Paroxetine in Social Phobia

Catherine Mancini, M.D., F.R.C.P.(C),
and Michael Van Ameringen, M.D., F.R.C.P.(C)

Background: Several open trials suggest the efficacy of the selective serotonin reuptake inhibitors (SSRIs) in social phobia. This study attempted to assess the efficacy of paroxetine, a new SSRI, in the treatment of social phobia.

Method: Paroxetine was administered to 18 patients who had a primary DSM-III-R diagnosis of social phobia, generalized type (diagnosed by using the Structured Clinical Interview for DSM-III-R), in a 12-week open, clinical trial. Treatment began at 10 mg of paroxetine 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.

Results: All 18 patients completed the 12-week trial. Fifteen (83.3%) were considered responders (moderate or marked improvement), and 3 (16.7%) were considered to be nonresponders (minimal improvement or no change of their symptoms). All 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 paroxetine in the treatment of social phobia, generalized type. Controlled studies will be required to further investigate this preliminary finding as well as to compare paroxetine with other pharmacologic treatments of social phobia.

(J Clin Psychiatry 1996;57:519–522)

Received Aug. 9, 1995; accepted Aug. 28, 1996. From the Department of Psychiatry, McMaster University, Hamilton, Ontario, Canada.

The authors acknowledge the assistance of Ms. Carol Wilson who assisted in data collection and entry for this study.

Reprint requests to: Catherine Mancini, M.D., F.R.C.P.(C), Anxiety Disorders Clinic, 3G Psychiatry, Chedoke-McMaster Hospitals, 1200 Main Street West, Hamilton, Ontario, L8N 3Z5, Canada.

Few controlled studies have evaluated the use of medications in the treatment of social phobia. Controlled trials support the efficacy of the monoamine oxidase inhibitor (MAOI) phenelzine[1] and the high-potency benzodiazepine clonazepam.[2] The reversible inhibitors of monoamine oxidase-A, moclobemide[3] and brofaromine,[4,5] have also shown efficacy in controlled trials of social phobic patients. However, a subsequent controlled trial of moclobemide did not support the efficacy of moclobemide in the treatment of social phobia.[6] Uncontrolled trials suggest a role in treatment for the benzodiazepine alprazolam,[7,8] the MAOI tranylcypromine,[9] and the azaspirodecanedione buspirone.[10,11] Although an uncontrolled trial suggested a role for atenolol in the treatment of generalized social phobia,[12] the lack of efficacy of atenolol was subsequently found by Liebowitz et al.[1]

Two open trials[13,14] and two case series[15,16] have suggested that the selective serotonin reuptake inhibitor (SSRI) fluoxetine may be effective in the treatment of social phobia. More recently, there have been two open trials of sertraline[17,18] and a placebo-controlled trial of fluvoxamine[19] and sertraline[20] that suggest efficacy in the treatment of social phobia. The success of the SSRIs in treating social phobia is noteworthy since the side effect profile of the SSRIs is different from that of the benzodiazepines and the MAOIs.

This study was undertaken to determine whether paroxetine, a new SSRI, could be an alternative treatment choice for patients with social phobia.

METHOD

Eighteen patients meeting DSM-III-R criteria for social phobia, generalized type, entered the open pilot study of paroxetine for the treatment of social phobia. Patients had been referred for treatment to two anxiety disorder clinics at McMaster University in Hamilton, Canada. All patients were evaluated using the Structured Clinical Interview for DSM-III-R, Patient Version[21] (SCID) and gave informed consent.

Patients who were aged 18 to 65 years entered the trial if they had a primary diagnosis of social phobia, 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 felt to be effective in social phobia or were involved in any form of psychotherapy.

Paroxetine was initially started at 10 mg/day and increased every 2 weeks up to a maximum of 60 mg/day.

The dose was titrated upward within this limit until a clinical response was achieved. If intolerance occurred, the dose was adjusted accordingly. 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 included the Beck Depression Inventory[22] (BDI), the State-Trait Anxiety Inventory[23] (STAI), the Fear Questionnaire (including the social phobia subscale),[24] the Sheehan Disability Scale[25] (completed at baseline and Week 12 only), and the Social Adjustment Scale Self-Report[26,27] (SAS-SR; completed at baseline and Week 12 only). To assess social anxiety and avoidance, patients completed the Fear of Negative Evaluation Scale,[28] the Social Avoidance and Distress Scale,[28] and the Social Anxiety Thoughts Questionnaire.[29] Clinicians completed the Liebowitz Panic and Social Phobic Disorders Rating Form[30] at baseline and Weeks 4, 8, and 12 to rate changes from baseline. This scale incorporates the Clinical Global Impression scale (CGI: Severity and Change measures) and rates 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. Responders at endpoint had a rating on the CGI-Change scale of "moderately" or "markedly improved." Repeated measures of analysis of variance (ANOVA) were used to compare baseline measures with outcome measures at Weeks 4, 8, and 12, except for the Sheehan Disability Scale and the SAS-SR, which were used to compare baseline to Week-12 scores. The Bonferroni correction was used to control for the study-wise alpha level.

RESULTS

The sample included 13 men and 5 women who had a mean ± SD age of 33.3 ± 8.1 years, a mean age at onset of 13.6 ± 7.2 years, and a mean duration of illness of 19.8 ± 10.0 years. At baseline, the mean ± SD overall severity of illness for the sample assessed by using the Liebowitz Panic and Social Phobic Disorders Rating Form was 5.3 ± 0.8, suggesting that most patients were "markedly ill." Concurrent diagnoses are shown in Table 1.

All 18 patients who entered the trial completed 12 weeks of treatment. Fifteen (83.3%) were considered responders; 9 had a CGI-Change score of 1 (markedly improved), and 6 had a CGI-Change score of 2 (moderately improved). Three patients (16.7%) were considered nonresponders, 2 with a CGI-Change score of 3 (minimal improvement) and 1 with a CGI-Change score of 4 (no change). By Week 12, the mean CGI-Change score was 1.7 ± 0.9 and the mean CGI-Severity score was 3.7 ± 1.6 (mild-to-moderately ill). The mean time for responders to achieve a rating of at least 2 (moderately improved) on the CGI-Change scale was 7.2 ± 3.1 weeks.

Table 1. Concurrent Diagnoses in 18 Patients With Social Phobia

Diagnosis	N	%
Major depression	2	11
Dysthymia	11	61
Panic disorder	1	6
Panic disorder with agoraphobia	4	22
Agoraphobia	1	6
Simple phobia	2	11
Obsessive-compulsive disorder	2	11
Generalized anxiety disorder	1	6
Alcohol abuse/dependence	2	11
Substance abuse/dependence	0	0

The mean dose of paroxetine at endpoint was 36.1 ± 15.0 mg/day, with a dose range of 20 to 60 mg/day. The mean dose at endpoint for responders was not significantly different from that for nonresponders (34.7 ± 15.1 vs. 43.3 ± 15.3 mg/day; $t = 0.91$, $df = 16$, $p = .38$).

Repeated measures of ANOVA revealed significant differences ($p < .005$) from baseline through Weeks 4, 8, and 12 for the Fear of Negative Evaluation Scale, the Social Avoidance and Distress Scale, the Social Anxiety Thoughts Questionnaire, the STAI, the BDI, and all measures of the Liebowitz Panic and Social Phobic Disorders Rating Forms (including the CGI-Severity scale) and the SAS-SR (Table 2).

Fifteen (83.3%) of 18 patients had treatment-related side effects. None of the side effects necessitated withdrawal from this open trial. Five patients (27.8%) suffered from jitteriness and tremulousness. Four patients (22.2%) suffered from nausea, 2 (11.1%) from anorexia, and 1 (5.6%) had loose stools. Four patients (22.2%) complained of fatigue, 3 patients (16.7%) complained of sexual dysfunction, and 3 (16.7%) of insomnia. Two patients (11.1%) reported vivid dreams, 2 (11.1%) complained of agitation, and 2 (11.1%) complained of irritability. Hypersomnia, weight gain, weakness, blurred vision, sweating, and a stiff neck each were found to occur in 1 patient (5.6%) only. At endpoint (Week 12), 3 patients (16.7%) continued to complain of fatigue, and the following side effects each continued to be experienced by 1 patient (5.6%): vivid dreams, hypersomnia, weight gain, jitteriness, and sexual dysfunction.

CASE REPORTS

Case 1

Ms. A, a 27-year-old divorced female computer analyst, presented with a 13-year history of social anxiety that began after a major family move. She began to feel uncomfortable when speaking in front of people and began to skip classes if she knew she had to present in front of the class. She would avoid social situations with her peers, was extremely anxious when interacting with unfamiliar people, and had begun to experience anxiety even

Table 2. Mean Scores for Clinical and Psychometric Measures in 18 Social Phobics Before and During Paroxetine Treatment

Measure	Baseline Mean	Baseline SD	Week 4 Mean	Week 4 SD	Week 8 Mean	Week 8 SD	Week 12 (Endpoint) Mean	Week 12 (Endpoint) SD	df	F	p Value (ANOVA Repeated Measures)
Fear of Negative Evaluation Scale	23.3	6.4	20.9	8.1	17.2	8.5	14.2	8.3	3,33	8.70	< .001
Social Avoidance and Distress Scale	22.7	5.0	19.5	6.4	15.9	9.4	12.2	9.2	3,33	8.95	< .001
Social Anxiety Thoughts Questionnaire	71.9	13.3	59.6	19.9	55.1	17.2	51.8	19.6	3,33	10.38	< .001
Fear Questionnaire											
Agoraphobia	11.8	10.8	9.8	11.3	7.7	9.1	5.8	7.1	3,39	3.82	.017
Social phobia	22.5	8.9	20.9	9.1	18.4	12.0	15.1	10.4	3,39	3.86	.016
Total	44.6	24.9	40.9	27.7	35.1	23.2	28.0	16.9	3,39	4.62	.007
State-Trait Anxiety Inventory											
State	50.6	11.6	42.1	11.2	38.9	9.7	35.4	9.3	3,39	8.92	< .001
Trait	56.4	10.0	50.2	13.3	44.5	11.8	42.3	11.1	3,39	9.49	< .001
Beck Depression Inventory	17.3	9.4	11.8	10.1	9.7	6.9	7.3	7.0	3,39	15.80	< .001
Social Adjustment Scale											
Self-Report Total	2.31	0.42					1.90	0.37	1,16	25.86	< .001
Sheehan Disability Scale											
Work	4.2	2.9					1.9	2.1	1,16	8.86	.009
Social	8.1	2.3					4.1	3.4	1,16	20.32	< .001
Family	3.3	3.1					1.9	2.1	1,16	3.97	.064
Clinical Global Impression-Severity of Illness	5.3	0.8	5.2	1.0	4.6	1.5	3.7	1.6	3,51	22.40	< .001
Clinical Global Impression-Change			3.1	1.1	2.1	1.0	1.7	0.9			

at family gatherings. She had difficulties dealing with authority figures, using the telephone, and eating in front of strangers. When working, she experienced marked anxiety while being observed and when giving any type of formal presentation to her peers, which was problematic because part of her job involved giving computer demonstrations and seminars. As a result of her severe social anxiety, she had elected not to pursue a university education. Dating was extremely difficult for her, and she had not dated since her divorce 3 years ago.

By Week 12 of the study, she had been prescribed paroxetine 30 mg daily for 8 weeks. She was no longer experiencing anticipatory anxiety or dread prior to a group or social situation. She was able to go out socially to luncheons. Although Ms. A continued to experience some nervousness at meetings, she was not avoiding them. She was giving seminars and computer training courses with little or no anxiety and had begun dating once again. (Her Week-12 rating on the CGI was 1, markedly improved.)

Case 2

Mr. B, a 29-year-old married father of two children working as a professional housepainter, presented with a lifetime history of social anxiety. He described himself as having been a "shy, anxious" child and adolescent who avoided using the telephone and dating because of his social anxiety. He had difficulties reading or doing presentations in front of the class. Over the past 10 years, the social anxiety had increased to the point where he had difficulties in almost all social situations. For example, he felt extremely uncomfortable asking questions during parent/teacher meetings to the point that he worried his children would suffer. He knew his social anxiety was also causing marital problems because his wife was very outgoing and his avoidance of social activities was putting a strain on their marriage.

Mr. B was maintained on paroxetine 20 mg daily. By Week 12, he found that he was having less difficulty talking to coworkers and working while being observed. He was attempting to make conversation with strangers and was generally finding most social situations less anxiety provoking. Mr. B was interacting more with his wife and family, and his wife noticed the improvement in his social anxiety. (His Week-12 rating on the CGI was 2, moderately improved.)

DISCUSSION

Findings of an increased cortisol response in social phobic patients who were administered a fenfluramine challenge suggest that social phobia may be the result of a dysregulated serotonin system[31] and that a supersensitivity of the central serotonin system may be involved. Paroxetine, along with fluoxetine and sertraline, is the third SSRI found to be beneficial in the treatment of social phobia in open trials. Fluvoxamine and sertraline have been shown to be efficacious in social phobia in placebo-controlled trials. These positive pharmacologic studies give support to the involvement of the serotonin system in social phobia.

To evaluate the clinical significance of our findings, we examined the scores of the psychometric measures of the re-

sponders at endpoint with respect to being within one standard deviation of the mean score for normal controls. For the Fear of Negative Evaluation Scale, the Social Avoidance and Distress Scale, the Social Anxiety Thoughts Questionnaire, and the Fear Questionnaire-social phobia subscale,[32] we found that 100%, 86.7%, 73.3%, and 73.3%, respectively, of the responders were within one standard deviation of the mean scores. Sixty percent of responders fell within one standard deviation of the mean for a community sample on the Social Adjustment Scale Self-Report. Therefore, these findings suggest that the results of our study are likely to be clinically significant as well as statistically significant.

This study has several limitations including the open-label design, lack of a control group, and potential for rater bias. A placebo response could explain our findings, since this has been documented to occur in controlled pharmacologic trials in social phobia.[1–4,6,19] In addition, the flexible-dose design does not allow one to comment on the possible effectiveness of one dose over another.

Although 14 (77.8%) of 18 patients did have at least one current comorbid diagnosis, the significant improvement found on all measures of social anxiety supports the fact that improvement was occurring in the social phobic symptoms. Only 2 of 18 patients suffered from concurrent major depression, strengthening the argument that the reported improvement on the CGI occurred as a result of improvement of the social phobic symptoms rather than improvement of comorbid major depression. It is also of note that 4 (26.7%) of the 15 responders had no comorbid diagnosis and were judged to be markedly improved. However, given the high degree of comorbidity and the SSRI responsiveness of the comorbid conditions, it is not possible to determine how much of the response was specific to social phobia.

Although 15 (83.3%) of 18 patients reported treatment-related side effects, no patients dropped out of the study, because the side effects were well tolerated.

Paroxetine, as with the other SSRIs, may be an effective alternative to MAOIs, which require compliance with a strict diet and often cause distressing side effects; to 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. It may be an alternative to the other SSRIs, since patients may have a different response or tolerance to drugs in the same class. Placebo-controlled studies of paroxetine using larger populations and employing a fixed-dose design are warranted. As well, studies comparing paroxetine to other pharmacologic and psychological treatments of social phobia should be considered in the future.

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

REFERENCES

1. Liebowitz MR, Schneier F, Campeas R, et al. Phenelzine vs atenolol in social phobia: a placebo-controlled comparison. Arch Gen Psychiatry 1992;49:290–300
2. Davidson JRT, Potts NS, Richichi E, et al. Treatment of social phobia with clonazepam and placebo. J Clin Psychopharmacol 1993;13:423–428
3. Versiani M, Nardi E, Mundim FD, et al. Pharmacotherapy of social phobia: a controlled study with moclobemide and phenelzine. Br J Psychiatry 1992;161:353–360
4. Humble M, Fahlen T, Koczkas C, et al. Social phobia: efficacy of brofaromine versus placebo. In: New Research Program and Abstracts of the 145th Annual Meeting of the American Psychiatric Association; May 6, 1992; Washington, DC. Abstract 483:166
5. Van Vliet LM, Den Boer JA, Westenberg HGM. Psychopharmacological treatment of social phobia: clinical and biochemical effects of brofaromine a selective MAO-A inhibitor. Eur Neuropsychopharmacol 1992;2:21–29
6. Schneier FR, Davies SO, Goetz D, et al. A controlled trial of moclobemide in social phobia. Presented at the 1996 Annual Meeting of the American Psychiatric Association; May 8, 1996; New York, NY
7. Lydiard RB, Laraia MT, Howell EF, et al. Alprazolam in the treatment of social phobia. J Clin Psychiatry 1988;49:17–19
8. Reich J, Yates W. A pilot study of treatment of social phobia with alprazolam. Am J Psychiatry 1988;145:590–594
9. Versiani M, Mundim FD, Nardi AE, et al. Tranylcypromine in social phobia. J Clin Psychopharmacol 1988;8:279–283
10. Munjack DJ, Bruns J, Baltazar PL, et al. A pilot study of buspirone in the treatment of social phobia. Journal of Anxiety Disorders 1991;5:87–98
11. Schneier FR, Saoud JB, Campeas R, et al. Buspirone in social phobia. J Clin Psychopharmacol 1993;13:251–256
12. Gorman JM, Liebowitz MR, Fyer AJ, et al. Treatment of social phobia with atenolol. J Clin Psychopharmacol 1985;5:298–301
13. Black B, Uhde T, Tancer M. Fluoxetine for the treatment of social phobia. J Clin Psychopharmacol 1992;12:293–295
14. Van Ameringen M, Mancini C, Streiner D. Fluoxetine efficacy in social phobia. J Clin Psychiatry 1993;54:27–32
15. Schneier FR, Chin SJ, Hollander E, et al. Fluoxetine in social phobia. J Clin Psychopharmacol 1992;12:62–64
16. Sternbach H. Fluoxetine treatment of social phobia. J Clin Psychopharmacol 1990;10:230–231
17. Van Ameringen M, Mancini C, Streiner D. Sertraline in social phobia. J Affect Disord 1994;31:141–145
18. Czepowicz VD, Johnson MR, Lydiard RB, et al. Sertraline in social phobia. J Clin Psychopharmacol 1995;15:372–373
19. Van Vliet LM, Den Boer J, Westenberg HGM. Psychopharmacological treatment of social phobia: a double blind placebo controlled study with fluvoxamine. Psychopharmacology 1994;115:128–134
20. Katzelnick DJ, Kobak KA, Greist JH, et al. Sertraline for social phobia: a double-blind, placebo-controlled crossover study. Am J Psychiatry 1995;152:1368–1371
21. Spitzer RL, Williams JBW, Gibbon M, et al. Structured Clinical Interview for DSM-III-R, Patient Version. New York, NY: Biometric Research, New York State Psychiatric Institute; 1988
22. Beck AT, Ward CH, Mendolson M, et al. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561–571
23. Spielberger CD, Grsuch RL, Lushene RE. Manual for the State-Trait Anxiety Inventory. Palo Alto, Calif: Consulting Psychologists Press; 1970
24. Marks IM, Mathews AM. Brief standard self-rating for phobic patients. Behav Res Ther 1979;17:263–267
25. Sheehan DV. The Anxiety Disease. New York, NY: Scribner; 1983
26. Weissman MM, Bothwell S. Assessment of social adjustment by patient self-report. Arch Gen Psychiatry 1976;33:1111–1115
27. Weissman MM, Prusoff BA, Thompson WD, et al. Social adjustment by self-report in a community sample and in psychiatric outpatients. J Nerv Ment Dis 1978;166:317–326
28. Watson D, Friend R. Measurement of social evaluative anxiety. J Consult Clin Psychol 1969;33:448–457
29. Hartman LM. Cognitive components of anxiety. J Clin Psychol 1984;40:137–139
30. Liebowitz MR, Gorman JM, Fyer AJ, et al. Pharmacotherapy of social phobia: an interim report of a placebo-controlled comparison of phenelzine and atenolol. J Clin Psychiatry 1988;49:252–257
31. Tancer ME. Neurobiology of social phobia. J Clin Psychiatry 1993;54(12, suppl):26–30
32. Cox BJ, Swinson RP, Shaw BF. Value of the Fear Questionnaire in differentiating agoraphobia and social phobia. Br J Psychiatry 1991;159:842–845