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A randomized, placebo-controlled trial of risperidone augmentation for patients with difficult-to-treat unipolar, non-psychotic major depression

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Abstract

Objective—Patients (30–50%) with non-psychotic major depression will not respond despite an adequate trial of antidepressant medication. This study evaluated risperidone as an augmenting agent for patients who failed or only partially responded to an adequate trial of an antidepressant medication.

Method—Ninety-seven patients with unipolar non-psychotic major depression who were not responsive to antidepressant monotherapy were randomized to risperidone (0.5–3 mg/day) or placebo augmentation in a four-week, double-blind, placebo controlled treatment trial. The primary outcome measure was remission defined by a score of ≤ 10 on the Montgomery–Asberg Depression Rating Scale (MADRS). Secondary outcomes measures were the Hamilton Rating Scale for Depression, the Clinician Global Impression of Severity scale and the overall satisfaction item of the Quality of Life and Enjoyment Questionnaire.

Results—Subjects in both treatment groups improved significantly over time. The odds of remitting were significantly better for patients in the risperidone vs. placebo arm (OR = 3.33, $p = .011$). At the end of 4 weeks of treatment 52% of the risperidone augmentation group remitted (MADRS ≤ 10) compared to 24% of the placebo augmentation group (CMH(1) = 6.48, $p = .011$), but the two groups were converging. Patients in the risperidone group also reported significantly more improvement in quality-of-life than patients in the placebo group. There were no between-group differences in the number of adverse events reported, however, weight gain was significantly higher in the group receiving risperidone.

Conclusion—Augmentation of an antidepressant with risperidone for patients with difficult-to-treat depression leads to more rapid response and a higher remission rate and better quality-of-life.

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Contributors

Drs. Keitner, Ryan, Nemeroff and Keller designed the study. Drs. Keitner, Ryan, and Solomon managed the literature searches and analysis.

Drs. Ryan and Garlow undertook the statistical analysis. Drs. Keitner and Ryan wrote the first draft of the manuscript.

All authors contributed to and have approved the final manuscript.

Keywords

Antidepressants; Antipsychotic; Clinical drug studies; Mood disorders – unipolar

1. Introduction

An estimated 30–50% of depressed patients do not respond, or only partially respond, to an adequate treatment with antidepressant medication (Appelberg et al., 2001; Fava and Davidson, 1996; Fleck and Horwath, 2005; Hirschfeld et al., 2002; Keitner et al., 2006; Rubio et al., 2004). Furthermore, rapid recovery of severe depression is the exception rather than the rule (Lewis, 2003). In the STAR*D project only 28% of patients remitted and less than 50% responded to the first antidepressant mono-therapy trial (Rush et al., 2004; Trivedi et al., 2006). Depressed patients who do not respond to adequate antidepressant treatment pose a clinical dilemma. Switching antidepressants, combining antidepressants, and augmenting the first-line antidepressant treatment with lithium or thyroid hormone therapy are frequently used treatment options for antidepressant non-responders (Fleck and Horwath, 2005; Keller, 2005; Thase, 2002). Augmentation with an atypical antipsychotic has become another option for patients with difficult-to-treat depression as, unlike the typical antipsychotic medications, atypical antipsychotic agents present low risks for EPS, TD, and other motor disturbances, and may have a broader spectrum of efficacy, possibly due to blockade of D_2 and/or 5-HT receptors (Blier and Szabo, 2005; Nelson, 2003; Ostroff and Nelson, 1999).

A few studies, albeit with different designs, have supported the efficacy of atypical antipsychotic agents in treating depression. One of the first to do so was an open-label risperidone augmentation study of eight patients, all of whom remitted within 1 week and all of whom maintained their improvement at a three-month follow-up (Ostroff and Nelson, 1999). In a double-blind, randomized risperidone augmentation trial, patients improved after 4 weeks and maintained the improvement at the 6-week endpoint (Gharabawi et al., 2006). In two large double-blind studies using a combination of medications (i.e., not augmentation trials per se), patients reported a rapid response to the combined use of olanzapine and an antidepressant, though the treatment effect was not sustained at the study endpoints of 8 and 12 weeks (Corya et al., 2006; Shelton et al., 2005). A more recent report of parallel studies of patients with Treatment Resistant Depression (TRD) found that one study showed no treatment differences using an olanzapine/fluoxetine combination while the second study, and the pooled data, did find significant improvement in patients who received the combination therapy (Thase et al., 2007). Aripiprazole has been shown to have positive results when used as adjunctive therapy for patients diagnosed with major depression (Berman et al., 2007) and a meta-analysis concluded that augmenting antidepressant medications with atypical antipsychotics (olanzapine, risperidone, and quetiapine) resulted in significantly stronger remission and response rates (Papakostas et al., 2007).

These and other studies suggest that using atypical antipsychotics as an adjunct to antidepressant medication may be a promising treatment for some patients with major depression. Of interest, study designs often differ in the lack of a standard definition of the study population (e.g., differences between difficult-to-treat and treatment resistant depressions, Thase, 2002; Kupfer and Charney, 2003; Shelton et al., 2005), the variation in lead-in trial time (4–8 weeks, Appelberg et al., 2001; Licht and Qvitzau, 2002; Bouhours et al., 2004; Papakostas et al., 2005; Corya et al., 2006; Berman et al., 2007; Alexopoulos et al., 2008), differences in study length and the range of cut-offs and instruments defining remission (e.g., 8–10 on MADRS) (Nemeroff, 2005; Shelton et al., 2005; Berman et al., 2007; Papakostas et al., 2007; Thase et al., 2007).

In this study we specified the population as patients with difficult-to-treat depression, the lead-in time of at least 5 weeks, a study period of 4 weeks, and a remission cut-off of 10 on the Montgomery–Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979). The primary objective was to compare the efficacy of augmentation with risperidone vs. placebo in patients with difficult-to-treat depression, defined as patients who failed to respond or only partially responded to antidepressant monotherapy. We focused on difficult-to-treat depression as a useful concept that may have more generalizability than TRD and, according to a recent STAR*D report, may be part of a continuum that leads to TRD (Thase et al., 2007; Rush et al., 2006). We selected 5 weeks as a lead-in period as it met the higher range of duration (3–5 weeks) defining an adequate treatment trial (Keller, 1988; Sackheim, 2001). We chose a 4-week treatment trial as the previous studies had suggested that, if the adjunctive atypical medication worked, it would do so relatively quickly (in 1–2 weeks). We chose the MADRS as it is more sensitive to change than the (Hamilton Depression Scale (HAM-D) (Hamilton, 1960) and would be more likely to register a change within the 4-week trial (Mulder et al., 2003).

We addressed the following: Do patients with difficult-to-treat depression respond to risperidone augmentation? Does risperidone augmentation produce a more rapid response than continuing on the prescribed antidepressant? What is the side effect profile of patients receiving risperidone augmentation? Does risperidone augmentation alter the patient's perception of his/her quality-of-life? We hypothesized that patients in the risperidone augmentation arm would have a better clinical outcome than patients in the placebo augmentation group.

2. Method

2.1. Overview

The two-phase study was conducted at two tertiary care hospitals affiliated with academic medical centers. Phase I consisted of an open-label treatment trial with antidepressant monotherapy lasting for at least 5 weeks. Depressed patients were eligible for the open-label phase of the study if they were not currently treated with antidepressant medication, their current medication dose or duration did not meet criteria for an adequate trial, or their prescribed antidepressant treatment was not well documented. The particular antidepressant used was based on clinician choice. An adequate trial was defined a priori and was adapted from previously published guidelines (Table 1) (Keller, 1988; Sackheim, 2001). We did not limit the type of antidepressant medications so that we could capture the range of antidepressant medication treatments used by clinicians. Nor did we limit number of previous failed trials. Patients who partially responded or did not respond in Phase I were eligible to enter Phase II, the randomized trial, if they continued to meet the study inclusion/exclusion criteria listed below. Patients were eligible to enter Phase II directly if their current failed antidepressant trial met the defined criteria for adequacy, the trial was clearly documented, and they met all study criteria (Fig. 1). Before enrolling, patients were given a physical examination, EKG, SCID I and II, and standard laboratory screening.

Institutional Review Boards approved the protocol at both study sites. After complete description of the study to the subjects, written informed consent was obtained.

2.2. Patient selection

Ninety-seven outpatients who met criteria for unipolar non-psychotic major depression and failed to respond, or only partially responded, to at least a 5-week open-label trial of an adequate dose of antidepressant monotherapy consented to participate in this double-blind, randomized, placebo-controlled treatment study of risperidone augmentation. Two patients

withdrew (1 from each site) after receiving the first dose of study medication. Inclusion criteria for the randomized portion (Phase II) of the study were (1) major depressive episode according to the Structured Clinical Interview for DSM-IV; (2) Montgomery–Asberg Depression Rating Scale (MADRS), (Montgomery and Asberg, 1979) score ≥ 15 ; (3) age 18–65 years; (4) currently receiving, but failing to respond, to an adequate trial of an antidepressant medication at an adequate dose for an adequate duration; (5) ability to read and write English.

Patients were excluded from the study if they (1) met criteria for bipolar I or bipolar II disorder; (2) had psychotic features; (3) were deemed an imminent suicide risk; (4) met criteria for substance dependence or abuse in the previous three months; (5) had a concurrent medical illness or history of seizures that would contraindicate use of the study medication; (6) were receiving ECT; or (7) were pregnant or breastfeeding. Patients currently taking herbal medications (e.g., St. John's Wort, kava, SAM-e, folic acid supplements) were also excluded. Patients were prohibited from initiating psychotherapy after entry into Phase II.

2.3. Intervention

In Phase II of the study patients continued on the same dose of their antidepressant medication and were randomized in a 2:1 ratio to receive adjunctive risperidone or placebo for the 4-week treatment trial. Unequal randomization is a strategy that can be used to detect differences between groups when using a small sample size, to facilitate recruitment, and to minimize the number of patients assigned to placebo (Kraemer and Thiemann, 1987; Leon and Solomon, 2003; Venter and Maxwell, 1999). Risperidone was initiated at 0.5 mg/day with the option of increasing the dose to 2 mg/day by day 21. If a patient did not respond to 2 mg by day 21, the clinician could increase the dose to 3 mg for the remainder of the study. Patients were seen weekly by a study psychiatrist to assess symptom severity and side effects and to adjust the dose of the study drug. The antidepressant medication remained at a fixed dose throughout the 4-week trial. Early reports of adjunctive atypical antipsychotic medication use found that, if the adjunctive medication worked, it typically did so within 1 week or less. Therefore, we were able to limit the Phase II trial to 4 weeks. Benztropine (1 mg/p.o.), administered once or twice daily, was permitted for those who experienced extrapyramidal side effects. Sedative use (Zolpidem, Zaleplon – both at 5 mg qhs) was permitted to treat insomnia, but prohibited the day before a clinical evaluation in order to minimize their impact on symptom severity rating scales. Trazodone was prohibited for the treatment of insomnia. No other psychotropic medications were permitted.

2.4. Outcome measures

The main outcome ratings used in the study were the MADRS (Montgomery and Asberg, 1979), the Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960), the Clinical Global Impression of Severity (CGI-S) (Guy, 1976) and the overall functioning item of the Quality of Life and Enjoyment Questionnaire (Q-LES-Q) (Endicott et al., 1993). The MADRS was chosen *a priori* as the primary outcome measure because it is more sensitive to change than the HAM-D and more strongly reflects clinical judgment (Calabrese et al., 1999; Jahn et al., 2004; Mulder et al., 2003). The HAM-D was included as a secondary measure because it is a widely used measure that provides a reference for comparison with other studies. The MADRS is a 10-item clinician rated scale that assesses the core symptoms of depression (Calabrese et al., 1999). Symptoms are rated from 0 (minimal) to 6 (severe) and total scores range from 0 to 60. The HAM-D is a 17-item clinician rated scale that is weighed towards somatic complaints (Calabrese et al., 1999). Trained research raters, blind to treatment arm, administered both the MADRS and HAM-D at baseline and weekly for 4 weeks.

The CGI-S rating is a measure of global severity of illness rated on a 7-point scale ranging from 1 (no symptoms) to 7 (very severe). The study psychiatrist, blind to treatment arm, completed weekly CGI-S ratings for each patient. The Q-LES-Q is a self-report instrument designed to measure the degree of enjoyment and satisfaction experienced by subjects in various areas of daily functioning. The Q-LES-Q was completed at baseline and at the end of weeks 2 and 4. By design, the item on overall life satisfaction and functioning is reported as an outcome measure. Incidence of side effects, elicited weekly by the study psychiatrist, was compared between the two treatment arms to evaluate safety issues.

2.5. Statistical analyses

Preliminary analyses were used to compare sociodemographic and illness characteristics of patients at the two sites and to ensure comparability between the two treatment groups on patient age, gender, and severity of illness. Any significant differences found between sites were controlled for in subsequent analyses. The data analytic strategy included modified intent-to-treat (ITT) and completer analyses. The modified ITT group consisted of all patients randomized into the treatment trial who received at least one dose of study medication (risperidone or placebo), and completed at least 1 set of assessments. Two subjects were lost to follow-up after week 1, leaving a sample of 95 suitable for data analysis (Kraemer and Thiemann, 1987). The completer group ($N = 82$) included patients who received 4 weeks of study medication. A subset of patients ($N = 77$) completed the Q-LES-Q, added after the study began.

The primary outcome variable, remission, was defined *a priori* as a MADRS rating of ≤ 10 and response was defined as a 50% decrease on the MADRS from baseline to end of study. Remission on the HAM-D was defined as a score of ≤ 7 and response as a 50% decrease from baseline to end of study. Remission and response rates in the two treatment arms were compared using Pearson's chisquare test or the Cochran–Mantel–Haenszel (CMH) test to control for site differences. Repeated measures analysis of covariance (ANCOVA) was used to measure differences between the two treatment groups while controlling for baseline values. Because previous studies noted rapid treatment effects with atypical augmentation, we purposefully compared rates of change between the two groups on a weekly basis. Odds ratios were generated to determine if risperidone augmentation affected the chance of recovery or response. Clinician CGI ratings and the Q-LES-Q overall functioning item were compared over time between the two treatment groups. Statistical tests were 2-tailed and set at the .05 level of significance. We conducted post hoc analyses to compare weight gain by treatment group for three standard categories of Body Mass Index (BMI): normal ($BMI < 25$), overweight ($BMI \geq 25$ and < 30), and obese ($BMI \geq 30$).

3. Results

There were no differences between the placebo augmentation group vs. the risperidone augmentation group in gender, race, age at study entry, age at onset of major depression, severity of current episode, or by entry into the randomized trial via Phase I or Phase II. Number of prior depressive episodes differed significantly between the placebo group (mean = 5.9, $SD = 8.5$) and the risperidone augmentation group (mean = 2.8, $SD = 2.4$) due to a single outlier in the placebo group ($F = 6.39$, $df = 1, 81$, $p = .013$). When the outlier was removed (1 case of 42 reported previous episodes) there were no significant differences between treatment groups (Table 2).

There were significant site differences in gender and number of previous episodes, and a trend towards significance on the number of comorbid psychiatric illnesses. When compared to the Emory site, the Brown site reported a higher percentage of female patients (72.5% vs. 39.1%, Pearson's $\chi^2 = 11$, $df = 1$, $p = .001$), a greater number of previous depressive

episodes (mean = 3.8, SD = 3.4 vs. mean = 2.5, SD = 1.5, $F = 5.75$, $df = 1.79$, $p = .019$), and more comorbid psychiatric illnesses (96% vs. 85%, Pearson's $\chi^2 = 3.67$, $df = 1$, $p = .056$). The median length of the current depressive episode was 52 weeks for patients in the placebo group (mean = 111.4, SD = 159.3) and 60 weeks for patients in the risperidone group (mean = 230.3, SD = 346.9). There was a significant site effect in length of episode ($F = 4.50$, $df = 1.86$, $p = .037$). When the data were pooled, the difference between the two groups (placebo vs. risperidone) was non-significant ($F = 3.25$, $df = 1.86$, $p = .075$). Severity of depression at baseline was comparable between patients receiving placebo or risperidone measured by the MADRS, the HAM-D (Table 2), and the CGI ratings (moderate-markedly ill: 90.9% vs. 92.2%, CMH = .03, $df = 1$, $p = .860$). Patients received the following antidepressants: escitalopram (26.0%), citalopram (9.4%), sertraline (18.8%), fluoxetine (11.5%), bupropion (12.5%), venlafaxine (10.4%), paroxetine (7.3%), nefazadone (2.1%), mirtazapine and imipramine (each 1%). Patients were started on a dose of 0.5 mg/day of study medication that could be increased to a maximum dose of 3 mg/day. At the end of the study the mean dose of risperidone was 1.6 mg/day (SD = .73) with a range of .5–3.0 mg/day).

3.1. Remission

In the modified ITT analysis at the end of 4 weeks of treatment 51.6% of the risperidone augmentation group remitted (32/62) as measured by the primary outcome variable, MADRS ratings, compared to 24.2% of the placebo augmentation group (8/33) (CMH = 6.48, $df = 1$, $p = .011$). Significant differences were apparent after 2 weeks on study medication: 37.3% of the risperidone group remitted vs. 15.6% of the placebo group (Fig. 2). After 1 week on study medication there was a significant difference in change scores, indicating both a time effect and a treatment effect. The time effect continued throughout the study period whereas the treatment effect lost significance by week 4. That is, patients in both groups continued to improve over time but the groups no longer differentiated by augmentation medicine. The odds of remitting were significantly better for patients in the risperidone augmentation group compared to the placebo group (odds ratio = 3.33, 95% CI = 1.303, 8.526, $p = .011$). HAM-D scores showed a similar pattern but without attaining significance. At endpoint, 35.5% of the risperidone augmentation group remitted (22/62) compared to 18.2% of the placebo group (6/33) (CMH = 3.10, $df = 1$, $p = .078$). Results for patients who completed the study paralleled the modified ITT analysis but did not reach significance. 52.7% (29/55) of the risperidone group remitted (MADRS score) by the end of the study compared to 29.6% (8/27) of the placebo group (CMH = 3.78, $df = 1$, $p = .052$). 38.2% of the risperidone group remitted (HAM-D) vs. 22.2% of the placebo group (CMH = 2.31, $df = 1$, $p = .129$).

3.2. Response

In the modified ITT analysis after 4 weeks of treatment 54.8% of the risperidone augmentation group responded compared to 33.3% of the placebo group (CMH = 3.88, $df = 1$, $p = .049$). Significant differences in response rates began after 1 week on study medication with 24.2% of the risperidone group meeting improvement criteria compared to 6.1% of the placebo group (CMH = 4.68, $df = 1$, $p = .031$). A larger percentage of patients in the risperidone treatment group (vs. placebo group) also responded according to the HAM-D scores, but the difference did not reach significance (45.2% vs. 30.3% (CMH = 2.07, $df = 1$, $p = .151$). For completers, 56.4% of the risperidone group met response criteria (MADRS score) vs. 40.7% of the placebo group (CMH = 1.63, $df = 1$, $p = .201$). HAM-D response ratings for completers were 47.3% for the risperidone group vs. 37.0% for the placebo group (CMH = 1.03, $df = 1$, $p = .311$).

3.3. Severity ratings

At baseline clinicians rated 90.1% (30/33) of patients in the placebo group and 92.2% (59/64) of the patients in the risperidone group as moderately or markedly ill (CMH = .03, $df = 1$, $p = .860$). Clinician CGI change scores improved significantly in both groups (risperidone: 4.2–2.8, $df = 61$, $p < .001$, placebo: 4.1–3.2, $df = 32$, $p < .001$) over the course of the study. The time effect was significant throughout the study, but the treatment effect reached significance only at week 3. By endpoint differences in mean change scores by treatment group were -1.4 ($SD = 1.2$) for the risperidone group and $-.9$ ($SD = 1.0$) for the placebo group ($F = 2.92$, $df = 1.91$, $p = .091$).

3.4. Side effects

There was no significant difference between groups in the overall number of adverse events reported. Patients in the risperidone group were significantly more likely to report increased appetite while patients in the placebo group were significantly more likely to report fatigue and abdominal gas. The most common side effects reported by patients treated with risperidone were increased appetite, dry mouth, and constipation whereas placebo-treated patients reported headache, constipation, and insomnia (Table 3). Twenty-one percent (7/33) of the patients in the placebo group dropped compared to 12.9% (8/62) in the risperidone augmentation group.

There was a significant difference in weight gain between the two treatment groups with patients on risperidone gaining a mean of 4.3 ($SD = 5.0$) pounds by the end of study compared to .3 ($SD = 3.6$) pounds in the placebo group ($F = 15.23$, $df = 1.91$, $p = .0002$). We examined weight gain by BMI categories of normal weight (BMI: 18.5 to <25), overweight (BMI: 25 to <30), and obese (BMI: ≥ 30) and by a 7% increase in weight from baseline to end of study. In the risperidone treatment arm the mean weight gain from baseline to end of study for patients with normal BMI at baseline was 3.5 ($SD = 2.9$) pounds, 3.3 ($SD = 4.7$) pounds for overweight patients, and 5.6 ($SD = 5.4$) pounds for obese patients. Two patients met or exceeded a 7% increase from their baseline weight. Both were in the risperidone treatment group, 1 overweight at baseline and 1 obese at baseline.

3.5. Overall functioning

Patients were asked to rate overall life satisfaction and contentment during the previous week. Change scores between baseline and end of study were significantly higher (better) for patients in the risperidone group (1.3–2.5) compared to patients in the placebo group (1.2–1.7; $F = 6.44$, $df = 1.62$, $p = .014$). Similar to other outcome measures, significant differences between the two treatment groups were reported after 2 weeks on medication.

4. Discussion

This study assessed the efficacy of an atypical antipsychotic agent combined with an antidepressant medication for patients with difficult-to-treat unipolar, non-psychotic major depression. The rate of remission and the odds of remitting after 4 weeks of treatment were significantly better for patients receiving risperidone vs. placebo augmentation. Response was evident after 1–2 weeks of augmentation. Patients in the risperidone augmentation group reported significantly better overall functioning and no difference in the frequency of adverse events. However, risperidone-treated patients were more likely to gain weight than patients in the placebo group and the two groups were beginning to converge by the study endpoint.

Remission of major depression is difficult to achieve for many patients and less than 50% of depressed patients will respond to standard treatments (Hirschfield et al., 2002; Keitner et al.,

2006; Rush et al., 2004; Trivedi et al., 2006). Several treatment strategies are available for depressed patients who fail to respond, or only partially respond, to an adequate trial of antidepressant monotherapy but the next step after a failed adequate medication trial remains unclear (Keller, 2005; Nelson, 2003). In this study we found a significant and rapid treatment effect when an antidepressant medication was augmented with risperidone at relatively low doses for patients who failed at least one adequate trial of antidepressant monotherapy.

The fact that treatment differences were not sustained at the end of the trial may be due to study treatment, patient selection, patient drops, and/or power. Augmentation with an atypical antipsychotic agent may be unnecessary for some patients who respond to monotherapy, albeit at a slower rate. Trivedi et al. (2001) suggested that some patients who do not respond after 3–4 weeks of medication may respond after 6–8 weeks. Licht and Qvitzau (2002) also advocate continuing treatment for 8 weeks before changing strategies unless there is clinical deterioration. However, for the patient population in this study, who were not naïve to treatment, the likelihood that the patient and clinician would continue on the same medication(s) for 8 weeks with no response may be unrealistic. The fact that 21% of the placebo group dropped from the study (vs. 12.9% of the risperidone group) may be due to inadequate response to medication. Rapid response to an adjunctive atypical followed by convergence with a control group was found in the recent study by Berman et al. (2007) and the combination studies also reported a quick response followed by a leveling off after a few weeks (Shelton et al., 2005; Corya et al., 2006).

Our sample of patients with difficult-to-treat depression, rather than patients with treatment resistant depression (TRD), possibly led to a more heterogeneous sample of depressed patients. We explicitly broadened our inclusion criteria, however, in order to increase generalizability and to address the needs of the significant numbers of depressed patients who have less than an optimal response to first line treatment. We do not yet know if difficult-to-treat depression represents a unique subtype (Kupfer and Charney, 2003), or if it is one part of a wide spectrum of depressions that characterize the staging systems (Thase et al., 2007). Findings from the STAR*D study suggest that two treatment failures are likely to signify a TRD (Rush et al., 2006; Trivedi et al., 2006).

Finally, the small to moderate treatment effect may indicate that the study was underpowered. That other studies testing atypical antipsychotics as augmenting agents (Berman et al., 2007; Ostroff and Nelson, 1999; Shelton et al., 2001) and those with larger samples (Corya et al., 2006; Shelton, 2006) report a similar pattern (i.e., rapid response followed by convergence of treatment groups), suggests otherwise. In fact, a compelling reason to initiate an atypical antipsychotic augmenting agent sooner rather than later may be because several studies, including this one, have reported a significant response as early as 1 week into treatment (Barbee et al., 2004; Bouhours et al., 2004; Ostroff and Nelson, 1999; Shelton et al., 2001).

Limitations to this study include the relatively short treatment trial and a modest sample size. In addition, we were unable to obtain complete information on the number of failed treatment trials and the specific number of weeks a patient was on an antidepressant medication before enrolling in the study. These factors, as well as other patient and illness characteristics may explain different patterns of response (e.g., rapid vs. no/slow/incomplete response (Fava, 2003; Trivedi et al., 2005). Subsequent reports on findings from this study will address potential predictors of remission and response.

Although atypical antipsychotics are generally well tolerated, their mechanism of action remains poorly understood (Bluer and Szabo, 2005; Simon and Nemeroff, 2005). Several

questions remain to be addressed in future studies in order to understand the possible role of atypical antipsychotics in the treatment of depression. The dose and duration of the antipsychotic augmentation strategy are of particular importance. It is also unclear if one can use an antipsychotic agent to enhance the effect of an antidepressant medication for a short period of time, and then prescribe it periodically as a booster. This strategy may well alleviate concerns about the long-term use of antipsychotic agents, but the timing, dosing, and effectiveness of such a strategy remains to be studied. In this study patients did not report extrapyramidal side effects, but the dose was low and the trial was of short duration. Future reports will examine side effects in more detail, as well as changes in prolactin levels, weight gain, and clinical and patient characteristics. Clinicians need to weigh the severity of the patient's current depression, his/her medical history, comorbid illnesses, magnitude of disability and dysfunction, cost of treatment, interactions with other potential confounds, and side effects, including weight gain, to decide on the best treatment options for each patient. The augmentation option with an atypical antipsychotic medication may be the most appropriate when speed of response is particularly desirable.

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Conflict of interest

Gabor I. Keitner, MD – Research support Investigator Initiated Study for Janssen Pharmaceutica.

Research support – AstraZeneca

Speaker – Janssen Pharmaceutica

Steven J. Garlow, MD – Research support Investigator Initiated Study for Janssen Pharmaceutica.

Consultant – Solvay

Honoraria – Physicians Post Graduate

Speaker – Eli Lilly and Pfizer

Christine E. Ryan, PhD – Research support Investigator Initiated Study for Janssen Pharmaceutica.

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David A. Solomon, MD – Research support Investigator Initiated Study for Janssen Pharmaceutica.

Charles B. Nemeroff, MD, PhD – Research support Investigator Initiated Study for Janssen Pharmaceutica.

In the past three years, Dr. Nemeroff consulted to, served on the Speakers' Bureau and/or Board of Directors, has been a grant recipient, and/or owned equity in one or more of the following: Abbott Laboratories, Acadia Pharmaceuticals, American Foundation for Suicide Prevention (AFSP), American Psychiatric Institute for Research and Education (APIRE), AstraZeneca, BMC-JR LLC, Bristol-Myers-Squibb, CeNeRx, Corcept, Cypress Biosciences, Cyberonics, Eli Lilly, Entrepreneur's Fund, Forest Laboratories, George West Mental Health Foundation, Glaxo-SmithKline, i3 DLN, Janssen Pharmaceutica, Lundbeck, National Alliance for Research on Schizophrenia and Depression (NARSAD), Neuroentics, NIMH, NFMH, NovaDel Pharma, Otsuka, Pfizer Pharmaceuticals, Quintiles, Reevax, UCB Pharma, Wyeth-Ayerst.

Currently, Dr. Nemeroff serves on the Scientific Advisory Board for AstraZeneca, Johnson & Johnson, Pharma Neuroboost, Forest Laboratories, Quintiles and NARSAD.

He is a grant recipient from NIH, NARSAD and AFSP. He serves on the Board of Directors of AFSP, APIRE, NovaDel Pharmaceuticals and the George West Mental Health Foundation. He owns equity in CeNeRx and Reevax. He owns stock or stock options in Corcept, Cypress Biosciences and NovaDel.

Martin B. Keller, MD – Research support Investigator Initiated Study for Janssen Pharmaceutica. *Consultant/Honoraria*

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Fig. 1.
Schema for entry and flow in study.

P	Placedo					
	33	33	32	30	26	33
s	Risperidone					
	62	62	59	57	54	62

Fig. 2.
% Remitted by treatment group – modified ITT MADRS 10.

Table 1**Adequate dose and duration of a range of antidepressant medications**

An adequate trial of an antidepressant is defined as a minimum of 5 weeks of treatment with an adequate dose of at least 3 weeks. Adequate doses of SSRIs are defined as:

Citalopram	20 mg	Paroxetine	20 mg
Fluoxetine	20 mg	Sertraline	100 mg
Fluvoxamine	150 mg	Escitalopram	10 mg

An adequate trial of commonly used atypical antidepressants is defined as a minimum of 5 weeks of treatment with an adequate dose of at least 3 weeks. Adequate doses are defined as:

Bupropion	200 mg	Trazodone	400 mg
Mirtazapine	30 mg	Venlafaxine	150 mg
Nefazadone	300 mg		

Adapted from Keller (1988) and Sackheim (2001).

Table 2

Patient characteristics at baseline by treatment group

	Placebo – N = 30	Risperidone – N = 64	Test – Stat (df)	<i>p</i>
Gender <i>N</i> (%) ^a			χ^2 (df)	
Female	18 (54.5)	37 (57.8)		
Male	15 (45.5)	27 (42.2)	.09 (1)	.76
Race <i>N</i> (%)				
Non-white	5 (15.2)	4 (6.3)		
White	28 (84.8)	59 (93.7)	2.05 (1)	.15
Age (Yrs)			<i>F</i> (df)	<i>p</i>
Mean (SD)	44.6 (11.1)	45.5 (11.6)		
Range	24–59	20–63	.13 (1.95)	.72
Age depression onset (Yrs)				
Mean (SD)	25.4 (11.8)	27.5 (14.4)		
Range	5–46	7–57	.46 (1.87)	.497
No. of depressive episodes ^b				
Mean (SD)	5.9 (8.5)	2.8 (2.4)		
Range	1–42	1–13	6.39 (1.81)	.013
MADRS			<i>t</i> (df)	<i>p</i>
Mean (SD)	25.5 (5.4)	25.8 (5.7)	–.254 (67)	.80
HAM-D				
Mean (SD)	18.6 (4.3)	19.5 (4.7)	–.946 (70)	.35
CGI, <i>N</i> (%)			70 ² (6)	
Normal	–	–		
Borderline ill	–	–		
Mildly ill	3 (9.1)	5 (7.8)		.77
Moderately ill	23 (69.7)	44 (68.8)		
Markedly ill	7 (21.2)	15 (23.4)		
Severely ill	–	–		
Extremely ill	–	–		

^aSite effect: $\chi^2 = 11.0$, *df* = 1, *p* = .001^bSite effect: *F* = 5.75, *df* = 1.79, *p* = .019, no treatment effect (*F* = 2.62, *df* = 1.79, *p* = .110) when outlier removed.

Table 3

Side effect/AE profile by treatment groups

	Placebo		Risperidone		χ^2 (df = 1)	p
	N	%	N	%		
Any event	27	81.8	54	84.4	.10	.75
Abdominal gas	2	6.1	0	0.0	3.96	.05
Constipation	3	9.1	8	12.5	.25	.62
Dry mouth	1	3.0	9	14.1	2.87	.09
Fatigue	2	6.1	0	0.0	3.96	.05
Increased appetite	0	0.0	10	15.6	5.75	.02
Insomnia	3	9.1	2	3.1	1.59	.21
Headache	5	15.2	6	9.4	.72	.40
Tired	2	6.1	0	0.0	3.96	.05
Weight gain	1	3.0	2	3.1	.00	.98