An Open-Label Trial of Risperidone Augmentation for Refractory Anxiety Disorders

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Work on this study was supported by an investigator-initiated study grant from Janssen, L.P., Titusville, N.J.

Financial disclosure appears at the end of the article.

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Background: There is a paucity of data to support "next-step" treatments for the many patients with anxiety disorders who remain symptomatic after initial pharmacotherapy.

Method: Thirty patients with a primary diagnosis of an anxiety disorder—panic disorder (PD), social anxiety disorder (SAD), or generalized anxiety disorder (GAD)—refractory to initial pharmacotherapy with an adequate (or maximally tolerated) antidepressant and/or benzodiazepine trial of at least 8 weeks' duration prior to study initiation received open-label augmentation with flexibly dosed risperidone for 8 weeks. Participants were diagnosed using the Structured Clinical Interview for DSM-IV.

Results: Risperidone augmentation at a mean ± SD dose of 1.12 ± 0.68 mg/day (range, 0.25–3.00 mg/day) resulted in a significant reduction in anxiety symptoms across disorders as measured by the Clinical Global Impressions-Severity of Illness scale and Hamilton Rating Scale for Anxiety (HAM-A) scores and for each disorder-specific primary outcome measure—the Panic Disorder Severity Scale, the Liebowitz Social Anxiety Scale, and HAM-A—in the intent-to-treat sample. Seventy percent (21/30) of participants completed the 8-week trial, with premature discontinuation due primarily to sedation and weight gain.

Conclusions: Although conclusions are limited by the open-label, relatively brief nature of this trial, our data suggest that augmentation with low-dose risperidone may be a useful option for patients with PD, SAD, or GAD refractory to adequate initial intervention with antidepressants and/or benzodiazepines. Longer-term, controlled safety and efficacy data are needed to understand the place of risperidone augmentation in the algorithm of treatment options for refractory anxiety disorders.

(J Clin Psychiatry 2006;67:381–385)

Anxiety disorders, including generalized anxiety disorder (GAD), panic disorder with or without agoraphobia (PD), and social anxiety disorder (SAD) are common and impairing.[1] Most patients with these anxiety disorders receive initial pharmacotherapy with antidepressants such as the selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) and/or benzodiazepines; although these agents are clearly effective, many treated patients remain symptomatic.[2,3] Across anxiety disorders, data from clinical trials suggest that 30% to 60% of patients do not have a clinically significant reduction (or "response") in symptoms after up to 6 months of treatment.[4] Further, 8-year, longitudinal, naturalistic follow-up data demonstrate relatively low rates of remission of these anxiety disorders ranging from 31% to 76%, with rates of relapse up to 64%, often despite persistent treatment.[5] Thus, there is a clear need for additional interventions for many patients with anxiety disorders who do not respond or remit with initial pharmacotherapy. While clinical "next-step" options may include switching agents, adding or switching to a psychosocial intervention such as cognitive-behavioral therapy, or augmenting with additional pharmacotherapy, there is a paucity of data supporting decisions by clinicians about the safety and efficacy of "next-step" treatment strategies for patients with GAD, PD, and SAD.[6]

Risperidone is a novel antipsychotic agent with potent effects at the serotonergic, as well as dopaminergic, receptor and a more favorable side effect profile than standard neuroleptics, including a lower potential for causing

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extrapyramidal symptoms.[7] Prior reports suggest potential efficacy of risperidone for a number of anxiety disorders, including obsessive-compulsive disorder,[8,9] acute stress disorder,[10] and posttraumatic stress disorder (PTSD).[11–13] The purpose of this study is to examine the efficacy of one potential strategy for refractory anxiety, the addition of the atypical antipsychotic risperidone, for the treatment of patients with PD, SAD, or GAD who remain refractory despite treatment with an SSRI or SNRI antidepressant and/or a benzodiazepine. We hypothesized that risperidone would be efficacious as indicated by general and disorder-specific measures of anxiety across all 3 of the anxiety disorders.

METHOD

Participants

Thirty adult outpatients were recruited through advertisement and clinical referral for participation in an 8-week, open-label, flexible-dose study of adjunctive risperidone. These patients had a primary diagnosis of GAD, PD, or SAD (generalized subtype) refractory to an ongoing, initial pharmacotherapy trial with an adequate (or maximally tolerated) dose of an established anxiolytic (SSRI or SNRI antidepressants, e.g., paroxetine ≥ 20 mg/day, and/or benzodiazepines, e.g., clonazepam ≥ 2 mg/day) initiated at least 8 weeks prior to study initiation. In patients with multiple anxiety disorders, the primary disorder was defined as that identified by the patient and clinician as causing the most distress and disability.

Participants were diagnosed by a study psychiatrist using the Structured Clinical Interview for DSM-IV (SCID).[14] In order to include a population of patients with significant persistent symptoms despite initial pharmacotherapy, inclusion criteria were based on specific rating scale scores for each of the primary anxiety disorders as follows: a Hamilton Rating Scale for Anxiety (HAM-A)[15] score ≥ 16 for GAD; a Liebowitz Social Anxiety Scale (LSAS)[16] score ≥ 70 for SAD; or a Massachusetts General Hospital Anchored Panic CGI Severity Rating (Panic CGI-S)[17] scale ≥ 4 ("moderate"), as well as a Clinical Global Impressions-Severity of Illness score (CGI-S) of "moderate" or greater (≥ 4) for all diagnoses. The presence of secondary comorbid depression (with a Hamilton Rating Scale for Depression score ≤ 18) was permitted.

Exclusion criteria included comorbid current or past bipolar disorder, schizophrenia, or other psychotic conditions; current suicidality; a history of alcohol or substance abuse or dependence within the last 6 months; or a positive toxicology screen consistent with substance abuse at baseline. Pregnant women, patients with significant unstable medical illness or ongoing psychotherapy for the treatment of the primary anxiety disorder, and those with prior intolerance of risperidone were also excluded. All patients provided informed consent approved by the Institutional Review Board at Massachusetts General Hospital.

Treatment

Risperidone was initiated at 0.25 mg/day for the first week and flexibly titrated up to a maximum of 3.00 mg/day over the next 7 weeks based on response and tolerability. Participants were seen weekly for the first 2 weeks of the study, and then at 2-week intervals for the remainder of the 8-week trial.

Statistical Analysis

After confirming normality of the data, significance was examined with 2-tailed paired t tests with an α level of 0.05. Analyses were performed examining baseline-to-endpoint change for an intent-to-treat sample of all patients with at least 1 assessment while on risperidone treatment, using a last-observation-carried-forward method. The primary outcome measures, the HAM-A and CGI-S, were examined across disorders, as were secondary outcome measures including the Anxiety Sensitivity Index (ASI)[18] scores (a measure of fear of anxiety and somatic sensations) and assessments of quality of life and function (the Quality of Life Enjoyment and Satisfaction Questionnaire: Q-LES-Q)[19] and the Sheehan Disability Scale (SDS).[20] Each of the disorder-specific outcome measures (the HAM-A for GAD, the Panic Disorder Severity Scale [PDSS][21] for panic disorder, and the LSAS[16] for SAD) was examined only for the subgroup with the respective primary anxiety disorder. Treatment-induced movement disorders were assessed for all patients with the use of the Simpson-Angus Scale[22] and the Barnes Akathisia Scale[23] administered at baseline and endpoint.

RESULTS

Thirty patients (43.3% women; mean ± SD age 40.76 ± 13.98 years) were recruited through advertisement and clinical referral and entered the trial; all had at least 1 assessment while on medication therapy. The primary anxiety disorder was GAD for 53.3% (N = 16), PD for 23.3% (N = 7), and SAD for 23.3% (N = 7). Seven (23.3%) patients were diagnosed with more than 1 anxiety disorder (with secondary PD, SAD, or GAD), and 5 (16.7%) met criteria for current major depressive disorder or dysthymia.

Participants had a high level of persistent symptoms at baseline, with a mean ± SD CGI-S score of 5.0 ± 0.9, or "markedly ill," and a HAM-A score of 23.0 ± 5.4 (Table 1 for disorder-specific ratings). The dose of the medication to which risperidone was added was held constant throughout the trial and consisted of an antidepressant alone for 56.7% (N = 17), a benzodiazepine alone for 10.0% (N = 3), and the combination of an antidepressant with a benzodiazepine for 33.3% (N = 10). Mean ± SD

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Table 1. Symptomatic Change With Risperidone Augmentation for Patients With Refractory Anxiety Disorders

Measure	N	Baseline Score Mean (SD)	Endpoint Score Mean (SD)	Mean Change Score (SD)	t score (df)	p
All disorders						
HAM-A	30	23.03 (5.45)	17.07 (8.01)	5.97 (8.29)	3.94 (29)	.0005*
CGI-S	30	5.00 (0.91)	3.47 (1.48)	1.53 (1.63)	5.14 (29)	< .0000*
HAM-D	30	15.23 (4.03)	11.76 (5.51)	3.47 (4.95)	3.84 (29)	.0006*
Q-LES-Q	18	52.39 (7.87)	57.72 (7.54)	–5.33 (8.53)	–2.65 (17)	.017*
SDS	18	14.72 (6.36)	8.89 (6.18)	5.83 (4.83)	5.12 (17)	.0001*
ASI	18	28.77 (13.16)	22.28 (11.72)	6.50 (12.07)	2.28 (17)	.035*
Primary generalized anxiety disorder only						
HAM-A	16	25.06 (3.45)	18.31 (8.83)	6.75 (8.34)	3.24 (15)	.0055*
Primary panic disorder only						
PDSS	7	16.43 (5.59)	11.43 (4.35)	5.00 (5.29)	2.50 (6)	.046*
Panic CGI-S	7	4.86 (1.07)	3.86 (0.69)	1.00 (1.29)	2.05 (6)	.086
Primary social anxiety disorder only						
LSAS	7	81.29 (19.73)	38.43 (24.03)	42.86 (33.85)	3.35 (6)	.0154*

*Significant at $p < .05$.
Abbreviations: ASI = Anxiety Sensitivity Index, CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, LSAS = Liebowitz Social Anxiety Scale, Panic CGI-S = MGH Anchored Panic CGI Severity Rating, PDSS = Panic Disorder Severity Scale, Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire, SDS = Sheehan Disability Scale.

duration of this initial pharmacotherapy treatment prior to initiation of risperidone augmentation was 150.0 ± 209.4 weeks (median = 53 weeks, range, 9–865 weeks).

The endpoint dose of risperidone was mean ± SD 1.12 ± 0.68 mg/day (range, 0.25–3.00 mg/day). Seventy percent of participants (21/30) completed the 8-week trial. Five patients discontinued due to side effects (sedation or weight gain), 1 discontinued due to change in work schedule, 1 discontinued due to "stigma of medication," and 2 were lost to follow-up.

Efficacy of Risperidone Augmentation

At study endpoint, there was a significant decrease in score on the primary outcome measures, the HAM-A ($t = 3.94$, $p = .0005$) and the CGI-S ($t = 5.14$, $p < .0000$) (see Table 1), across all 3 primary anxiety disorders (N = 30). In addition, ASI, Q-LES-Q, and SDS scores were also significantly improved at endpoint (see Table 1).

For each primary anxiety disorder subgroup, there was also a significant reduction in the primary anxiety disorder–specific rating scale scores as follows: a 6.8-point decrease in the HAM-A score for patients with GAD ($t = 3.24$, $p = .0055$), a 5.0-point decrease in the PDSS score for patients with PD ($t = 2.50$, $p < .046$), and a 42.9-point decrease in the LSAS score for patients with SAD ($t = 3.35$, $p < .0154$) (see Table 1).

Safety of Risperidone Augmentation

All participants experienced at least 1 side effect, generally of mild to moderate intensity for those who completed the trial. No patients developed dystonias, and the Simpson-Angus Scale scores ($t = 2.77$, $df = 19$, $p = .012$) and the Barnes Akathisia Scale scores ($t = 2.12$, $df = 19$, $p = .047$) were each significantly reduced at study endpoint. Two patients reported mild akathisia (1 for a few minutes, and the other persistent) during the trial. Side effects occurring in at least 10% of the sample were sedation/fatigue (N = 14), increased appetite and weight gain (N = 11), dizziness (N = 8), nausea/gastrointestinal distress (N = 7), dry mouth (N = 6), headache (N = 5), blurred vision (N = 5), muscle cramps (N = 4), urinary urgency or incontinence (N = 4), sexual dysfunction (N = 3), and vivid dreaming (N = 3). The mean ± SD weight gain was 3.9 ± 4.7 lb at endpoint; 2 participants gained more than 7% of their body weight during the trial.

DISCUSSION

Low-dose risperidone augmentation resulted in clinically and statistically significant improvement across a broad range of anxiety and quality-of-life measures in our sample of patients with PD, SAD, and GAD refractory to an adequate initial pharmacotherapy trial. These findings support an increasing body of clinical, as well as research, experience suggesting the potential efficacy of risperidone,[8–13] as well as other atypical antipsychotics including olanzapine,[24,25] quetiapine,[26] and aripiprazole,[27] for the treatment of anxiety.

Antipsychotics in general have long been recognized as having anxiolytic properties,[28,29] but concerns about the safety profile of typical antipsychotics have limited their use for anxiety disorders. Atypical antipsychotics have a potentially more favorable side effect profile than older agents and have novel receptor profiles that include differing degrees of activity in the serotonin system, such as agonism at the 5-HT_{1A} receptors and antagonism at the 5-HT_2 receptors, that may be pertinent for anxiolysis.[30,31] These features of atypical antipsychotics have led to a growing interest in the use of these agents for the treat-

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ment of anxiety disorders. However, though the atypical antipsychotics as a class have lower risk for tardive dyskinesia and extrapyramidal syndromes[7] than the older neuroleptics, it is important to note that we are still learning about the long-term safety of these agents. For example, recent evidence suggests that clozapine, olanzapine, and quetiapine all increase risk for abnormalities in lipids and may increase risk for diabetes, while risperidone has not been notable for the induction of metabolic abnormalities.[32] Risperidone has, however, been shown to result in increased levels of prolactin, which may result in galactorrhea for some individuals.[33]

In our short-term study, the most prominent side effects of risperidone were sedation and weight gain, resulting in treatment discontinuation for 17% of our sample. Longer studies are needed to determine the full impact of chronic risperidone therapy on weight gain and other related health outcomes before a complete risk-benefit assessment of its optimal use in anxiety disorders can be determined. Side effect data available to date suggest that atypical antipsychotics should generally be reserved for patients refractory to prior adequate trials of more standard anxiolytic agents such as antidepressants and benzodiazepines.

A number of significant limitations should be considered when drawing conclusions from our study. First, our 8-week trial does not provide long-term efficacy or safety data about the use of risperidone over time for patients with anxiety disorders. Second, the open nature of treatment is likely to result in overestimation of the effect of our intervention. Third, our assessment of refractoriness to prior treatment was based on historical patient reports that include, by design, patients with variable lengths of prior treatment (beyond 8 weeks) and prior response, so we were unable to systematically examine the relationship of these variables to the effectiveness of our augmentation strategy. The nature of this study precludes our ability to determine the relative efficacy of increasing intensity (i.e., dose) or duration of the initial pharmacotherapy trial with our augmentation strategy. Nonetheless, our sample, with persistent symptoms despite a median prior treatment length of 53 weeks and a mean of 150 weeks with at least standard doses of anxiolytic medications, represents a clearly refractory population.

Our data suggest that augmentation with low-dose risperidone may be a useful option for patients with PD, SAD, or GAD refractory to initial intervention with antidepressants and/or benzodiazepines. Risperidone should be initiated at low doses, with individual titration to achieve optimal tolerability and efficacy. Placebo-controlled, longer-term study and clinical trials comparing the safety and effectiveness of options for "next-step" interventions are needed to understand the optimal place of risperidone augmentation in the algorithm of treatment options for refractory anxiety disorders.

Drug names: aripiprazole (Abilify), clonazepam (Klonopin and others), clozapine (Clozaril, FazaClo, and others), olanzapine (Zyprexa), paroxetine (Paxil and others), risperidone (Risperdal), quetiapine (Seroquel).

Financial disclosure: Dr. Simon has received grant/research support from AstraZeneca, Cephalon, Forest, GlaxoSmithKline, Janssen, Eli Lilly, and UCB Pharma and has served on the speakers/advisory boards for Forest and Pfizer. Dr. Hoge has received grant/research support from AstraZeneca, Cephalon, Forest, GlaxoSmithKline, Janssen, and UCB Pharma. Dr. Worthington has received grant/research support from Abbott, American Cyanamid, AstraZeneca, Bristol-Myers Squibb, Cephalon, Cyberonics, Forest, GlaxoSmithKline, Janssen, Johnson & Johnson, Lictwer Pharma, Eli Lilly, Lorex, Novartis, Organon, Otsuka, Pfizer, Pharmavite, Roche, Sanofi-Sythelabo, Solvay, UCB Pharma, and Wyeth-Ayerst and has served on the speakers/advisory boards for Bristol-Myers Squibb, Forest, GlaxoSmithKline, Janssen, Eli Lilly, Pfizer, Searle, Solvay, and Wyeth-Ayerst. Dr. Kinrys has received grant/research support from AstraZeneca, Bristol-Myers Squibb, Cephalon, Elan, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Pfizer, Sepracor, UCB Pharma, and Wyeth-Ayerst; is a consultant for Cephalon, Pfizer, and Wyeth-Ayerst; and has served on the speakers/advisory boards for Forest, GlaxoSmithKline, Sepracor, UCB Pharma, and Wyeth-Ayerst. Dr. Pollack has received grant/research support from Cephalon, Forest, GlaxoSmithKline, Janssen, Eli Lilly, Pfizer, UCB Pharma, and Wyeth and has served on the speakers/advisory boards for Bristol-Myers Squibb, Cephalon, Forest, GlaxoSmithKline, Janssen, Eli Lilly, Novartis, Otsuka, Pfizer, Roche, Solvay, UCB Pharma, and Wyeth. Mss. Fischmann and Christian report no other significant financial relationships relevant to this study.

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