Adjunctive Risperidone in Generalized Anxiety Disorder: A Double-Blind, Placebo-Controlled Study

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Objective: Although significant advances have been made in recent years in the treatment of generalized anxiety disorder (GAD), many patients remain symptomatic despite ongoing treatment, underscoring the need for adjunctive new treatments to help improve response.

Method: Forty patients with a primary diagnosis of DSM-IV GAD, who continued to experience GAD symptoms despite current anxiolytic treatment of at least 4 weeks' duration, as evidenced by Hamilton Rating Scale for Anxiety (HAM-A) total score ≥ 18 and Clinical Global Impressions-Severity of Illness scale score of moderate or greater, completed a 1-week screening phase and were then randomly assigned to 5 weeks of double-blind adjunctive treatment with placebo or risperidone at flexible doses of 0.5 to 1.5 mg/day. Patients continued to take their anxiolytics throughout the study. The study was conducted from June 2001 through March 2003.

Results: Adjunctive risperidone was associated with statistically significant improvements in core anxiety symptoms, as demonstrated by greater reductions in HAM-A total scores ($p = .034$) and HAM-A psychic anxiety factor scores ($p = .047$) compared with placebo. Although change scores on other outcome variables, including response rates, were higher in the risperidone group, differences did not achieve statistical significance.

Conclusion: Study findings suggest that risperidone at low doses may represent a useful tool in the management of symptomatic GAD patients.

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Generalized anxiety disorder (GAD) is a serious and chronic disorder associated with significant morbidity and disability and a lifetime prevalence of 5.1% in the United States.[1] Despite data indicating the efficacy of different pharmacologic agents (including selective serotonin reuptake inhibitors [SSRIs] and serotonin noradrenergic reuptake inhibitors [SNRIs]) in the treatment of GAD, a considerable proportion of GAD patients remain symptomatic despite treatment that often involves multiple medications.[2–5] Results from a 3-year follow-up of a clinical population of 164 patients with an active diagnosis of GAD indicated that over 70% of the patients received treatment, with 35% of patients taking 1 psychoactive medication, 31% taking 2 medications, and 18% taking more than 2 medications. Remission probability, however, was only 0.28 at 3 years, and relapses were common, with a probability of 0.27 at 3 years for those who previously experienced full remission.[5] Thus, it is important to identify therapeutic strategies that will potentially improve outcomes in patients who remain symptomatic despite ongoing standard anxiolytic treatment.

Risperidone has been shown to have anxiolytic effects in patients with schizophrenia and schizoaffective disorder[6,7] and in patients with posttraumatic stress disorder.[8] Its modulation of the 5-HT system may be the mechanism by which risperidone exerts an anxiolytic effect. The goal of the present controlled study was to examine the effi-

cacy and tolerability of adjunctive risperidone in DSM-IV GAD patients who remain symptomatic despite ongoing anxiolytic treatment.

METHOD

This double-blind, placebo-controlled, flexible-dose study was approved by the Medical University of South Carolina Human Research Review Board, and all subjects provided written informed consent to participate in the study. The study was conducted from June 2001 through March 2003.

Patients

Eligible participants were male and female outpatients, aged ≥ 18 years, who met DSM-IV criteria for a primary diagnosis of GAD as determined by the Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Version (SCID-P).[9] Participants who had a diagnosis of major depressive disorder within 1 month of study entry and subjects with substance use disorders within 6 months of study entry were excluded. Subjects with current or past history of bipolar or any psychotic disorder were also excluded. Presence of comorbid anxiety disorders and dysthymia that did not dominate the clinical presentation (for at least 6 months) was not exclusionary. Criteria to confirm that the subjects were experiencing GAD symptoms included a total score ≥ 18 on the Hamilton Rating Scale for Anxiety[10] (HAM-A), a score ≥ 2 on items 1 and 2 of the HAM-A (anxious mood and tension), at least a moderate score (4) on the Clinical Global Impressions-Severity of Illness scale[11] (CGI-S), and a Covi Anxiety Scale[12] total score higher than a Raskin Severity of Depression Scale[13] score. Patients who met these criteria despite treatment with an anxiolytic or antidepressant agent at adequate or maximum-tolerated stable doses for at least 4 weeks, prescribed by a psychiatrist or primary-care clinician in the community, were eligible for the study.

Dosing

After a 1-week screening period, the patients were randomly assigned (1:1) for 5 weeks to once-daily risperidone or matching placebo. The dose of risperidone was increased weekly from 0.5 mg/day to a maximum of 1.5 mg/day, according to tolerability and clinical response. Patients continued to take their anxiolytics throughout the study.

Outcome Measures

The primary outcome measure was the change from baseline to endpoint on the HAM-A total score. Secondary measures included changes from baseline on the HAM-A psychic anxiety and somatic subscales, the CGI-S, the Hospital Anxiety and Depression Scale[14] (HAD), the Montgomery-Asberg Depression Rating Scale[15] (MADRS), the Sheehan Disability Scale[16] (SDS), and the Quality of Life, Enjoyment and Satisfaction Questionnaire[17] (Q-LES-Q). Treatment response was defined as a score of 1 or 2 (much or very much improved) on the CGI-Improvement scale (CGI-I). The Abnormal Involuntary Movement Scale[18] (AIMS) was completed weekly.

Data Analysis

Baseline comparisons of demographic and clinical variables and changes from baseline to endpoint (last observation carried forward [LOCF]) for continuous outcome variables were assessed using an independent sample t test; categorical measures were compared using either χ^2 tests or Fisher exact tests, as appropriate. Significance level for the primary comparison was $\alpha = .05$; secondary comparisons are considered supportive evidence and should be evaluated cautiously in terms of inflation of type I error.

RESULTS

Of the 40 randomized patients, 1 patient in the risperidone group did not receive at least 1 medication dose, and thus the intention-to-treat (ITT) sample includes 19 patients in the risperidone group and 20 in the placebo group. No statistically significant differences between the risperidone and placebo groups in baseline demographic characteristics were evident: their mean ± SD ages were 47.8 ± 13.9 years in the risperidone group and 52.4 ± 9.4 years in the placebo group ($t = 1.19$, $df = 37$, $p = .241$); ages at the onset of GAD symptoms were 28.2 ± 18.7 years and 29.9 ± 13.6 years, respectively ($t = 0.31$, $df = 37$, $p = .755$); 17 of the 19 risperidone patients and 16 of the 20 placebo patients were women ($p = .661$), and 18 and 19, respectively, were white ($p = .999$). No statistically significant differences between the 2 groups in baseline clinical characteristics were evident: mean ± SD baseline HAM-A total scores were 22.1 ± 3.8 in the risperidone group and 20.4 ± 1.7 in the placebo group ($t = 1.84$, $df = 37$, $p = .083$); CGI-S scores were 4.2 ± 0.4 and 4.1 ± 0.2, respectively ($t = 1.10$, $df = 37$, $p = .279$); HAD anxiety subscale scores were 13.0 ± 4.0 and 12.6 ± 3.0 ($t = 0.40$, $df = 37$, $p = .692$); and MADRS scores were 14.2 ± 3.3 and 14.3 ± 3.8 ($t = 0.08$, $df = 37$, $p = .969$). Comorbid diagnoses included social anxiety disorder in 5 patients and agoraphobia, dysthymia, and panic disorder in 1 patient each.

Thirty-one patients completed the 5-week treatment period, 15 of the 19 patients in the risperidone group and 16 of the 20 patients in the placebo group. The most common reasons for discontinuation were adverse events (3 patients in the risperidone group and 1 in the placebo group). The mean daily dose of risperidone at study endpoint was 1.1 ± 0.4 mg. All patients had received at least 1

Table 1. Concomitant Treatment Data for the Intention-to-Treat (ITT) Sample of Patients With Generalized Anxiety Disorder (N = 39)[a]

Risperidone (N = 19)				Placebo (N = 20)			
Patient	Anxiolytic	Dose (mg/day)	Duration (days)	Patient	Anxiolytic	Dose (mg/day)	Duration (days)
1	Buspirone	30	40	20	Alprazolam	2.0	479
2	Citalopram	20	157	21	Buspirone	30	724
3	Alprazolam	1.0	1347	22	Paroxetine	20	84
	Temazepam	30	1347		Mirtazapine	45	572
4	Buspirone	30	279		Clonazepam	2.0	359
5	Citalopram	30	580		Lorazepam	1.0	359
	Buspirone	5.0	580	23	Clonazepam	1.0	3144
6	Gabapentin	600	122		Imipramine	75	3144
7	Sertraline	75	198	24	Gabapentin	1200	200
8	Sertraline	150	244	25	Paroxetine	20	60
	Alprazolam	0.5	5311	26	Buspirone	45	1202
9	Fluoxetine	20	147		Temazepam	30	1202
	Alprazolam	1.5	4513		Alprazolam	0.25	1202
	Trazodone	50	4513	27	Venlafaxine	150	200
10	Buspirone	20	31	28	Citalopram	40	113
11	Fluoxetine	40	2866	29	Paroxetine	20	2620
	Alprazolam	0.25	114	30	Sertraline	50	284
	Zolpidem	5.0	114		Clonazepam	0.5	59
12	Sertraline	100	2879		Gabapentin	1600	1380
13	Diazepam	30	128	31	Fluoxetine	20	685
14	Citalopram	30	734		Citalopram	5.0	685
	Alprazolam	3.0	734		Diazepam	2.5	3972
15	Bupropion	150	203	32	Bupropion	400	188
16	Venlafaxine	150	94		Estazolam	1.0	188
	Clonazepam	0.5	370	33	Sertraline	100	36
17	Citalopram	40	1300		Alprazolam	0.5	36
	Alprazolam	0.75	3491	34	Clonazepam	2.0	45
18	Sertraline	50	201		Trazodone	50	130
	Alprazolam	1.25	2072	35	Sertraline	100	809
19	Venlafaxine	150	982		Gabapentin	300	443
				36	Sertraline	100	315
				37	Bupropion	300	1981
				38	Sertraline	100	1790
					Clonazepam	2.0	730
					Trazodone	100	1825
				39	Buspirone	60	2963

[a]One patient did not have at least 1 postbaseline efficacy assessment and is thus not included in the ITT sample.

prior treatment trial for GAD symptoms before their current anxiolytic treatment. Concomitant anxiolytics being received by the patients throughout the trial, daily doses, and treatment duration are listed in Table 1. One concomitant anxiolytic was being received by 20 patients, 2 by 12 patients, and 3 or more by 7 patients (Table 1). The duration of treatment ranged from 31 to 5311 days. No significant differences between the groups in the use of concomitant SSRIs ($\chi^2 = 0.03$, p = .870), SNRIs (Fisher exact test, p = .605), benzodiazepines ($\chi^2 = 0.03$, p = .870), or other antidepressant and anxiolytic agents (Fisher exact test, p = .235) were observed.

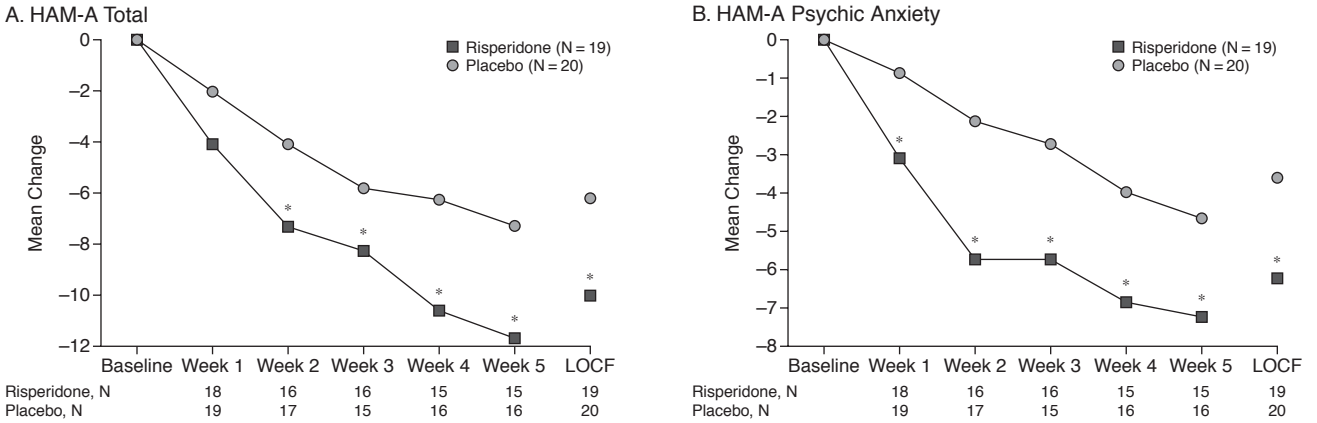
Efficacy

Adjunctive risperidone was significantly more effective than placebo in reducing levels of anxiety in the ITT sample, as measured by the mean changes from baseline to endpoint (using LOCF) in HAM-A total scores and HAM-A psychic anxiety subscale scores. Mean ± SD HAM-A total change scores were –9.8 ± 5.5 in the risperidone group and –6.2 ± 4.9 in the placebo group (t = 2.20, df = 37, p = .034), and mean HAM-A psychic anxiety change scores were –6.3 ± 3.7 in the risperidone group and –3.8 ± 4.0 in the placebo group (t = 2.05, df = 37, p = .047). Patients in the risperidone group also showed greater improvements than did the placebo patients on each of the other scales at endpoint (HAM-A somatic anxiety factor, CGI-S, MADRS, HAD anxiety subscale, SDS, and Q-LES-Q); none, however, were significant at endpoint.

The mean changes from baseline were significantly greater in the risperidone-treated patients than the placebo patients starting at week 2 on the HAM-A total scale (t = 2.85, df = 31, p = .008) and at week 1 on the HAM-A psychic anxiety subscale (t = 2.34, df = 35, p = .025) (Figure 1). On the HAM-A somatic subscale, a significant between-group difference was seen at week 5 only (t = 2.47, df = 29, p = .020).

Treatment response (CGI-I rating of much or very much improved) was achieved by 11 patients (58%) in the risperidone group and by 7 (35%) in the placebo group (p = .152).

Figure 1. Mean Changes From Baseline in HAM-A Total Scores and HAM-A Psychic Anxiety Scores (ITT sample N = 39)



*p < .05 versus placebo.
Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, ITT = intention-to-treat, LOCF = last observation carried forward.

Safety

Risperidone was generally well tolerated. The most common treatment-emergent adverse events included somnolence (9 patients in the risperidone group and 3 in the placebo group), dizziness (4 in the risperidone group and 3 in the placebo group), and blurred vision (3 in the risperidone group). Severity of movement disorders was reduced in both groups. Mean ± SD changes in AIMS scores were –0.63 ± 3.3 in the risperidone group and –0.05 ± 0.2 in the placebo group (p = .432). No patients required adjunctive treatment with anticholinergic agents. Mean increases in weight were 2.3 ± 3.7 lb in the risperidone group and 3.1 ± 4.3 lb in the placebo group (p = .537).

DISCUSSION

This pilot study evaluated the effectiveness of adjunctive risperidone in patients with GAD who were not responding adequately to anxiolytic agents prescribed by a treating clinician. We found that the addition of risperidone at low doses was superior to placebo as demonstrated by significantly greater mean change in the primary outcome variable—total HAM-A scores. Significantly greater improvements were also observed in scores on the HAM-A psychic anxiety subscale. Mean changes from baseline at week 2 on the HAM-A total scale and at week 1 on the HAM-A psychic anxiety subscale were significantly greater in patients receiving adjunctive risperidone than placebo. Between-group differences on the other study measures did not reach statistical significance at endpoint. At these low doses of risperidone, between-group differences in reported adverse events were not clinically significant in this short study.

The main limitations of the current study, which result largely from the pilot/exploratory nature of the trial, include the inability to interpret negative conclusions for some of the secondary variables because of low power (i.e., failure to find a statistically significant effect can be a function of either a small and clinically insignificant effect size or low power of the test to find clinically relevant effects) and the heterogeneity of prescribed anxiolytic agents as well as treatment duration (with a minimum of 4 weeks); these may confound the potential clinical impact of the study findings.

Despite these limitations, the study results provide us with a clinical rationale for further development of this line of inquiry. The study also supports older research findings suggesting the potential efficacy of typical antipsychotics, such as trifluoperazine, thiothixene, or thioridazine in patients with GAD, or anxiety neurosis as it was known earlier.[19,20] The next step should involve replication of the study results in a larger, longer, and more uniformly treated sample including prospective evaluation of treatment adequacy.

Drug names: alprazolam (Xanax, Niravam, and others), bupropion (Wellbutrin and others), buspirone (BuSpar and others), citalopram (Celexa and others), clonazepam (Klonopin and others), diazepam (Valium and others), estazolam (Prosom and others), fluoxetine (Prozac and others), gabapentin (Neurontin and others), imipramine (Tofranil and others), lorazepam (Ativan and others), mirtazapine (Remeron and others), paroxetine (Paxil, Pexeva, and others), risperidone (Risperdal), sertraline (Zoloft), temazepam (Restoril and others), thiothixene (Navane and others), trazodone (Desyrel and others), trifluoperazine (Stelazine and others), venlafaxine (Effexor), zolpidem (Ambien).

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