Clinical Effects of Buspirone in Social Phobia: A Double-Blind Placebo-Controlled Study

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Background: The results of open pilot studies suggest that the serotonin-1A (5-HT_{1A}) receptor agonist buspirone might be effective in social phobia.

Method: In the present study, the efficacy of buspirone was investigated in patients with social phobia using a 12-week double-blind placebo-controlled design. Thirty social phobic patients (DSM-IV) were treated with either buspirone 30 mg daily or placebo. Efficacy of treatment was measured using the Social Phobia Scale (subscores anxiety and avoidance) and the Hamilton Rating Scale for Anxiety.

Results: Taking a reduction of 50% or more on the Social Phobia Scale as a criterion for clinically relevant improvement, only 1 patient on buspirone and 1 on placebo were classified as responder to treatment. A subjective and clinically relevant improvement was reported by 4 patients (27%) on buspirone and 2 patients (13%) on placebo. There were no statistically significant differences between buspirone and placebo on any of the outcome measures. Generally speaking, buspirone was well tolerated.

Conclusion: The results of the study do not support the results of open studies, in which a reduction of social anxiety and social avoidance was reported in patients with social phobia treated with buspirone.

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Social phobia is one of the more common psychiatric disorders, occurring in about 2% of the population.[1] Social phobia can be very disabling and may interfere with work and social life. It has a high comorbidity rate, and the risk of developing depression or alcohol abuse is considerable.[2–4] Traditionally, treatment of social phobia has consisted of behavioral therapy, e.g., cognitive therapy.[5] More recently, attention has been focused on the pharmacologic treatments of social phobia.

In social phobia, both the nonselective and irreversible monoamine oxidase inhibitors (MAOIs) as well as the selective and reversible MAO-A inhibitors appear to be effective treatments.[6–11]

The serotonin reuptake inhibitor clomipramine has been studied in patient populations with anxiety disorders. Most investigators reported a reduction of anxiety in social phobic patients.[12–15] Most serotonin selective reuptake inhibitors (SSRIs), like fluoxetine, citalopram, and paroxetine, have been studied only in open-label trials.[16–20] The results of these studies and of two open-label studies with sertraline,[21,22] mostly in small patient groups, are positive as shown by an improvement on the Clinical Global Impression (CGI) scale. In a double-blind placebo-controlled study,[23] we investigated the efficacy of fluvoxamine in 30 social phobic patients. Treatment with this SSRI resulted in a decrease in social anxiety as well as social avoidance. The efficacy of SSRIs was confirmed by a placebo-controlled crossover study from Katzelnick and coworkers[24] with sertraline.

The results of these studies in social phobia (and other anxiety disorders) suggest that serotonergic neuronal systems are implicated in the mechanism of action of these drugs.[25] Which 5-HT receptor subtype or subtypes are involved is as yet unclear. It is of interest therefore to study the efficacy of serotonin selective drugs in the various domains of anxiety.

Buspirone is an azapirone acting as a full receptor agonist at the somatodendritic 5-HT_{1A} autoreceptor and as a partial agonist at the postsynaptic 5-HT_{1A} receptor. In addition, buspirone has a modest effect on the dopamine system.[26] The major metabolite 1-(2-pyrimidinyl)-piperazine (1-PP) has α_2-adrenoceptor antagonistic properties. Several placebo-controlled trials have shown that the 5-HT_{1A} receptor agonist buspirone is effective in the treatment of generalized anxiety disorder. Most studies indicate that buspirone is as effective as the benzodiazepine diazepam.[27–31] The results of three open pilot studies suggest that buspirone might also be effective in the treatment of social phobia,[1,32,33] but well-designed trials are lacking.

The aim of the present study was to evaluate the efficacy of the 5-HT_{1A} receptor agonist buspirone in the treatment of social phobia.

MATERIAL AND METHODS

Patients

Thirty patients were recruited from the outpatient clinic of the Department of Psychiatry of the University Hospital in Utrecht, The Netherlands. Informed consent was obtained from all patients. The study was approved by the Ethics Committee of the University Hospital. Included in the study were patients suffering from social phobia, specific or generalized subtype, according to DSM-IV criteria.[34] Excluded were patients with another anxiety disorder, major affective disorder or psychotic disorder, alcohol or drug abuse; and pregnancy or lactation and those patients suffering from medical problems on the basis of a complete medical evaluation. Patients with a personality disorder according to the DSM-IV were also excluded. A score of 15 or higher on the Hamilton Rating Scale for Depression (HAM-D)[35] was an exclusion criterion. During treatment, the use of other psychotropic drugs as well as sympathicomimetics and cimetidine was not allowed. Occasional use of oxazepam to a maximum of 30 mg daily was permitted, but only if required.

Thirty patients were enrolled and treated for 12 weeks using a double-blind placebo-controlled design. Patients were randomly allocated to one of the two treatment groups. The dose of buspirone was gradually increased from 15 mg in the first week to 30 mg from the third week on (10 mg t.i.d.).

Symptom Assessments

Efficacy of the treatment was assessed using the Social Phobia Scale (SPS)[36] and the Hamilton Rating Scale for Anxiety (HAM-A)[37] at baseline and at Weeks 1, 2, 4, 8, and 12. The SPS is a self-rating 4-point scale consisting of 22 commonly occurring social phobic situations. The SPS scores can be subdivided into an anxiety subscore (SPS-anx) and avoidance subscore (SPS-avoid). The HAM-A is a 14-item list rating general somatic and cognitive anxiety symptoms.

At the outset and the end of the study period, patients completed the 90-item Symptom Checklist (SCL-90).[38] The scores of this checklist can be subdivided into seven subscores, e.g., anxiety, phobic anxiety, and interpersonal sensitivity.

The HAM-D[35] was completed at baseline and at the end of treatment. Adverse events were assessed by open questioning at Weeks 1, 2, 4, 8, and 12.

Laboratory Measurement

Plasma 3-methoxy-4-hydroxyphenylglycol (MHPG), the major metabolite of norepinephrine, levels were determined at admission, between 10 and 11 a.m. MHPG was measured to detect the baseline value as a possible predictor of response to treatment. Blood was collected in siliconized glass tubes containing EDTA. The tubes were centrifuged immediately, and plasma was separated. Samples were stored in polypropylene tubes at 20°C until analysis. MHPG was measured by a liquid chromatographic procedure with amperometric detection.

Statistical Analysis

The treatment effects as assessed with the SPS and HAM-A were analyzed by multivariate analysis of variance with repeated measures on the factor time. Between-group effects (mean group differences) and within-group effects (time and time-by-group interactions) were assessed. Bartlett's test for homogeneity of group variances was performed on all measures. (In case of a significant time-by-group interaction, a post hoc pairwise comparison was made by time using the Tukey multicomparison test.) The contrasts at the different timepoints are reported as significant when the probability value was less than 5%. The HAM-D scores were evaluated by one-way analysis of variance. The SCL-90 scores were tested by means of the Student t test. The SYSTAT statistical package (SPSS, Inc., Evanston, Ill.) was used for all analyses.

RESULTS

Clinical Variables

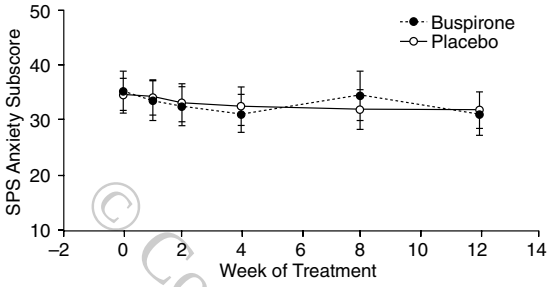
Thirty patients were enrolled in the study; 19 were men and 11 women. The mean ± SD age was 41.6 ± 8.1 years in the buspirone group and 32.9 ± 9.6 years in the placebo group. This difference in age between the two groups was statistically significant ($F = 27$; $p = .014$). The mean ± SD age at onset was 19.4 ± 7.3 years in the buspirone group and 17.1 ± 4.7 years in the placebo group. The duration of illness was 22.2 ± 9.7 and 15.8 ± 9.7 years, respectively. The two treatment groups did not differ significantly in mean age at onset and duration of illness. Thirteen patients suffered from a specific subtype of social phobia; 17 patients, from a generalized form. Fourteen patients knew a first- or second-degree relative with social phobic complaints. One third of the total patient sample used alcoholic beverages to reduce social phobic anxiety and symptoms in social situations.

Of the 15 patients randomly assigned to receive placebo, 3 patients dropped out for reasons of inefficacy or distance to the hospital. One patient dropped out at Week 2, 1 at Week 3, and 1 at Week 8. There were no dropouts among the 15 patients randomly assigned to receive buspirone.

Most patients had attended behavioral or cognitive therapy previously, but without any clinically relevant outcome.

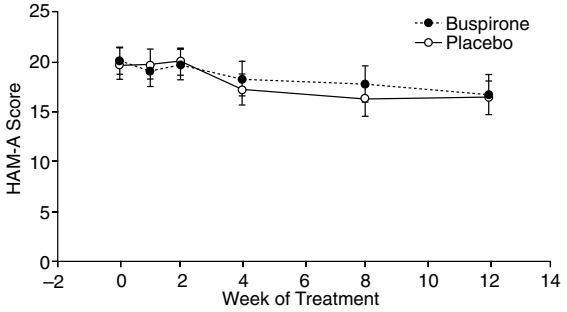
At the outset of the study, only 2 patients (1 in the buspirone and 1 in the placebo group) used oxazepam occasionally in feared social situations, and continued to do so during the study period.

Figure 1. Mean ± SE Score on the Anxiety Subscale of the Social Phobia Scale (SPS) in Patients Suffering From Social Phobia Treated With Buspirone (N = 15) or Placebo (N = 15)*



*There was a statistically significant treatment effect in both groups (p = .018), but no significant differences between the two treatments.

Figure 2. Mean ± SE Hamilton Rating Scale for Anxiety Score (HAM-A) in Patients With Social Phobia Treated With Buspirone or Placebo*



*There was a significant reduction in both groups (p = .001), without differences between the two treatment groups.

At the end of the study, 4 patients taking buspirone and 2 taking placebo considered themselves as "somewhat improved" or "much improved." One patient treated with buspirone stopped medication because of side effects; the others continued treatment under double-blind conditions. By using a reduction on the anxiety subscale of the SPS of 50% or more at endpoint as criterion for clinically relevant improvement, 1 (7%) subject taking buspirone and 1 (7%) taking placebo were classified as responder to treatment. By using an identical reduction on the HAM-A as criterion, 3 subjects (20%) taking buspirone and 1 (7%) taking placebo were responders to treatment.

Treatment outcome was assessed with the SPS and HAM-A. Treatment resulted in a small decrease in symptomatology as assessed with the SPS, but the improvement was not statistically different between patients using placebo and patients taking buspirone (Figure 1). The baseline values of the SPS were not different between the two groups.

Ratings on the avoidance subscale of the SPS also decreased slightly during treatment in both groups. Ratings on this subscale declined from 25.7 ± 3.8 (mean ± SE) at baseline to 22.9 ± 3.9 at Week 12 in the buspirone group, and from 26.7 ± 3.0 at baseline to 24.3 ± 3.4 at Week 12 in the placebo group.

Global anxiety as assessed with the HAM-A is depicted in Figure 2. Baseline HAM-A ratings were not different between the groups. In both groups, there was an equal and gradual decrease of 3.3 points in HAM-A scores. There was a statistically significant change from baseline in both treatment groups (p = .001), but no statistically significant difference between the buspirone and the placebo group.

The HAM-D ratings at baseline were 7.3 ± 0.6 (mean ± SE) in the buspirone group and 8.5 ± 0.7 in the placebo group (range, 4–14). At endpoint, these ratings were 6.8 ± 0.7 in the buspirone group and 7.4 ± 0.9 in the placebo group.

Table 1. Side Effects Reported by Patients Treated With Buspirone (All 13) or Placebo (8 of 15)

Side Effect	Buspirone	Placebo
Nausea/abdominal distress	3	0
Restlessness/electrified feelings	4	1
Sleep disturbances/more vivid dreaming	7	2
Depressive feelings[a]	2	0
Sexual disturbances	2	0
Dizziness	7	7
Headache	1	4

[a]Not present at the outset of treatment.

The general symptom index of the SCL-90 decreased from 1.07 ± 0.15 at baseline to 0.80 ± 0.13 at Week 12 in the buspirone group and from 1.10 ± 0.16 to 0.85 ± 0.18 in the placebo group. Statistical analysis showed a statistically significant treatment effect for the subscores somatization (p = .004), interpersonal sensitivity (p = .044), and anxiety (p = .035). The effects on the factors obsessive-compulsive symptoms, hostility, and phobic anxiety were not significant, while the effect on depression just failed to reach statistical significance. There were no significant differences between the two treatment conditions.

Side Effects

Generally speaking, buspirone was well tolerated. Thirteen of 15 patients treated with buspirone and 8 of 15 patients taking placebo experienced one or more side effects, mostly during the first weeks of treatment. Only 1 patient decided to stop taking medication at the end of Week 12 because of side effects. A list of the side effects reported in both treatment conditions is depicted in Table 1.

There were no clinically relevant changes in blood pressure and pulse rate during treatment in either group.

Laboratory Measurement

Baseline plasma MHPG levels (ng/mL) were 3.87 ± 0.30 (mean ± SE) in the buspirone group and

3.91 ± 0.27 in the placebo group. There was no correlation between baseline plasma MHPG level and response to treatment or scores on the SPS, HAM-A, HAM-D, or SCL-90.

DISCUSSION

The major finding of the present placebo-controlled study is that the 5-HT_{1A} receptor agonist buspirone is not superior to placebo in the treatment of social phobia. Only 4 patients using buspirone (and 2 taking placebo) reported a subjective improvement. Both treatment groups showed a small decrease on nearly all psychometric scales, but there were no statistically significant differences between treatment with buspirone or placebo. The present study is, to the best of our knowledge, the first double-blind placebo-controlled trial investigating the efficacy of buspirone in social phobia.

The effects of buspirone in the patients responding to treatment were more distinct on general anxiety, as assessed with the HAM-A, than on specific social phobic anxiety and social phobic avoidance, as measured with the SPS. These findings might suggest a differential efficacy of buspirone on general anxiety and not on specific social phobia. This differential treatment response supports the construct of social phobia and generalized anxiety disorder as distinct disorders. Treatment with buspirone did not result in a statistically significant reduction from placebo of interpersonal sensitivity, a subscore of the SCL-90, which has been reported to be increased in social phobic patients and showed a reduction after treatment with the reversible MAO-A inhibitor brofaromine.[9]

Munjack and coworkers[32] reported an anxiolytic effect of buspirone for anxiety in general and a partial response for social phobic symptoms, although a "dramatic reduction in a few patients" was observed. Schneier and others[33] reported a reduction in general anxiety and social phobic anxiety and avoidance in social phobia in buspirone-treated patients. The results of both studies should be interpreted with caution owing to the low numbers of patients, the low percentage of completers (± 60%), and the open design of the trials.

A factor, which might explain the negative findings of the present study, might be the dosage of buspirone used in this trial. A dose of 30 mg daily was chosen on the basis of the dosage used in generalized anxiety disorder. Munjack et al.[32] and Schneier et al.[33] used higher and flexible doses (mean = 48 and 45.6 mg/day, respectively). Schneier et al. reported that responders used a mean daily dosage of 57 mg, whereas nonresponders used 38 mg of buspirone daily. Increasing the dose in the nonresponder group did not increase the percentage of responders. It might be possible that a dose of buspirone higher than the 30 mg used in the present study would have improved the efficacy in social phobia.

Another factor explaining the negative findings might be the inclusion of some patients with less severe symptoms, as reflected by the initial total SPS scores of around 60. In most drug trials, these scores are higher. Including social phobic patients with less severe symptoms could underestimate the potential benefit of the drug.

In general, buspirone was well tolerated and showed only few and well-known serotonergic side effects. The finding that 2 patients taking buspirone developed depressive symptoms is remarkable considering the fact that 5-HT_{1A} receptor agonists have been found to possess antidepressant properties.[39–41]

There is some evidence implying the activity of the noradrenergic system in the pathophysiology of anxiety disorders, although very little is known about its role in social phobia.[42] In a recent study (van Vliet IM, Westenberg HGM, Slaap BR, et al. Manuscript submitted), we found significantly higher baseline plasma MHPG levels in social phobics as compared to controls. It has been suggested that elevated baseline plasma MHPG levels are related to the level of anticipatory anxiety.[8,43] In the present study, plasma MHPG was measured to detect the baseline value as a possible predictor of response to treatment. This hypothesis could not be tested adequately owing to the small number of responders.

In conclusion, the results of the present double-blind placebo-controlled study do not suggest that the 5-HT_{1A} receptor agonist buspirone is effective in the treatment of social phobia, although an improvement of some symptoms was observed in a few patients.

Drug names: buspirone (BuSpar), cimetidine (Tagamet), clomipramine (Anafranil), diazepam (Valium and others), fluoxetine (Prozac), fluvoxamine (Luvox), oxazepam (Serax and others), paroxetine (Paxil), sertraline (Zoloft).

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