Nefazodone in Social Phobia

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Background: A variety of drug treatments have been shown to be effective in the treatment of social phobia. This study attempted to assess the efficacy of nefazodone, a new novel serotonergic drug, in the treatment of social phobia.

Method: Nefazodone was administered to 23 patients who had a primary DSM-IV diagnosis of social phobia, generalized type (diagnosed by the Structured Clinical Interview for DSM-IV), in a 12-week open clinical trial. Treatment began at 100 mg of nefazodone daily and was increased according to clinical response and side effects. Patients completed self-report measures at baseline and at weeks 4, 8, and 12. These measures included the Fear of Negative Evaluation scale, the Social Avoidance and Distress scale, the Social Anxiety Thoughts Questionnaire, the Fear Questionnaire, the State-Trait Anxiety Inventory, the Beck Depression Inventory, the Social Adjustment Scale Self-Report, and the Sheehan Disability Scale. Clinicians completed the Liebowitz Panic and Social Phobic Disorders rating form and the Brief Social Phobia Scale.

Results: Twenty-one of the 23 patients completed the 12-week trial. Sixteen (69.6%) were considered responders (moderate or marked improvement), and 7 (30.4%) were considered to be nonresponders (minimal improvement or no change in symptoms). Measures of social anxiety, social phobic avoidance, depression, and social functioning showed a statistically significant change at endpoint.

Conclusion: These findings support a role for nefazodone in the treatment of social phobia, generalized type. Controlled studies will be required to further investigate this preliminary finding as well as to compare nefazodone with other pharmacologic treatments of social phobia.

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The pharmacologic treatment of social phobia is rapidly evolving. There are a variety of drug groups that have been shown to be effective in the treatment of social phobia in placebo-controlled trials. These include the monoamine oxidase inhibitors (MAOIs)[1] such as phenelzine, the reversible inhibitor of monoamine oxidase A (RIMA) brofaromine,[2–4] the high-potency benzodiazepines alprazolam[5] and clonazepam,[6] and the selective serotonin reuptake inhibitors (SSRIs) fluvoxamine,[7] sertraline,[8] and paroxetine.[9] The RIMA moclobemide has been found to be effective in 2 studies[10,11] and no different from placebo in another 2 studies.[12,13] The azapirone buspirone was recently found to be ineffective in a controlled trial.[14]

Given the suggested efficacy of the SSRIs in social phobia, we decided to embark on an open trial of a new novel serotonergic drug, nefazodone, in the treatment of generalized social phobia. Nefazodone hydrochloride is a phenylpiperazine antidepressant that selectively blocks 5-HT_{2A} receptors postsynaptically and moderately inhibits serotonin and norepinephrine reuptake.[15] This pharmacologic profile is different from that of the SSRIs, whose primary pharmacologic action is to block serotonin reuptake presynaptically.

METHOD

Twenty-three patients meeting DSM-IV criteria for social phobia, generalized type, entered an open-label trial of nefazodone. Patients had been referred for treatment to a university-affiliated anxiety disorders clinic in Hamilton, Canada. All patients were evaluated using the Structured Clinical Interview for DSM-IV-Patient Version[16] (SCID-I/P) and gave informed consent.

Patients aged 18 to 65 years entered the trial if they had a primary diagnosis of social phobia, generalized type; that is, social phobia was causing the most disability to the patient. Patients were free of antidepressant medications for at least 2 weeks prior to starting the trial and were excluded from the trial if they were taking any medications believed to be effective in the treatment of social phobia or were involved in any form of psychotherapy.

Nefazodone was initially started at 100 mg/day in 2 divided doses and increased by 100 mg/day in weekly increments until the total dosage reached 300 mg/day. Further increases of 100 mg/day occurred every 2 weeks accord-

ing to clinical response and adverse events. The maximum dose for this study was set at 600 mg/day so patients were treated with doses between 300 mg/day and 600 mg/day. Patients were seen every 4 weeks during the course of the trial.

All patients completed self-report measures of anxiety, depression, and social adjustment at baseline and weeks 4, 8, and 12. These measures included the Beck Depression Inventory,[17] the State-Trait Anxiety Inventory,[18] the Fear Questionnaire (including the social phobia subscale),[19] and the Sheehan Disability Scale.[20] The Social Adjustment Scale Self-Report[21,22] was completed at baseline and week 12 only. For the assessment of social anxiety and avoidance, patients completed the Fear of Negative Evaluation scale,[23] the Social Avoidance and Distress scale,[23] and the Social Anxiety Thoughts Questionnaire at baseline and weeks 4, 8, and 12.[24] Clinicians completed the Brief Social Phobia Scale[25] and the Liebowitz Panic and Social Phobic Disorders rating form[26] at baseline and weeks 4, 8, and 12 to rate changes from baseline. This last scale incorporates the Clinical Global Impressions scale Severity of Illness (CGI-S) and Improvement (CGI-I) measures and rates both the frequency and severity of anxiety episodes, overall functioning, phobic avoidance, and anticipatory anxiety.

Patients had to complete at least 8 weeks of the 12-week trial to be included in the endpoint analysis. Analyses were performed on 2 related data sets. The first contains only the original observations; no attempt was made to replace missing data. The second data set carried forward the prior observation to replace missing data using the last-observation-carried-foward method. The pattern of results was the same using either data set. Results using only the original observations are reported here. A signifigance level of .05 is assumed throughout.

Responders at endpoint had a rating on the CGI-I of "moderately improved" or "markedly improved"; nonresponders had a CGI-I rating of "minimally improved" or "no change." Repeated measures analysis of variance (ANOVA) was used to assess change across the 4 measuring occasions (baseline and weeks 4, 8, and 12) for all outcome measures except for the Social Adjustment Scale Self-Report. This latter outcome measure was assessed only at baseline and week 12, and thus a t test was used. The Bonferroni correction was used to control the study-wise alpha level.

RESULTS

The sample included 8 men and 15 women who had a mean age of 34.8 ± 9.8 years, a mean age at onset of 13.9 ± 6.8 years, and a mean duration of illness of 21.0 ± 9.9 years. At baseline, the mean overall severity of illness score for the sample assessed by the Liebowitz Panic and Social Phobic Disorders rating form was 5.5 ± 0.7, suggesting that most of the patients were "markedly ill." Concurrent diagnoses are shown in Table 1.

Table 1. Concurrent Diagnoses in 23 Patients With Generalized Social Phobia[a]

Diagnosis	N	%
Major depression	3	13.0
Dysthymia	5	21.7
Panic disorder with agoraphobia	2	8.7
Specific phobia	3	13.0
Obsessive-compulsive disorder	3	13.0
Generalized anxiety disorder	0	0.0
Alcohol abuse/dependance	1	4.3
Substance abuse/dependance	0	0.0

[a]Thirteen patients had at least 1 comorbid diagnosis.

Ten of 23 patients had no current comorbid conditions. One of 3 patients who suffered from comorbid obsessive-compulsive disorder (OCD) had a reduction in OCD symptoms. Both of the patients with comorbid panic disorder with agoraphobia showed a reduction in number of panic attacks and agoraphobic avoidance. Two of the 3 patients with comorbid major depressive disorder had a resolution of their depressive symptoms. Four of the 5 patients with dysthymic disorder showed a response to their depressive symptoms. None of the 3 patients with a comorbid specific phobia showed a change in their specific phobic avoidance. The 1 patient with comorbid alcohol dependence showed a substantial decrease in alcohol consumption.

Nineteen of the 23 patients had received previous treatment for their social phobia. Ten patients had previously been treated with at least 1 SSRI trial, with only 5 of the 10 patients having received an adequate trial, including adequate dose and duration of treatment. Two patients had been treated with buspirone, with only 1 patient receiving an adequate trial. Two patients had been treated with inadequate trials of tricyclic antidepressants. One patient was treated with an adequate trial of the RIMA moclobemide. Seven patients were previously treated with high-potency benzodiazepines, with only 1 patient having had an adequate trial. One patient was treated with an inadequate trial of a β-blocker. Three patients had received cognitive-behavioral therapy, with only 1 receiving an adequate trial. Two patients had received long-term, insight-oriented psychotherapy. One patient had previously been treated with brief hypnotherapy, and 1 patient had received brief pastoral counseling. One patient had been treated with an aluminum-zinc cream (for excessive sweating).

Twenty-one of the 23 patients who entered the trial completed 12 weeks of treatment. Both of the patients who dropped out of the trial withdrew because of lack of efficacy. All 23 patients completed 8 weeks of treatment and were included in endpoint analysis. Both patients who dropped out did so following their week 8 appointment. Sixteen (69.6%) were considered responders: 6 had a CGI-I score of 1 (markedly improved), and 10 had a CGI-I

Table 2. Mean Scores for Clinical and Psychometric Measures in 23 Patients With Social Phobia During Nefazodone Treatment[a]

	Week 0		Week 4		Week 8		Week 12		ANOVA Results		
Measure	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	df	p Value
Fear of Negative Evaluation scale	26.0	3.5	23.4	6.2	21.6	8.3	19.1	8.9	7.4	3,54	< .01
Social Avoidance and Distress scale	24.0	12.9	20.1	7.7	18.0	9.0	15.1	9.7	5.9	3,54	< .01
Social Anxiety Thoughts Questionnaire	65.8	21.2	67.2	16.0	57.9	19.5	58.8	16.0	2.1	3,54	.11
Fear Questionnaire											
Total score	39.0	16.3	38.4	15.8	34.4	18.4	29.2	17.0	4.5	3,54	< .01
Agoraphobia	9.0	7.8	8.1	7.9	7.2	7.0	6.4	6.5	2.3	3,51	.09
Social phobia	23.5	7.1	22.5	6.0	19.9	8.4	18.0	8.2	6.6	3,57	< .01
State-Trait Anxiety Inventory											
State scale	45.0	11.6	42.7	9.8	39.9	13.4	36.0	11.7	3.9	3,54	.01
Trait scale	50.4	10.1	48.6	9.2	44.0	13.7	40.5	12.1	9.4	3,54	< .01
Beck Depression Inventory	11.0	7.2	8.4	5.7	7.1	7.1	5.7	5.6	5.0	3,54	< .01
Social Adjustment Scale Self-Report	2.10	0.39	...	...	...	...	1.73	0.30	25.7	1,18	< .01
Sheehan Disability Scale											
Work	4.5	3.0	3.9	2.6	3.7	2.6	2.6	2.4	3.1	3,51	.04
Social	7.2	2.1	6.5	2.5	5.1	3.4	3.9	3.0	8.5	3,51	< .01
Family	1.8	2.3	1.7	1.8	2.0	2.7	0.7	1.2	1.4	3,51	.27
Clinical Global Impressions scale											
Severity of Illness	5.5	0.7	5.3	0.8	4.7	1.2	4.2	1.2	27.1	3,60	< .01
Improvement	...	...	3.5	0.7	2.6	0.9	2.1	1.0	27.9	2,40	< .01
Brief Social Phobia Scale total score	46.4	8.0	43.2	8.0	36.8	12.4	34.6	14.3	7.4	3,33	< .01

[a]Symbol: ... = scale not adminstered at this time point.

score of 2 (moderately improved). Seven patients (30.4%) were considered nonresponders (2 of whom dropped out of the trial): 3 had a CGI-I score of 3 (minimal improvement), and 4 had a CGI-I score of 4 (no change). By week 12, the mean CGI-I score for the 21 patients who completed the trial was 2.1 ± 1.0 and the mean CGI-S score was 4.2 ± 1.2 (moderately ill). The mean time for responders to achieve a rating of at least 2 (moderately improved) on the CGI-I scale was 9.0 ± 2.3 weeks.

The mean dosage of nefazodone at endpoint was 435.9 ± 116 mg/day, with a dosage range of 200–600 mg/day. The mean daily dose at endpoint for responders was not significantly different than for nonresponders (417.2 ± 112.1 vs. 478.6 ± 122.0; t = 1.2, df = 21, p = .25), although there was a trend toward higher doses for nonresponders.

Repeated measures ANOVA revealed significant differences from baseline through weeks 4, 8, and 12 for the Fear of Negative Evaluation scale, Social Avoidance and Distress scale, both the social phobia subscale and the total score of the Fear Questionnaire, both the state and trait subscales of the State-Trait Anxiety Inventory, the Beck Depression Inventory, the Social Adjustment Scale Self-Report, the social and work subscales of the Sheehan Disability Scale, the Brief Social Phobia Scale, and the CGI-S and CGI-I scales (Table 2).

Seventeen (73.9%) of the 23 patients had treatment-related side effects. None of the side effects necessitated withdrawal from the open trial. Ten patients (43.5%) suffered from excess fatigue/sedation. Four patients (17.4%) suffered from nausea, 3 (13.0%) reported poor memory, and 3 (13.0%) suffered from episodic flashes of light. Two patients (8.7%) reported poor concentration, and 2 (8.7%) complained of headaches. Sweating, nighttime illusions, hypersomnia, dry mouth, feeling keyed up, and a decrease in sex drive were found to occur in 1 patient (4.3%). At endpoint, 5 patients (21.7%) continued to complain of excess fatigue and 3 (13.0%) of a poor memory. Flashes of light, hypersomnia, nausea, and headaches were each reported by 1 patient (4.3%).

Case Report

Case 1. Ms. A, a 41-year-old divorced female elementary school music teacher, presented with a 28-year history of excessive social and performance anxiety. She avoided eating in the lunchroom at school or at formal dinner parties. She was unable to speak in any group situation and avoided dealing with authority figures. She was very uncomfortable making small talk with strangers and having people watch her work. In all of these situations, Ms. A worried that she would blush and perspire, which would lead to embarrassing herself and looking foolish. As a result of these concerns, she always wore a turtleneck sweater to hide these symptoms.

By week 12 of the study, taking 500 mg/day of nefazodone, Ms. A was able to speak in front of a group of music teachers, voice her opinion at a staff meeting, interact with other teachers in the staff room without wearing a turtleneck sweater, and talk to her principal casually about her career plans. She was also able to join a gym and talk to people while exercising, without worrying about being scrutinized. She now, generally, finds talking to strangers more comfortable. (Her week 12 CGI-I rating was 1, markedly improved.)

Case 2. Mr. B, a 26-year-old single accountant, presented with a history of significant social anxiety since

the age of 12 years. At that time, he developed anxiety symptoms whenever he had to make presentations or read in front of his class. His social anxiety continued throughout high school and college; for example, if he was working in a group, he would do all the "behind-the-scenes preparation" as long as someone else would agree to make the presentation. He had difficulties socializing in any group situation, even with members of his extended family. He avoided interacting with his girlfriend's family and dreaded attending social events where he might not know everyone. In his job, he experienced marked anxiety when interacting with his boss as well as with new clients. He had difficulty giving feedback to the employees he supervised and speaking up at meetings. He avoided socializing with his coworkers, including not eating lunch with them or attending events such as the Christmas party.

By week 12, on 450 mg/day of nefazodone, he stated that he was no longer experiencing anxiety when attending social functions involving his girlfriend's family. He was attending social events involving his coworkers and was able to give evaluations to those he supervised without difficulty. At management meetings he was able to speak up comfortably. He continued to experience anticipatory anxiety with the physical symptoms of sweating and shakiness prior to many social situations, such as meeting new clients, although the anxiety did decrease once he was in the situation. (His week 12 CGI rating was 2, moderately improved.)

DISCUSSION

To the best of our knowledge, this is the first study of nefazodone for the treatment of social phobia. This open-label trial suggests that nefazodone is a clinically effective treatment for social phobia, generalized type. These findings parallel those found with the SSRIs (fluoxetine,[27–30] sertraline,[31,32] and paroxetine[33,34]) in open trials. Fluvoxamine, sertraline, and paroxetine have been shown to be superior to placebo in controlled trials of the treatment of social phobia.[7,8,35] Previous findings of an increased cortisol response to a fenfluramine challenge suggest that social phobia may be the result of a dysregulation of the serotonin system.[36] The findings from this open trial and from previous SSRI studies in social phobia, as well as the findings from the fenfluramine challenge test, give support to the involvement of the serotonin system in social phobia.

This study has several limitations, including an open-label design with a lack of a control group and a potential for a rater bias. Improvement in this study could be accounted for by a placebo response, which has been noted to occur in controlled studies of social phobia.

Although 13 (56.5%) of the 23 patients had at least 1 current comorbid diagnosis, the significant improvement found on virtually all measures of social and performance anxiety supports the fact that the improvement was occurring on the social phobic symptoms. However, given the high degree of comorbidity and the drug responsiveness of the comorbid conditions, it is not possible to determine how much of the treatment response was specific to social phobia.

In spite of the fact that 17 (73.9%) of the 23 patients reported treatment-related side effects, no patients dropped out of the study because of the side effects. The side effects were generally well tolerated and diminished in frequency by endpoint.

The mean time to response was 9.0 weeks. This response rate is similar to that found with SSRIs. For example, den Boer and others[37] found that treatment with fluvoxamine required 12 weeks in order to produce a beneficial effect on the subjective level of anxiety during social situations. Only the MAOIs and the high-potency benzodiazepines have a more rapid onset of treatment response than nefazodone and SSRIs. This delay in response rate may be due to the fact that serotonin is involved in the regulation of other neurotransmitters involved in social phobia and these interactions take longer to effect change. In addition, although nefazodone may be useful in rapidly decreasing the physical and cognitive symptoms associated with social phobia, the avoidance or behavioral manifestations of social phobia tend to respond more slowly.

Nefazodone may be an effective alternative to MAOIs, which require compliance with a strict diet and often cause distressing side effects; to the high-potency benzodiazepines, which have a potential for abuse and dependency in this patient group; and to cognitive-behavioral treatment, which is not always readily available. Nefazodone may be an alternative to the SSRIs, because patients may have a different response or tolerance to drugs. For example, one of the most distressing side effects of the SSRIs is that of sexual dysfunction. Nefazodone causes a reported lower rate of sexual dysfunction,[38-41] and in this study only 1 patient complained of sexual dysfunction. Placebo-controlled studies of nefazodone in the treatment of social phobia are warranted. In addition, studies comparing nefazodone with the SSRIs, MAOIs, and cognitive-behavioral treatment should be considered in the future.

Drug names: alprazolam (Xanax), buspirone (BuSpar), clonazepam (Klonopin), fenfluramine (Pondimin), fluoxetine (Prozac), fluvoxamine (Luvox), nefazodone (Serzone), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft).

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