Role of Serotonin Drugs in the Treatment of Social Phobia

Manuel E. Tancer, M.D., and Thomas W. Uhde, M.D.

Social phobia is a common anxiety disorder that is underdiagnosed and undertreated. To date, three classes of serotonin drugs have been used to treat patients suffering from social phobia. These include the serotonin selective reuptake inhibitors (SSRIs), the partial 5-HT_{1A} agonist buspirone, and the 5-HT_3 antagonist ondansetron. Although none of the serotonin agents have yet been directly compared with the gold standard monoamine oxidase inhibitor phenelzine or the high potency triazolobenzodiazepines alprazolam or clonazepam, the SSRIs, as a class, appear to be clinically useful agents. Further studies using larger sample sizes and double-blind methodology are needed to clarify the role of serotonin drugs in the treatment of social phobia. *(J Clin Psychiatry 1997;58[suppl 5]:50–54)*

Social phobia is a common anxiety disorder with a 12-month prevalence of 7.9% in the general population.[1] Social phobia is associated with increased risk for major depression and alcohol abuse.[2,3] Schneier et al.,[4] examining data from the Epidemiologic Catchment Area, reported that approximately 13% of a national sample of patients with social phobia had sought professional help for their symptoms. Despite an enormous increase in interest and research in social phobia, there are many more questions than answers about this common, often disabling, disorder.

The pharmacotherapy of social phobia has recently been reviewed.[5,6] Monoamine oxidase inhibitors (MAOIs) in general, and phenelzine in particular, appear to be the most effective medication for the treatment of social phobia. This conclusion is based upon rates of response, magnitude of response compared with placebo, and anecdotal reports from patients who have been on phenelzine and at least one other agent. Despite the efficacy of MAOIs, there has been reluctance on the part of both physicians and patients to use this class of drug, in large part due to the need for a low tyramine diet, the risk of "hypertensive crisis," and the relatively high rates of orthostatic hypotension, sleep disturbance, and sexual dysfunction. Since the initial double-blind, placebo-controlled trials established the efficacy of phenelzine,[7–9] there has been a search for alternative, effective treatment modalities.

At the same time that a wide range of pharmacologic interventions have been examined for social phobia, there has been increasing interest in exploring the neurobiology of social phobia. The ultimate goal of such exploration would be to develop more effective and/or targeted treatments based on understanding the pathophysiology of social phobia. The neurobiological studies in social phobia have recently been reviewed.[10,11]

PHARMACOLOGIC CHALLENGE STUDIES

One methodology that has been widely used in psychiatric research is the pharmacologic challenge paradigm. The efficacy of the MAOIs led to an examination of the functional integrity of the monoamine neurotransmitter systems. The first study in social phobia employing this strategy was reported by Papp et al.[12] In this study, administration of epinephrine was used to try to reproduce the symptoms of social phobia. Although the epinephrine increased heart rates and blood pressure, social phobic symptoms were not experienced. Our laboratory subsequently used the α_2-adrenergic agonist clonidine as a probe of the norepinephrine system in patients with social phobia.[13] Using an intravenous dose of 2 μg/kg, we found that patients with social phobia had significantly blunted growth hormone–responses to clonidine compared with healthy volunteers. The degree of blunting was comparable to that in panic disorder patients.

Liebowitz et al.[14] proposed that abnormalities in the dopamine system may be involved in social phobia, based on the differential response of social phobia patients to MAOIs but not tricyclic antidepressants. Further support

From The Psychiatry Service, Detroit Veterans Affairs Medical Center (Dr. Tancer), and the Departments of Psychiatry and Behavioral Neurosciences and Pharmacology, Wayne State University School of Medicine (both authors), Detroit, Michigan.

Presented at the closed symposium "Perspectives on Fluvoxamine Therapy," held March 2, 1996, in Orlando, Florida, and sponsored by Solvay Pharmaceuticals in conjunction with the Medical University of South Carolina, Department of Psychiatry and Behavioral Science through an educational grant from Solvay Pharmaceuticals, Inc.

Reprint requests to: Manuel E. Tancer, M.D., Psychiatry Service (116A), Detroit Veterans Affairs Medical Center, 4646 John R. Street, Detroit, MI 48201.

for this hypothesis came from the observation that patients with Parkinson's disease had excess rates of social phobia, often preceding the physical stigmata of Parkinson's.[15] In order to test the dopamine hypothesis of social phobia and confirm the blunted growth hormone–response to clonidine, Tancer and colleagues[16] conducted a study in which 21 patients with social phobia and 22 healthy volunteers received probes for the dopamine system (levodopa 500 mg p.o.), norepinephrine system (clonidine 5 µg/kg p.o.), and placebo. In addition, as a test for the serotonin system, the subjects received the mixed presynaptic and postsynaptic serotonin releasing agent *d,l*-fenfluramine (60 mg). The order of drug administration was balanced using a Latin-square design, and the administration was double-blind.

Tancer and associates[16] found no evidence for the dopamine hypothesis in that neither measure of dopamine function, inhibition of prolactin and increased spontaneous eyeblink rate, differed between social phobic subjects and the volunteers. Unexpectedly, the blunted growth hormone–response to clonidine was not replicated. Surprisingly, we found an enhanced cortisol response following *d,l*-fenfluramine administration. There was a trend for the prolactin response to fenfluramine to also be enhanced, but the large variability in prolactin responses obscured group differences. Such an enhanced cortisol response to fenfluramine, most likely mediated via 5-HT_{1C} and/or 5-HT_2 receptors,[17] has been found in patients with panic disorder.[18,19] It is worth noting that none of the neurobiological findings in social phobia have been replicated, so the results, while exciting, are very preliminary. Pending replication of the results, we have cautiously suggested that the fenfluramine result is consistent with a supersensitivity of serotonin systems in patients with generalized social phobia. With this possible neurobiological abnormality in mind, we examined the extant literature with regard to clinical trials of serotonergic agents. The remainder of this paper will summarize the results of these studies.

To date, three classes of serotonergic agents have been studied in a least one double-blind placebo-controlled trial in patients with social phobia. These include the serotonin selective reuptake inhibitors (SSRIs) fluvoxamine and sertraline; buspirone, a partial agonist at the 5-HT_{1A} receptor subtype; and the 5-HT_3 antagonist ondansetron. Under each class, the double-blind trials will be presented first, followed, where available, by case series or non-blinded trials. It is important to note that the trials differ in the primary outcome measures employed, duration of study, and medication dosage, so head-to-head comparison is usually not possible.

SSRIs

Fluvoxamine was the first SSRI demonstrated to be superior to placebo using a double-blind, placebo-controlled design.[20] In a 12-week study, 30 patients meeting DSM-III-R[21] criteria for social phobia were randomly assigned to treatment with fluvoxamine (titrated up to 150 mg/day by Week 3) or with placebo. The Liebowitz Social Anxiety Scale (SAS) was used as the principal outcome measure. Two subjects dropped out during the trial: one fluvoxamine-treated subject secondary to side effects and one placebo subject secondary to lack of efficacy. At Week 12, but not before, fluvoxamine showed a statistically significant reduction in the SAS anxiety subscale compared with placebo. There was no group difference in the avoidance subscale of the SAS. When categorical outcomes were measured, substantial improvement, defined by a greater than 50% reduction in the SAS anxiety scale, was seen in 7 (47%) of 15 fluvoxamine-treated patients compared with 1 (8%) of 13 of the placebo-treated patients. Although only 1 patient dropped out of the trial secondary to side effects, adverse events, typical of this class of medication, were seen in the majority of participants: nausea/stomach complaints were reported by 10 fluvoxamine- compared with 2 placebo-treated subjects; increased anxiety was reported in 8 fluvoxamine- versus 1 placebo-treated patient; and sleepiness/tiredness was reported in 7 fluvoxamine- versus 1 placebo-treated subject.

The second published double-blind, placebo-controlled trial of an SSRI in social phobia was reported by Katzelnick et al.[22] The study employed a crossover design in which subjects were treated with either sertraline or placebo for 10 weeks. They then had a 2-week taper/medication-free interval after which the participants were crossed to the other treatment for 10 weeks. A flexible dose of sertraline was used (50–200 mg/day). Twelve patients with social phobia participated. The SAS was the primary outcome measure. Mean baseline SAS scores were 64.3. There was a mean decrease of 22 during sertraline treatment compared with 5 during the placebo arm. The Liebowitz Social Phobic Disorders Rating Form, a type of clinical global impression scale, was used as a secondary outcome measure. Six of 12 subjects were rated as "moderately improved" compared with 2 of 12 rated as "markedly improved" during the sertraline treatment. It is not clear from the manuscript how many subjects started the trial or how many people dropped out of the trial.

Several case series have been published suggesting that fluoxetine, sertraline, paroxetine, and fluvoxamine are effective in the treatment of social phobia. Three open-label trials of fluoxetine have been published. Schneier et al.[23] reported that 7 (58%) of 12 subjects had a positive clinical response to fluoxetine. This compares to 10 (71%) of 14 responders reported by Black et al.,[24] and 10 (62%) of 16 patients reported by Van Ameringen et al.[25] A fourth trial was recently reported[26] in 32 subjects with social phobia treated for 16 weeks. Three subjects did not complete the trial; 26 (90%) of 29 of the completers were rated as moderately or markedly improved on the Clinical Global

Impressions (CGI) scale. Length of time required for improvement varied, but was often not seen for 3 months.[26]

Three reports have been published suggesting that sertraline is effective in the treatment of patients with social phobia.[27–29] Van Ameringen and colleagues[27] reported on 22 social phobic patients. Twenty subjects completed at least 8 weeks of sertraline treatment and were evaluated. The authors used a flexible dose of sertraline (range, 100–200 mg/day; mean = 148 mg/day). Sixteen (80%) of 20 patients were rated as "responders" in that they had a CGI of 1 (not ill) or 2 (minimally ill). It is important to note that in this particular series, 9 of the 16 responders were clinically suffering from major depression at the time of the study. Martins et al.[28] reported on a 6-week open label trial of sertraline. Twenty-four subjects entered the trial, and 19 completed the trial following a 2-week medication-free baseline period. The primary outcome measure in this study was the Duke Brief Social Phobia Scale (BSPS). The authors defined "responders" as individuals exhibiting a > 25% reduction in the BSPS and reported that 11 (58%) of the 19 subjects responded to the sertraline. Czepowicz et al.[29] conducted a retrospective chart review of patients with social phobia who had received at least 100 mg/day of sertraline for a minimum of 4 weeks. Eleven subjects were found, 5 of whom had comorbid anxiety and/or depression. Seven (64%) of 11 were felt to be much or very much improved on the CGI.

Mancini and colleagues[30] reported on a 12-week open clinical trial in 18 patients with social phobia. All 18 subjects completed the trial. Fifteen (83%) of the 18 were considered "responders"—moderate or marked improvement—on the CGI.

DeVane et al.[31] recently presented data from a 7-week open-label study with fluvoxamine. In this study, a 1-week single-blind placebo run-in was followed by 6 weeks of single-blind fluvoxamine administration. The fluvoxamine dose was flexible, with a range of 50–150 mg/day. Fifteen subjects began the trial, and 10 completed the 7 weeks. The BSPS was the principal outcome measure. There was a significant reduction on the BSPS from 47.3 ± 12.5 at baseline to 22.8 ± 10.8 at the end of Week 6 of fluvoxamine. Benefit was noted as early as three weeks. Of the 5 subjects who failed to complete the study, three quit owing to adverse events (1 nausea, 2 drowsiness, and 2 "lost to follow-up.") It is worth noting that the onset of response in this study (3 weeks) was much earlier than that noted by van Vliet et al.[20] (Week 12). This difference may be due to the rating scale used or the nonblind medication administration.

BUSPIRONE, A PARTIAL 5-HT$_{1A}$ AGONIST

There has been one double-blind, placebo-controlled trial of buspirone in the treatment of 34 musicians with performance anxiety who also met criteria for social phobia.[32] The 6-week trial compared buspirone to placebo to buspirone plus cognitive-behavioral therapy to placebo plus cognitive-behavioral therapy. Twenty-nine subjects completed the trial. The mean dose of buspirone was 32 mg/day (range, 15–50 mg/day). The authors concluded that cognitive-behavioral therapy was superior to buspirone and that the addition of buspirone to behavioral therapy conferred no additional benefit, although some patients did appear to benefit from buspirone. The conclusions from this study are limited by the atypical nature of the socially phobic individuals (musicians), the fact that no social phobia specific scale was used as an outcome measure, and the small number of completers per cell (7 or 8).

Subsequently, two open-label trials of buspirone have been reported. Munjack et al.[33] conducted an 8-week trial in 17 patients; 11 completed the study. The mean dose of buspirone was 47.7 mg/day. There was no improvement seen on the social phobia specific scales, but patients were noted to have demonstrated nonspecific improvement. Schneier et al.[34] conducted a 12-week trial in 21 patients with social phobia, 17 of whom completed the study. Eight (47%) of 17 were felt to be responders (much to very much improved on the CGI). The mean dose of buspirone was 45.6 mg/day.

ONDANSETRON, A 5-HT$_3$ ANTAGONIST

The 5-HT$_3$ antagonist ondansetron is clinically used for the treatment of chemotherapy-induced nausea and vomiting. At lower doses, ondansetron appears to have antianxiety properties in animal models. Bell and DeVeaugh-Geiss[35] reported on a large, multicenter, double-blind, placebo-controlled trial of ondansetron for the treatment of social phobia. The study was a 1-week single-blind placebo run-in followed by a 10-week double-blind randomization to placebo (N = 139) or ondansetron 0.25 mg b.i.d. (N = 136). The primary outcome measure was the Duke BSPS. Ondansetron was significantly superior to placebo in reducing the BSPS score and was well tolerated. The authors felt that the "effect size" was small, and the medication is not being further developed for social phobia.

DISCUSSION

Three classes of serotonin drugs have been examined to date for the treatment of social phobia, the SSRIs, buspirone, which presumably acts via the 5-HT$_{1A}$ receptor system, and the 5-HT$_3$ antagonist ondansetron. Of these three classes, the SSRIs appear, as a class, to be effective in the treatment of social phobia. Buspirone needs further study in that the double-blind trial was small and probably not generalizable (musicians) to the whole population of social phobia, and the optimal dosing and duration are not clear. The 5-HT$_3$ antagonist (ondansetron) also requires

further study in that the clinical (as opposed to statistical) benefits of this drug appear limited.

The relationship between the possible serotonin supersensitivity and treatment response has yet to be examined and should be explored in a prospective fashion.

The SSRIs, clinically, do not appear to be as effective as the MAOIs, or even the high-potency benzodiazepine clonazepam[36] in the treatment of social phobia,[5] but double-blind direct comparisons are needed to confirm this clinical impression. Several issues, in particular duration of treatment, choice of primary outcome measures, and rate of dose titration, should be standardized in order to allow for comparison across studies.

Although there is considerable evidence that several classes of medications are clinically effective in the treatment of social phobia, the efficacy of behavioral interventions, most often in the form of cognitive behavioral therapy,[37,38] has also been established. Self-help books and self-help groups may also provide valuable support for some patients suffering from social phobia. Therefore, it is important to view pharmacotherapy for social phobia as only one of a variety of available options.[39] Studies comparing combinations of medication and cognitive-behavioral therapy with medication or cognitive-behavioral therapy alone are ongoing and will provide invaluable information regarding the most effective treatment(s) for patients with social phobia.

Social phobia is a common, often disabling, anxiety disorder that appears to respond to a variety of treatment interventions. It is hoped that increasing public and professional awareness of this disorder will lead to diagnosis and treatment for this disorder in more patients.

Drug names: buspirone (BuSpar), clonazepam (Klonopin), clonidine (Catapres), fenfluramine (Pondimin), fluoxetine (Prozac), fluvoxamine (Luvox), levodopa (Larodopa), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft).

REFERENCES

1. Kessler RG, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. Arch Gen Psychiatry 1994;51:8–19
2. Stein MB, Tancer ME, Gelernter CS, et al. Major depression in patients with social phobia. Am J Psychiatry 1990;147:637–639
3. Schneier FR, Martin LY, Liebowitz MR, et al. Alcohol abuse in social phobia. J Anxiety Disord 1989;3:15–23
4. Schneier FR, Johnson J, Hornig CD, et al. Social phobia: comorbidity and morbidity in an epidemiologic sample. Arch Gen Psychiatry 1992;49:282–288
5. Tancer ME, Uhde TW. Social phobia: a review of pharmacological treatment. CNS Drugs 1995;3:267–278
6. Potts NLS, Davidson JRT. Pharmacological treatments: literature review. In: Heimberg RG, Liebowitz MR, Hope DA, et al, eds. Social Phobia: Diagnosis, Assessment, and Treatment. New York, NY: Guilford Press; 1995: 334–365
7. Gelernter CS, Uhde TW, Cimbolic P, et al. Pharmacotherapy versus cognitive therapy for the treatment of social phobia. Arch Gen Psychiatry 1991; 48:938–945
8. 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
9. Versiani M, Nardi AE, Mundim FD, et al. Pharmacotherapy of social phobia: a controlled study with moclobemide and phenelzine. Br J Psychiatry 1992;160:353–360
10. Tancer ME, Lewis MH, Stein MB. Biological aspects. In: Stein MB, ed. Social Phobia. Washington, DC: American Psychiatric Press; 1995:229–257
11. Nickell PV, Uhde TW. Neurobiology of social phobia. In: Heimberg RG, Liebowitz MR, Hope DA, et al, eds. Social Phobia: Diagnosis, Assessment, and Treatment. New York, NY: Guilford Press; 1995:113–133
12. Papp LA, Gorman JM, Liebowitz MR, et al. Epinephrine infusions in patients with social phobia. Am J Psychiatry 1988;145:733–736
13. Tancer ME, Stein MB, Uhde TW. Growth hormone response to clonidine in social phobia: comparison to patients with panic disorder and healthy volunteers. Biol Psychiatry 1993;34:591–595
14. Liebowitz MR, Campeas R, Hollander E. MAOIs: impact on social behavior. Psychiatry Res 1987;22:89–90
15. Stein MB, Heuser IJ, Juncos JL, et al. Anxiety disorders in patients with Parkinson's disease. Am J Psychiatry 1990;147:207–210
16. Tancer ME, Mailman RB, Stein MB, et al. Neuroendocrine responsivity to monaminergic system probes in generalized social phobia. Anxiety 1994/1995;1:216–223
17. Bagdy G, Calogero AE, Murphy DL, et al. Serotonin agonists cause parallel activation of the sympathoadrenomedullary system and the hypothalamic-pituitary-adrenocortical axis in conscious rats. Endocrinology 1989; 125:2664–2669
18. Kahn RS, Asnis GM, Wetzer S, et al. Neuroendocrine evidence for serotonin receptor hypersensitivity in panic disorder. Psychopharmacology (Berl) 1988;96:360–364
19. Targum SD. Differential responses to anxiogenic challenge studies in patients with major depression and panic disorder. Biol Psychiatry 1990; 28:21–34
20. van Vliet IM, den Boer JA, Westenberg HGM. Psychopharmacological treatment of social phobia: a double-blind placebo controlled study with fluvoxamine. Psychopharmacology (Berl) 1994;115:128–134
21. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised. Washington, DC: American Psychiatric Press; 1987
22. 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
23. Schneier FR, Chin SJ, Hollander E, et al. Fluoxetine in social phobia. J Clin Psychopharmacol 1992;12:62–64
24. Black B, Uhde TW, Tancer ME. Fluoxetine for the treatment of social phobia. J Clin Psychopharmacol 1992;12:293–295
25. Van Ameringen M, Mancini C, Streiner DL. Fluoxetine efficacy in social phobia. J Clin Psychiatry 1993;54:27–32
26. Koponen HJ, Lepola UM, Juhani LEV. Fluoxetine in social phobia: a pilot study. Presented at the 15th National Conference of the Anxiety Disorders Association of America; April 7, 1995; Pittsburgh, Pa
27. Van Ameringen M, Mancini C, Streiner D. Sertraline in social phobia. J Affect Disord 1994;31:141–145
28. Martins EA, Pigott TA, Bernstein SE, et al. Sertraline in the treatment of patients with social phobia. Anxiety 1994/1995;1:291–297
29. Czepowicz VD, Johnson MR, Lydiard RB, et al. Sertraline in social phobia. J Clin Psychopharmacol 1995;15:372–373
30. Mancini C, Van Ameringen M, Wilson C. Paroxetine in social phobia: a pilot study. Presented at the 15th National Conference of the Anxiety Disorders Association of America; April 7, 1995; Pittsburgh, Pa
31. DeVane CL, Ware MR, Emmanual NP, et al. The evaluation of the safety, efficacy, and physiological effects of fluvoxamine in social phobia. Presented at the 34th Annual Meeting of the American College of Neuropsychopharmacology; Dec 11–15, 1995; San Juan, Puerto Rico
32. Clark DB, Agras WS. The assessment and treatment of performance anxiety in musicians. Am J Psychiatry 1991;148:598–605
33. Munjack DJ, Bruns J, Baltazar PL, et al. A pilot study of buspirone in the treatment of social phobia. J Anxiety Disord 1991;5:87–98
34. Schneier FR, Saoud JB, Campeas R, et al. Buspirone in social phobia. J Clin Psychopharmacol 1993;13:251–256
35. Bell J, DeVeaugh-Geiss J. Multicenter trial of a 5-HT_3 antagonist, ondansetron in social phobia. Presented at the 33rd Annual Meeting of the American College of Neuropsychopharmacology; Dec 12–16, 1994; San Juan, Puerto Rico
36. Davidson JRT, Potts N, Richichi E, et al. Treatment of social phobia with

clonazepam and placebo. J Clin Psychopharmacol 1993;13:423–428
37. Heimberg RG, Juster HR, Hope DA, et al. Cognitive-behavioral group treatment: description, case presentation, and empirical support. In: Stein MB, ed. Social Phobia. Washington, DC: American Psychiatric Press; 1995:293–321
38. Hope DA, Holt CS, Heimberg RG. Social phobia. In: Giles TR, ed. Handbook of Effective Psychotherapy. New York, NY: Plenum Press; 1993: 227–251
39. Uhde TW, Tancer ME. Social phobia. In: Beitman B, Klerman G, eds. Integrating Pharmacotherapy and Psychotherapy. Washington, DC: American Psychiatric Press; 1991:231–252