled in a 4-week period during which they continued open-label use of their standard antidepressant therapy given at an optimal dose.
- At the conclusion of the 4-week open-label period, patients who continued to meet DSM-IV criteria and exhibited symptoms of MDD (score >20 on patient-rated Carroll Depression Scale and score ≥4 [moderately ill] on the clinician-rated Clinical Global Impressions of Severity [CGI-S]) were eligible for randomization into the 6-week double-blind study phase.
- Exclusion criteria included:
  - women of child-bearing potential;
  - those with serious medical/neurologic illness or history of suicide attempt;
  - individuals with alcohol or substance abuse; and,
  - current treatment with a tricyclic antidepressant, a monoamine oxidase inhibitor, a mood stabilizer and/or antiepileptic, or a centrally acting agent for the treatment of attention deficit disorder or attention deficit hyperactivity disorder or narcolepsy.

## RANDOMIZATION AND DOSING

- Patients enrolled into the double-blind phase were randomized in a 1:1 ratio (stratified by the class of their antidepressant [i.e., SSRI or non-SSRI]) to receive risperidone or placebo augmentation to their antidepressant regimen.
- The dose of double-blind risperidone was titrated as: 0.25 mg once-daily for the first 3 days, 0.5 mg/day on days 4 to 15, and 1.0 mg/day on days 16 to 28. On day 29 of the 6-week study period, patients could continue their 1 mg dose or, in those considered by the investigator to have an insufficient response, the dose of double-blind medication could be increased (to 2 mg/day of risperidone) or patients could discontinue the double-blind phase and receive open-label risperidone for 4 weeks.
- At the conclusion of the 6-week double-blind treatment period, those who received at least 4 weeks of treatment were eligible to receive open-label risperidone for an additional 4 weeks.

## EFFICACY ASSESSMENTS

- The investigator-rated instruments of the 17-item grid version of the Hamilton Rating Scale for Depression (HRSD-17) and CGI-S were administered at baseline and at weeks 1, 2, 4 and 6 during the double-blind study phase.
- Patients completed (via a touch-tone telephone interactive voice response system) the efficacy instruments of Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), Patient Global Improvement Scale (PGI-S), and the Sheehan Disability Scale (SDS), at baseline and at each week of double-blind augmentation treatment.
- The primary efficacy parameter was the change in HRSD-17 total score from baseline to week 4 with missing values included using the last observation carried forward (LOCF) technique.
- Secondary efficacy parameters included changes from baseline to endpoint (with week 6 LOCF being the principal endpoint) in the investigator-rated HRSD-17 and CGI-S, and patient-rated measures of Q-LES-Q, PGI-S, and SDS.
  - Remission was defined as a HRSD-17 score of ≤7 in the week 6 LOCF.
  - Treatment responders were defined as those with a 50% or greater reduction in HRSD-17 score from baseline to week 6 LOCF.

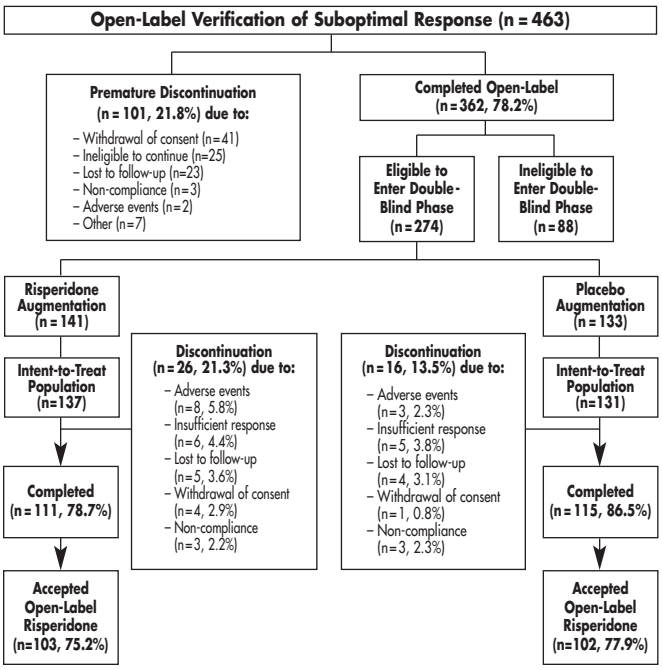
## DATA ANALYSES

- All efficacy analyses were conducted according to the intent-to-treat (ITT) principle (defined as all patients randomized who received at least one dose of double-blind study medication).
- The change from baseline in HRSD-17 was analyzed at each visit and endpoint using an analysis of covariance (ANCOVA) model with treatment, class of antidepressant therapy (strata), and the pooled site as factors, and baseline HRSD-17 as a covariate. Treatment group differences at baseline were tested using an analysis of variance (ANOVA) with effects for treatment, strata, and pooled site.
- Change and percent change from baseline and actual values for other efficacy parameters (i.e., CGI-S, Q-LES-Q, PGI-S, and SDS) were summarized, within-group differences were evaluated by paired t-test, and between-group comparisons analyzed using ANCOVA or ANOVA. Categorical variables were evaluated using the Cochran-Mantel-Haenszel (CMH) test, stratified by strata and/or pooled site, or rank tests as appropriate.
- All adverse events occurring in the safety population (defined as all study patients enrolled in the double-blind augmentation treatment phase who received at least one dose of study medication [or any portion of dose], regardless of their compliance with the protocol) were summarized.

# RESULTS

## PATIENT DISPOSITION

**Figure 2. Patient Disposition**




## PATIENT CHARACTERISTICS

- Baseline characteristics were similar between the treatment arms. (Table 1)

**Table 1. Patient Characteristics at Double-Blind Baseline**

| Characteristic | Risperidone (n = 137) | Placebo (n = 131) |
|---|---|---|
| Gender, n (%) | | |
| Female | 97 (70.8) | 100 (76.3) |
| Male | 40 (29.2) | 31 (23.7) |
| Age (years) mean, median, range | 45.9, 47.0, 20 – 65 | 46.4, 47.0, 20 – 64 |
| Race/ethnicity, n (%) | | |
| Caucasian | 105 (76.6) | 100 (76.3) |
| Hispanic | 7 (5.1) | 11 (8.4) |
| Black | 20 (14.6) | 19 (14.5) |
| Other | 5 (3.6) | 1 (0.8) |
| Education, n (%) | | |
| Elementary/primary school | 2 (1.5) | 1 (0.8) |
| Some high school | 7 (5.1) | 8 (6.1) |
| High school graduate | 44 (32.1) | 39 (29.8) |
| Some college | 48 (35.0) | 45 (34.4) |
| College graduate | 27 (19.7) | 30 (22.9) |
| Postgraduate education | 9 (6.6) | 8 (6.1) |
| Years since 1st MDD episode: mean, median, range | 16.7, 15.0, 0 – 50 | 16.7, 15.0, 0 – 46 |
| Primary antidepressant treatment (at baseline) | | |
| SSRIs | 81 (59.1%) | 78 (59.5%) |
| *Citalopram* | *4 (2.9%)* | *8 (6.1%)* |
| *Escitalopram* | *22 (16.1%)* | *25 (19.1%)* |
| *Fluoxetine* | *18 (13.1%)* | *20 (15.3%)* |
| *Paroxetine* | *14 (10.2%)* | *8 (6.1%)* |
| *Sertraline* | *23 (16.8%)* | *17 (13.0%)* |
| SNRIs | 31 (22.6%) | 26 (19.8%) |
| *Mirtazepine* | *1 (0.7%)* | *2 (1.5%)* |
| *Venlafaxine* | *30 (21.9%)* | *24 (18.3%)* |
| Other agents | 24 (17.6%) | 26 (19.9%) |
| *Bupropion* | *20 (14.6%)* | *16 (12.2%)* |
| *Trazodone* | *2 (1.5%)* | *1 (0.8%)* |
| *Other* | 2 (1.5%) | 9 (6.9%) |
| Troubling symptoms at baseline, percent of patients (mean severity score*) | | |
| Sadness | 72.3% (7.0) | 74.8% (6.7) |
| Trouble concentrating | 70.1% (7.2) | 71.8% (7.3) |
| Reduced involvement in pleasurable activities | 59.1% (7.4) | 64.9% (7.2) |
| Tense or uptight | 54.7% (6.5) | 57.3% (6.8) |
| Reduced sleep | 54.0% (6.7) | 50.4% (6.3) |
| Negative thoughts | 43.8% (6.6) | 42.0% (6.6) |
| Inability to feel emotions | 28.5% (5.9) | 24.4% (5.5) |
| Reduced appetite | 14.6% (3.4) | 11.5% (3.3) |

MDD = major depressive disorder; SNRI = serotonin/norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor
*Scored on a scale of 0 (not troubling) to 10 (extremely troubling).

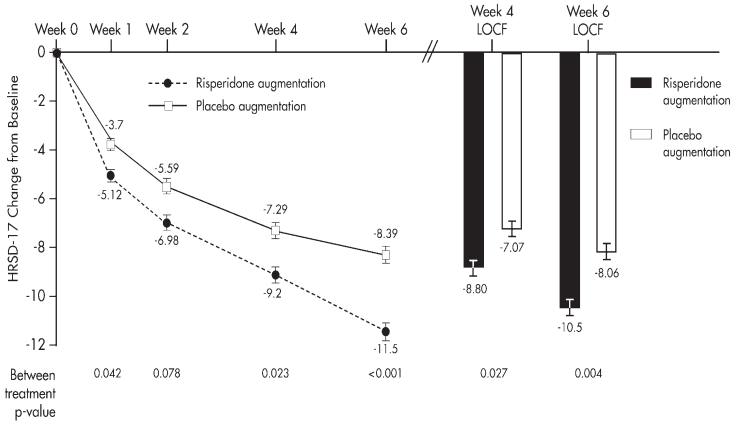
## RISPERIDONE DOSAGE

- During the first 28 days, the mean modal daily dose of risperidone was 0.89 mg ± 0.22 (range 0.25 to 1.0 mg), with nearly 80% of patients (79.6%, 109/137) receiving risperidone 1 mg/day.
- At day 29, dosage adjustments occurred in approximately 20% of patients in each augmentation group.
  - During weeks 1 to 6, the mean modal daily dose of risperidone was 1.12 mg ± 0.46, with 18% of patients receiving risperidone 2 mg/day and 71% receiving risperidone 1 mg/day.
  - During weeks 1 to 6, the mean modal dose equivalent of placebo was 1.17 ± 0.47 mg per day.

## INVESTIGATOR-RATED ASSESSMENTS OF EFFICACY

### *HAMILTON RATING SCALE FOR DEPRESSION (HRSD-17)*

**Figure 3. HRSD-17 Total Score Change from Double-Blind Baseline (Least Square Means ± Standard Error)**




- No substantial change in mean (± standard deviation) HRSD-17 score was observed during the 4-week open-label pre-randomization period (from 24.6 ± 4.97 at baseline to 24.4 ± 4.95 at week 4).
- At the double-blind baseline, the mean (± standard deviation) HRSD-17 scores were 24.2 ± 4.66 among patients randomized to risperidone augmentation and 24.6 ± 5.35 among those randomized to placebo augmentation.
- The decrease in HRSD-17 score (least square means ± standard error) from baseline to week 4 LOCF was significantly greater with risperidone- (-8.80 ± 0.63 vs. -7.07 ± 0.62 with placebo; p = 0.027). (Figure 3)
- A significant between-treatment difference in HRSD-17 total score was observed in the first week of augmentation (-5.12 ± 0.56 risperidone vs. -3.70 ± 0.55 placebo, p = 0.042), with the significance of the difference increasing in magnitude with continued treatment (week 6 LOCF HRSD-17 total scores of -10.5 ± 0.68 with risperidone vs. -8.06 ± 0.68 with placebo, p = 0.004).
- In the analysis of those receiving SSRI vs. non-SSRI cotherapy:
  - The risperidone-SSRI group (n = 81) had a mean decrease in HRSD-17 scores of -9.0 at week 4 compared with -7.2 in those treated with placebo-SSRI (n = 74; p = 0.014).
  - Among those receiving non-SSRI cotherapy, the risperidone (n = 51) and placebo (n = 52) treatment groups did not differ in change from baseline HRSD-17 score at week 4 (-7.7 vs. -7.0, respectively; p > 0.05).
- Among those who elected to receive open-label risperidone at the conclusion of the 6-week double-blind trial, HRSD-17 scores continued to improve in those who initially received risperidone augmentation (HRSD-17 total score of 9.8 ± 6.37 at the end of the additional 4 weeks of treatment) with a substantial decrease in HRSD-17 total score seen in those who had received placebo during the double-blind treatment period (from 16.3 at the end of double-blind treatment to 10.4 ± 6.4 at the end of the 4 week open-label risperidone-augmentation period).

### *PERCENTAGES OF PATIENTS IN REMISSION AND TREATMENT RESPONDERS*

- In the week 6 LOCF analysis significantly more patients with risperidone augmentation were in remission compared to those with placebo augmentation (20% vs. 10%, respectively; p = 0.016). (Figure 4)
- The percentage of patients classified as treatment responders was significantly higher among those given risperidone augmentation compared with placebo augmentation in the week 6 LOCF analysis (41% vs. 29%, respectively; p = 0.017). (Figure 5)

**Figure 4. Percentage of Patients in Remission (HRSD-17 ≤ 7)**

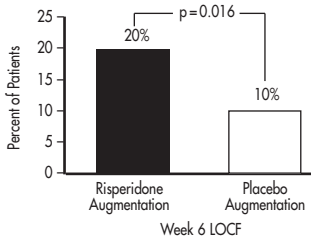
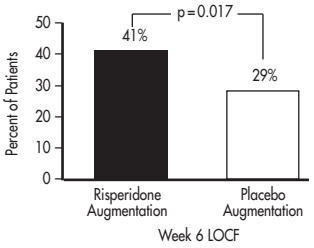



**Figure 5. Percentage of Patients Considered Treatment Responders (≥ 50% Decrease from Baseline HRSD-17 Score)**




### *CLINICAL GLOBAL IMPRESSIONS OF SEVERITY*

- The improvements in CGI-S scores from baseline were significantly greater with risperidone- as compared with placebo-augmentation to antidepressant therapy in the week 6 LOCF (4.4 to 3.1 vs. 4.5 to 3.5, p = 0.002). (Table 2)

## PATIENT-RATED MEASURES OF EFFICACY

### *Q-LES-Q, PGI-S, and SDS*

- In the week 6 LOCF analysis, significant improvements in all three patient-rated measures of efficacy were observed among those given risperidone augmentation compared with placebo augmentation. (Table 2)

**Table 2. Summary of Baseline and Week 6 LOCF Scores (Mean ± Standard Deviation) in Clinician- and Patient-Rated Measures of Efficacy**

| Measure of Efficacy | Risperidone-Augmentation | Placebo-Augmentation | p-value (Risperidone vs. Placebo) |
|---|---|---|---|
| ***Clinician-Rated Measure*** | | | |
| CGI-S | | | |
| Baseline | 4.4 (0.6) | 4.5 (0.6) | |
| Week 6 LOCF | 3.1 (1.2) | 3.5 (1.1) | 0.002 |
| ***Patient-Rated Measures*** | | | |
| Q-LES-Q, Total | | | |
| Baseline | 46.3 (11.1) | 45.5 (10.7) | |
| Week 6 LOCF | 59.6 (14.9) | 54.3 (13.1) | 0.002 |
| Q-LES-Q, Medication Satisfaction | | | |
| Baseline | 2.4 (0.8) | 2.4 (0.8) | |
| Week 6 LOCF | 3.3 (1.0) | 2.9 (1.0) | 0.001 |
| Q-LES-Q, Overall Life Satisfaction | | | |
| Baseline | 2.1 (0.7) | 2.2 (0.8) | |
| Week 6 LOCF | 3.0 (1.0) | 2.7 (0.9) | 0.002 |
| PGI-S Week 6 LOCF* | | | 0.016 |
| Very Much Improved | 7.1% | 5.8% | |
| Much Improved | 33.9% | 19.8% | |
| Minimally Improved | 31.5% | 38.8% | |
| SDS, Total | | | |
| Baseline | 19.5 (5.4) | 19.8 (5.7) | |
| Week 6 LOCF | 12.8 (7.6) | 16.3 (7.0) | <0.001 |
| SDS, Social Life Dimension | | | |
| Baseline | 6.9 (2.1) | 7.0 (2.1) | |
| Week 6 LOCF | 4.4 (2.9) | 5.7 (2.5) | <0.001 |
| SDS, Family Life/Home Responsibilities | | | |
| Baseline | 6.5 (2.0) | 6.7 (2.1) | |
| Week 6 LOCF | 4.4 (2.6) | 5.5 (2.5) | 0.001 |

LOCF=last observation carried forward;* PGI-S was not performed at baseline.

## SAFETY

- Overall, 46% of patients given risperidone augmentation and 55% of those given placebo augmentation to their standard antidepressant regimen experienced treatment-emergent adverse events.
- Headache, the most common treatment-emergent adverse event, was reported in 14.5% of placebo-treated patients compared to 8.8% of risperidone treated patients. (Table 3)
- Extrapyramidal symptom-related adverse events were infrequent with a similar incidence in the risperidone and placebo treatment groups.
- The incidences of akathisia, dystonia, and tremor were 0.7% (1 patient), 0%, and 0.7% (1 patient) with risperidone, respectively, and 0%, 0.8% (1 patient), and 0.8% (1 patient) with placebo, respectively.
- Five treatment-emergent adverse events considered serious were experienced by 2 placebo-augmentation patients (lower abdominal pain, vomiting, hypokalemia, hypomagnesaemia, and attempted suicide/overdose) and no events considered serious occurred in any patient augmented with risperidone.

**Table 3. Treatment-Emergent Adverse Events,* in Order of Total Incidence**

| Adverse Event, n (%) | Risperidone-Augmentation to Antidepressant | Placebo-Augmentation to Antidepressant |
|---|---|---|
| Headache | 12 (8.8) | 19 (14.5) |
| Somnolence | 7 (5.1) | 2 (1.5) |
| Dry Mouth | 7 (5.1) | 1 (0.8) |
| Insomnia | 6 (4.4) | 2 (1.5) |
| Weight increased† | 6 (4.4) | 2 (1.5) |
| Fatigue | 5 (3.6) | 0 |
| Edema, peripheral | 4 (2.9) | 1 (0.8) |
| Disturbance in attention | 3 (2.2) | 0 |

* Reported in ≥5% of patients in any treatment group or were ≥2% in the risperidone group *and* twice that of placebo.
† At the week 6 study visit, patients treated with risperidone and placebo gained a mean of 2.8 (± 5.2) and 0.3 (± 4.3) pounds, respectively ($p < 0.001$).

# LIMITATIONS

- The inclusion of patients currently receiving a range of antidepressant agents may be considered a limitation and precluded comparative analyses for specific risperidone-antidepressant treatment combinations. However, this design, along with the broad inclusion criteria (e.g., no minimum HRSD-17 score) and minimal exclusion criteria closely mimic clinical practice.
- Some differences in the objective and subjective response measures were seen in this study, with investigator-rated measures showing improvement before patient-rated measures of efficacy. This may be the result of patients requiring longer periods of treatment to adequately detect and appreciate any improvement in symptoms of depression. Interestingly, a large percentage of patients (over 75% in each treatment arm, Figure 2) elected to continue receiving open-label risperidone after the conclusion of the study, suggesting that the patients believed that risperidone augmentation was beneficial.

# DISCUSSION & CONCLUSION

- The results of this large, prospective, placebo-controlled, double-blind trial suggest that antidepressant therapy combined with placebo- or risperidone-augmentation is associated with greater symptom relief. Although a placebo effect on HRSD-17 scores were observed in this study, augmentation with risperidone produced a more robust effect on treatment response.
- The prospective design of this study provided confirmation of the clinician-rated as well as patient-perceived benefits of risperidone augmentation to a wide variety of antidepressant agents commonly used in clinical practice. These findings support the theory that combined therapy using agents with synergistic mechanisms of depression-related neurotransmitter effects improve clinical outcomes.
- An analysis of the number needed to treat estimated that risperidone augmentation would lead to one extra treatment responder for every six patients with suboptimal response to antidepressant and who completed 6 weeks of treatment.
- An early (within 1 week) and significant separation was seen between risperidone- and placebo-augmentation to antidepressant therapy in clinician-rated mean HRSD-17 score change from baseline with the between-treatment difference widening with continued treatment.
- Risperidone augmentation produced significant improvements in quality of life and functioning as measured through a battery of patient-rated instruments in the week 6 LOCF analyses.
- Overall, 84% of enrolled patients completed the double-blind study. No unexpected adverse events were reported during the 6-week double-blind phase of the study and no clinically meaningful differences in safety were noted between risperidone and placebo augmentation to antidepressant therapy.
- Our results support the need for future studies conducted over a longer treatment period to further elucidate the role of risperidone augmentation to standard antidepressant treatment in patients with major depressive disorders failing to respond to antidepressant therapy.

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