Nefazodone in the Treatment of Generalized Social Phobia: A Randomized, Placebo-Controlled Trial

Michael Van Ameringen, M.D., F.R.C.P.C.; Catherine Mancini, M.D., F.R.C.P.C.; Jonathan Oakman, Ph.D.; John Walker, Ph.D.; Kevin Kjernisted, M.D., F.R.C.P.C.; Pratap Chokka, M.D., F.R.C.P.C.; David Johnston, M.D., F.R.C.P.C.; Mark Bennett, B.A.; and Beth Patterson, B.Sc.N., B.Ed.

Objective: Numerous studies have demonstrated the efficacy of serotonergic antidepressants, particularly the selective serotonin reuptake inhibitors (SSRIs), in the treatment of social phobia. We evaluated the efficacy, safety, and tolerability of nefazodone, a 5-HT_2 antagonist, in patients with generalized social phobia (GSP).

Method: One hundred five patients with GSP (confirmed using the Structured Clinical Interview for DSM-IV) from 4 Canadian outpatient anxiety clinics were assigned randomly to nefazodone (300–600 mg/day, flexible dose) or placebo for 14 weeks of double-blind treatment. Data were collected from October 12, 1999, through December 8, 2001. Primary efficacy outcomes were the Clinical Global Impressions-Improvement scale (CGI-I) score and the Liebowitz Social Anxiety Scale score.

Results: In the intent-to-treat sample, 16 (31.4%) of 51 subjects taking nefazodone and 12 (23.5%) of 51 subjects taking placebo were rated as much or very much improved on the CGI-I at endpoint ($\chi^2 = 0.79$, $p = .38$). With the exception of the Social Phobia Scale, no significant differences were found in measures of social phobia when comparing the nefazodone and placebo groups.

Conclusion: These findings suggest that nefazodone is not an effective agent in the treatment of GSP. These data parallel some recent findings with the use of the SSRI fluoxetine in GSP. The lack of efficacy of 2 serotonergic antidepressants in GSP suggests that serotonin reuptake inhibition may not be the only mechanism of action required for efficacy to occur in the treatment of GSP.

(J Clin Psychiatry 2007;68:288–295)

Received Dec. 12, 2005; accepted July 3, 2006. From the Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, Ontario (Drs. Van Ameringen and Mancini); the University of Waterloo, Waterloo, Ontario (Dr. Oakman); the Department of Clinical Health Psychology (Dr. Walker) and the Department of Psychiatry (Dr. Kjernisted), University of Manitoba, Winnipeg, Manitoba; the Department of Psychiatry, Grey Nuns Community Hospital and Health Centre, Edmonton, Alberta (Dr. Chokka); the Department of Psychiatry, University of Calgary, Calgary, Alberta (Dr. Johnston); and the Anxiety Disorders Clinic, McMaster University Medical Centre, Hamilton Health Services, Hamilton, Ontario (Mr. Bennett and Ms. Patterson), Canada.

Partial funding for this study was provided by an investigator-initiated research grant from Bristol-Myers Squibb, Montreal, Quebec, Canada.

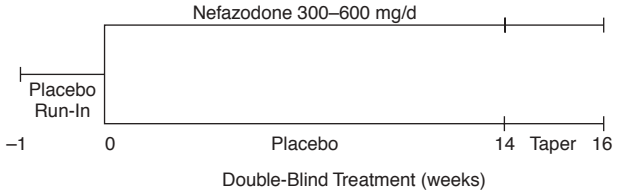
Dr. Van Ameringen has received grant/research support from AstraZeneca, Cephalon, GlaxoSmithKline, Janssen-Ortho Inc., National Institutes of Health, Novartis, Pfizer, and Wyeth-Ayerst; has served as a consultant for Biovail, Cephalon, GlaxoSmithKline, Janssen-Ortho Inc., Novartis, Pfizer, and Wyeth-Ayerst; and has served on the speakers bureaus of GlaxoSmithKline, Janssen-Ortho Inc., Pfizer, and Wyeth-Ayerst. Dr. Mancini has received grant/research support from Astra Zeneca, Cephalon, GlaxoSmithKline, Eli Lilly, Janssen-Ortho Inc., National Institutes of Health, Novartis, and Pfizer and has served as a consultant for and on the speakers bureau of GlaxoSmithKline. Drs. Oakman, Walker, Kjernisted, Chokka, and Johnston and Mr. Bennett and Ms. Patterson report no other financial affiliations relevant to the subject of this article.

Corresponding author and reprints: Michael Van Ameringen, M.D., F.R.C.P.C., Anxiety Disorders Clinic, 3G Clinic, McMaster University Medical Centre, Hamilton Health Sciences, 1200 Main St., West, Hamilton, Ontario, L8N 3Z5, Canada (e-mail: vanamer@mcmaster.ca).

Generalized social phobia (GSP) is an anxiety disorder characterized by excessive fear of exposure to social and performance situations.[1] GSP affects approximately 13.3% of individuals within the United States at some point in their lifetime.[2] In Canada, there has been some variability in reported prevalence rates. Results from the Canadian Community Health Survey[3] revealed a lifetime prevalence rate of DSM-IV GSP of 8.1%, whereas current (12-month) GSP has been reported by 3.0% to 7.2%[3–5] of Canadians. The burden of GSP is broad, often creating significant social and occupational impairment as well as educational and vocational underachievement.[6,7]

Both cognitive-behavioral therapy[8] and pharmacotherapy have been shown to be effective in treating GSP. A variety of drug classes have been found to be beneficial,

Figure 1. Study Design: Nefazodone Versus Placebo in Generalized Social Phobia



including monoamine oxidase inhibitors (MAOIs),[9–11] reversible MAOIs,[12–15] benzodiazepines,[16,17] selective serotonin reuptake inhibitors (SSRIs),[18–28] the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine,[29,30] and, most recently, the anticonvulsants gabapentin and pregabalin.[31,32] SSRIs are considered to be first-line treatments in the pharmacologic management of GSP, with fluvoxamine, sertraline, and paroxetine being supported by double-blind, placebo-controlled studies.[33] Despite widespread use, a considerable proportion of patients do not respond adequately to SSRIs or are unable to tolerate their side effects.[33] There is a clinical need for alternative pharmacologic agents.

Nefazodone is an antidepressant medication whose primary action is the inhibition of presynaptic 5-HT reuptake. It has also been found to have weak α_1-adrenergic blocking activity and moderate norepinephrine reuptake inhibition. Nefazodone differs from other SSRIs, however, as it appears to have the additional action of blocking postsynaptic 5-HT_{2A} receptors.[34] The effectiveness of nefazodone in treating symptoms of depression is well documented.[35–38] It has been found to have equal or superior antidepressant activity to imipramine,[39,40] paroxetine,[26] and sertraline.[41] Nefazodone was initially thought to be a safe and effective treatment, with a side effect profile similar to SSRIs and other antidepressants.[42] During the course of this study, however, safety concerns evolved concerning the effects of nefazodone on hepatic function. In the United States between December 1994 and May 2003, there were 94 reported cases of liver injuries, 55 cases of liver failure, 5 liver transplants, and 20 deaths associated with nefazodone.[43,44] The U.S. Food and Drug Administration estimated that, for patients using the drug for at least 1 year, the reported rate of liver failure is 1 case in every 250,000 to 300,000.[45] In Canada, between the introduction of nefazodone in 1994 and July 24, 2002, 123 adverse biliary reactions were reported to Health Canada,[46] and a recent report by the World Health Organization (WHO) found 449 reports of nefazodone-related hepatic reactions in the WHO Adverse Reaction Database.[47]

There have been 3 open trials suggesting the potential benefits of nefazodone in GSP. Worthington and colleagues[48] conducted a case series of 5 individuals, which showed a significant improvement from baseline to week 12 on the Liebowitz Social Anxiety Scale (LSAS), Brief Social Phobia Scale, and Clinical Global Impressions-Severity of Illness scale (CGI-S). In an open trial of 23 subjects conducted by Van Ameringen and colleagues,[49] 70% (16/23) were considered responders based on the CGI-Improvement scale (CGI-I). In another open trial of 12 subjects, Kelsey and colleagues[50] reported symptom improvement with a mean drop in LSAS score of 54%. These reports suggest that a placebo-controlled investigation of nefazodone in GSP is warranted. We conducted a 14-week, randomized, double-blind, parallel-group trial of nefazodone versus placebo in GSP.

METHOD

Patients with GSP, whose diagnosis was confirmed using the Structured Clinical Interview for DSM-IV,[51] were included in this double-blind, placebo-controlled, parallel-group trial. Four outpatient anxiety clinics in Canada (Hamilton, Winnipeg, Edmonton, and Calgary) participated in this 14-week study. The study protocol was approved by the institutional review boards at all of the centers. Written informed consent was obtained after the study procedures were fully explained to the patients. Data were collected from October 12, 1999, through December 8, 2001.

After an initial screening procedure, subjects were entered into a 1-week, single-blind, placebo run-in. Those subjects who continued to meet inclusion criteria were randomly assigned on a 1:1 basis to receive either nefazodone or placebo for 14 weeks (Figure 1).

Nefazodone or placebo was started at an initial dose of 100 mg/day in divided doses. Doses were increased to 200 mg/day by week 2, and up to 300 mg/day by week 4. Further increments of 100 mg were added every 2 weeks, until a maximum dose of 600 mg/day was reached. No other psychotropic medications were permitted with the exception of chloral hydrate (up to 1000 mg/night for sleep).

Patients were recruited from newspaper advertisements, media reports, and clinical referrals. Inclusion criteria for the study required subjects to be psychiatric outpatients between the ages of 18 and 65 years, to fulfill DSM-IV criteria for GSP for more than 1 year, and to be of at least moderate illness severity on the basis of the CGI-S rating.[52] Patients with comorbid secondary major depressive disorder were permitted to participate in the study provided that their baseline score on the Montgomery-Asberg Depression Rating Scale[53] was 19 or less, there was no risk of suicidality on the basis of mental status examination, and the onset of their social phobia predated the major depressive disorder by at least 5 years. Four patients in the nefazodone group and 6 patients in the

Table 1. Baseline Demographic Characteristics of Patients With Generalized Social Phobia

Characteristic	Nefazodone (N = 52)	Placebo (N = 53)	p Value
Age, mean (SD)	34.6 (9.7)	37.0 (11.6)	NS
Age at onset, mean (SD)	8.9 (5.2)	9.8 (6.2)	NS
Gender, N (%)			
Male	24 (46.2)	26 (49.1)	NS
Female	28 (53.8)	27 (50.9)	NS
Marital status, N (%)			
Married/common law	24 (46.2)	21 (39.6)	NS
Never married/single	22 (42.3)	24 (45.3)	NS
Divorced/separated	6 (11.5)	7 (13.2)	NS
Widowed	0 (0.0)	1 (1.9)	NS
Education, N (%)			
Grade school	1 (1.9)	1 (1.9)	NS
Some high school	6 (11.5)	5 (9.4)	NS
High school degree	6 (11.5)	14 (26.4)	NS
Some college	6 (11.5)	3 (5.7)	NS
College degree	12 (23.1)	11 (20.8)	NS
Some university	8 (15.4)	7 (13.2)	NS
University degree	10 (19.2)	8 (15.1)	NS
Graduate degree	2 (3.8)	2 (3.8)	NS
Postgraduate degree	1 (1.9)	2 (3.8)	NS
Occupation, N (%)			
Employed	37 (71.2)	34 (64.2)	NS
Student	8 (15.4)	8 (15.1)	NS
Unemployed	2 (3.8)	3 (5.7)	NS
Retired	2 (3.8)	3 (5.7)	NS
Homemaker	3 (5.8)	5 (9.4)	NS
Race, N (%)			
White	45 (86.5)	44 (83.0)	NS
Nonwhite	7 (13.5)	9 (17.0)	NS
Liebowitz Social Anxiety Scale score, mean (SD)	88.6 (21.2)	86.1 (17.3)	NS
Clinical Global Impressions-Severity of Illness scale score, mean (SD)	4.9 (0.6)	4.8 (0.8)	NS

placebo group reported a comorbid depressive disorder (either major depressive disorder [N = 7] or dysthymia [N = 3]). There was no significant difference found in the rates of comorbid depressive disorders across groups ($\chi^2 = 1.03$, df = 1, not significant).

Current comorbid Axis I disorders such as panic disorder with agoraphobia, obsessive-compulsive disorder, body dysmorphic disorder, or alcohol/substance abuse were excluded from this study. Those with a lifetime history of bipolar affective disorder, schizophrenia, psychoses, delirium, dementia, or other cognitive disorders were also excluded, as were individuals reporting 2 previous treatment failures for GSP.

Patients were evaluated at weeks 1, 2, 3, 5, 7, 9, 12, and 16. Primary efficacy measures were (1) the percentage of responders at endpoint defined as those rated on the CGI-I as 1 (very much improved) or 2 (much improved) and (2) the mean change from baseline to endpoint on the LSAS[54] total score. The LSAS and CGI-I were completed by experienced physician raters, all of whom were experienced in clinical trials of social phobia and in the administration of these measures. Prior to starting the study, specific conventions for these measures were reviewed with each principal investigator at each study site. Secondary efficacy measures included the CGI-S, the Social Phobia Inventory,[55] the Social Phobia Scale (SPS) and the Social Interaction Anxiety Scale,[56] the Beck Depression Inventory,[57] the Beck Anxiety Scale,[58] the Sheehan Disability Scale,[59] and the RAND 36-Item Health Survey.[60]

Adverse event reporting was based on spontaneous patient self-reports. Because of concerns regarding potential hepatotoxicity, liver function tests[47] were performed at baseline, week 6, and endpoint.

All efficacy analyses were carried out on the intent-to-treat sample using the last-observation-carried-forward method, defined as all patients who received 1 dose of double-blind medication and attended 1 postbaseline efficacy evaluation. Power analysis was based on an expected effect size of d = 0.69, which was based on the best evidence available at the time of study design.[10,21,49] This estimate is highly similar to effect size estimates for SSRIs available from more recent meta-analytic work (d = 0.65).[61] Our study had power equal to 0.90 to detect an effect size of d = 0.69 (48 patients to start in the placebo group and 54 to start in the nefazodone group, allowing for differential attrition of 20% in the drug-treated group and 10% in the placebo-treated group, yielding 43 completers per group).

Categorical measures were analyzed with a continuity corrected χ^2 test, and continuous measures were evaluated with a mixed analysis-of-variance (ANOVA) model, in which the change from baseline to final visit was treated as a within-subjects factor, while the nefazodone/placebo comparison was treated as the between-subjects factor.

RESULTS

The sample included 113 subjects enrolled in 4 sites across Canada; 105 of those subjects were randomly assigned to treatment: 52 to the nefazodone group (24 males, 28 females) and 53 to the placebo group (26 males, 27 females). Eight (7%) of the 113 subjects did not complete the placebo run-in (3 patients had abnormal laboratory values; 3 reported adverse events including drowsiness, headache, and abdominal cramping; and 2 were lost to follow-up). The mean ± SD age of subjects was 34.6 ± 9.7 years in the nefazodone group and 37.0 ± 11.6 years in the placebo group, with a mean age at onset of 8.9 ± 5.2 years (nefazodone) and 9.8 ± 6.2 years (placebo). Patient demographics are listed in Table 1. At baseline, the mean ± SD CGI-S score was 4.9 ± 0.6 (nefazodone), 4.8 ± 0.8 (placebo), and 4.8 ± 0.7 for the total sample. The mean ± SD LSAS score was 88.6 ± 21.2 (nefazodone), 86.1 ± 17.3 (placebo), and 87.3 ± 19.5 (total sample), suggesting that most patients were "markedly ill."

Efficacy data were analyzed for 102 subjects, yielding a power of 0.90 to detect an effect size as small as 0.46.

Three patients who were randomly assigned to treatment did not take at least 1 dose of the study medication. Of these 3 patients, 1 was lost to follow-up, 1 was taking a disallowed concomitant medication, and 1 was a responder after the placebo run-in phase. Thirty-six (70.6%) of 51 patients in the nefazodone group completed the trial compared with 44 (86.3%) of 51 in the placebo group. In the intent-to-treat sample, 16 (31.4%) of 51 subjects in the nefazodone group were responders, as defined by a CGI-I score of 1 or 2, compared with 12 (23.5%) of 51 subjects in the placebo group ($\chi^2 = 0.79$, df = 1, not significant). In the completer sample, 12 (33.3%) of 36 nefazodone-treated patients were responders compared with 9 (20.5%) of 44 patients given placebo ($\chi^2 = 1.70$, df = 1, not significant). CGI-I scores were entered into a mixed-model ANOVA with study visit as the repeated measure and treatment group as the between-subjects factor. Using the Greenhouse-Geisser correction for nonsphericity of the data, the main effect of visit was significant ($F = 24.996$, df = 2,837, $p < .01$), indicating that patients in both groups improved over the course of the study. There was no differential improvement across groups ($F = 1.799$, df = 2,837, $p = .15$). The change in LSAS score from baseline to endpoint was significant for the intent-to-treat sample ($F = 36.7$, df = 2,35, $p < .01$); however, there was no evidence of differential improvement across groups ($F = 1.72$, df = 2,35, $p = .18$). When only study completers were examined, the change in LSAS score from baseline to endpoint was significant ($F = 37.55$, df = 2,29, $p < .01$), and there was little evidence of differential improvement across groups ($F = 2.45$, df = 2,29, $p = .08$ with Greenhouse-Geisser correction and df = 6, $p = .02$ if no correction is made for violation of assumption of sphericity). Mean (SD) scores on the LSAS at the conclusion of the study were 59.6 (4.8) in the nefazodone-treated group and 68.7 (4.2) in the placebo-treated group.

Repeated-measures ANOVA revealed no significant differences for observer or self-report measures of social anxiety, generalized anxiety, or depressive symptoms, with the exception of the SPS (Tables 2 and 3). The mean ± SD dose of nefazodone in the intent-to-treat group at endpoint was 493.9 ± 128.1 mg/day compared with 557.1 ± 91.3 mg/day of placebo.

A post hoc analysis using more stringent criteria for response (decrease in LSAS score ≥ 50%), as well as remission (LSAS score ≤ 30), was performed. In this analysis, 10 patients (19.6%) taking nefazodone were considered responders compared with 7 patients (13.7%) taking placebo ($\chi^2 = 0.635$, $p = .425$). An equal proportion of patients considered to be in remission was found in the nefazodone and placebo groups (5 patients each). The effect size based on LSAS score for nefazodone was 0.23.

The most commonly reported adverse events for nefazodone (N = 51) versus placebo (N = 51) (> 10% of sample) included headache (N = 18 [35.3%] vs. N = 15 [29.4%], p = .53), fatigue (N = 10 [19.6%] vs. N = 6 [11.8%], p = .28), dizziness/lightheadedness (N = 17 [33.3%] vs. N = 4 [7.8%], p < .01), nausea/vomiting (N = 12 [23.5%] vs. N = 4 [7.8%], p = .03), somnolence/drowsiness (N = 10 [19.6%] vs. N = 6 [11.8%], p = .28), dry mouth (N = 12 [23.5%] vs. N = 1 [2.0%], p < .01), and indigestion (N = 6 [11.8%] vs. N = 5 [9.8%], p = .75). No significant differences between the proportion of patients in nefazodone versus placebo groups for liver function test abnormalities at endpoint were found, including alanine aminotransferase (> 35 U/L, 5/48 [10.4%] vs. 5/48 [10.4%], $\chi^2 = 0$, not significant), aspartate aminotransferase (> 35 U/L, 2/48 [4.2%] vs. 2/48 [4.2%], $\chi^2 = 0$, not significant), total bilirubin (> 18 μmol/L, 7/48 [14.6%] vs. 2/48 [4.2%], $\chi^2 = 3.07$, not significant), and alkaline phosphatase (> 120 U/L, 0/48 [0%] vs. 2/48 [4.2%], $\chi^2 = 2.04$, not significant). None of the minor liver function test abnormalities led to early discontinuation of study subjects or to the premature termination of the study.

DISCUSSION

Unlike the previously reported open-label trials, nefazodone was not found to be an efficacious treatment for GSP according to the primary outcome measures of the LSAS and CGI-I (intent-to-treat sample). Nefazodone did outperform placebo on the SPS, however, and several of the other self-rated secondary measures were just short of significance. These results suggest that nefazodone may have been effective in ameliorating some symptoms of social phobia, albeit not to the degree that it has been seen with other effective treatments for GSP. Subjects reported significantly more adverse events with nefazodone than placebo, although there were no significant differences in liver function tests.

The effect size for nefazodone in this study was 0.23, which is substantially lower ($p < .05$) than the effect sizes typically found in a recent meta-analysis of SSRI medications in the treatment of GSP (effect size = 0.65, 95% CI = 0.50 to 0.81).[61]

The findings in our study are similar to those recently found with fluoxetine, which has been evaluated in 3 randomized, controlled trials in the treatment of social phobia, with only 1 study reporting that fluoxetine was found to perform better than placebo.[20,62,63]

The lack of efficacy of nefazodone and likely fluoxetine may reveal some potentially important differences between antidepressant agents and how they relate to efficacy in GSP. SSRIs and nefazodone share with the class of serotonin reuptake inhibitor medications the common mechanism of blocking 5-HT reuptake. Indeed, it is this mechanism of action to which clinical effects are typically attributed. However, despite the high-potency serotonin

Table 2. Intent-to-Treat Analysis of Psychometric Measures: Observer Rated[a]

Scale	Week							Analysis of Variance		
	0	1	3	5	7	10	14	F	df	p Value
Liebowitz Social Anxiety Scale score								1.724	6	.113
Nefazodone	88.6 (21.2)	85.9 (22.0)	81.3 (24.7)	77.8 (25.5)	74.3 (25.8)	70.5 (27.5)	65.1 (27.7)			
Placebo	86.1 (17.3)	83.0 (19.8)	80.4 (20.5)	78.2 (21.7)	74.4 (24.7)	72.2 (25.6)	71.2 (26.1)			
Clinical Global Impressions-Severity of Illness scale score								2.630	6	.16
Nefazodone	4.9 (0.6)	4.9 (0.6)	4.8 (0.8)	4.6 (0.9)	4.5 (1.0)	4.4 (1.0)	4.1 (1.1)			
Placebo	4.8 (0.8)	4.8 (0.8)	4.7 (0.8)	4.86 (0.9)	4.6 (0.9)	4.5 (1.0)	4.4 (1.0)			
Montgomery-Asberg Depression Rating Scale (MADRS) score[b]								0.524	1	.471
Nefazodone	5.5 (4.8)						5.0 (4.4)			
Placebo	4.7 (4.3)						3.4 (3.0)			

[a]All values are expressed as mean (SD).
[b]The MADRS was completed at week 0 (baseline), as an MADRS score ≤ 19 was required to meet inclusion criteria, and at week 14 (endpoint) to evaluate change in depressive symptom severity.

Table 3. Intent-to-Treat Analysis of Psychometric Measures: Self-Report[a]

Measure	Week							Analysis of Variance		
	0	1	3	5	7	10	14	F	df	p Value
Social Phobia Scale score								2.634	6	.016
Nefazodone	38.0 (2.2)	37.7 (2.0)	35.3 (2.0)	32.0 (2.0)	30.2 (2.0)	27.8 (2.1)	24.0 (2.2)			
Placebo	37.7 (2.2)	36.9 (2.0)	33.8 (2.0)	33.8 (2.0)	30.5 (2.1)	30.1 (2.1)	29.3 (2.2)			
Social Interaction Anxiety Scale score								2.038	6	.059
Nefazodone	46.3 (1.5)	45.0 (1.6)	43.4 (1.7)	40.4 (1.6)	39.4 (1.8)	37.4 (1.9)	34.4 (1.8)			
Placebo	44.4 (1.5)	44.0 (1.6)	42.1 (1.7)	41.2 (1.6)	39.2 (1.8)	38.7 (1.9)	37.7 (1.8)			
Social Phobia Inventory score								1.834	6	.09
Nefazodone	62.2 (1.5)	60.1 (1.6)	57.7 (1.7)	54.4 (1.7)	53.0 (1.8)	50.8 (1.9)	48.8 (1.9)			
Placebo	61.9 (1.5)	59.0 (1.6)	57.5 (1.7)	55.5 (1.7)	54.4 (1.8)	53.5 (1.9)	52.2 (2.0)			
Beck Depression Inventory score[b]								0.073	2	.939
Nefazodone	10.0 (7.3)				8.8 (6.6)		8.3 (8.1)			
Placebo	9.5 (7.3)				7.9 (7.0)		7.5 (6.8)			
Sheehan Disability Inventory score										
Work								2.051	6	.057
Nefazodone	3.4 (2.8)	4.4 (2.4)	4.2 (2.5)	4.1 (2.4)	3.5 (2.5)	3.5 (2.4)	3.0 (2.4)			
Placebo	3.3 (2.7)	4.5 (2.4)	4.5 (2.3)	4.5 (2.4)	4.4 (2.4)	4.4 (2.4)	3.9 (2.6)			
Social								1.622	6	.138
Nefazodone	6.4 (2.6)	6.4 (2.3)	6.1 (2.4)	5.6 (2.7)	5.0 (2.7)	5.0 (2.7)	4.3 (2.7)			
Placebo	6.4 (2.1)	6.7 (1.9)	6.4 (1.9)	6.1 (2.2)	4.9 (2.3)	5.5 (2.3)	5.3 (2.3)			
Family								1.848	6	.088
Nefazodone	2.7 (2.6)	2.5 (2.5)	2.6 (2.6)	2.6 (2.4)	2.2 (2.4)	2.4 (2.4)	2.2 (2.4)			
Placebo	2.2 (2.4)	2.7 (2.0)	2.7 (1.8)	2.9 (2.1)	2.8 (2.0)	2.9 (2.2)	2.4 (2.0)			

[a]All values are expressed as mean (SD).
[b]The Beck Depression Inventory was completed at weeks 0, 7, and 14 to monitor treatment-emergent depressive symptoms and to evaluate change in depressive symptom severity.

antagonism of both paroxetine and fluoxetine,[64] these are arguably the most and least effective of the SSRIs for GSP.

SSRI medications vary substantially in their physicochemical, pharmacodynamic, and pharmacokinetic properties.[64] This variability may well be one important cause of the differences in clinical efficacy of different serotonergic medications. Nefazodone notably differs from the SSRIs in that it appears to be much less potent and requires higher doses than other agents in this drug class. For example, nefazodone only reaches a 20% to 40% inhibition of serotonin uptake at a dose of 300 mg/day for 14 days, whereas the SSRIs and venlafaxine inhibit 70% to 80% at their lowest usually effective doses.[65–68] Nefazodone's in vitro binding affinity has been found to be as great as 3 orders of magnitude weaker than comparable SSRIs.[65]

At a standard dose of 300 mg/day, the primary mechanism of nefazodone's antidepressant action is its blockade of 5-HT_{2A} receptors, a less robust mechanism of action when compared with serotonin reuptake inhibition.[69] Furthermore, nefazodone lacks selectivity for the 5-HT_{1A} and 5-HT_{2C} receptors, which the SSRIs may indirectly activate via their more potent blockade of the 5-HT transporter.[70,71] These pharmacokinetic differences between other SSRIs, venlafaxine, and nefazodone may provide at least a partial account for the lack of nefazodone's effectiveness in GSP. Perhaps, a combination of 5-HT_{2A} blockade with serotonin reuptake inhibition may be a superior mechanism than either mechanism alone[69] in the treatment of GSP.

To further complicate this picture, in addition to the variation between drugs, it is also possible that individual differences in patient characteristics (and their interactions with the pharmacologic properties of various medications) may also account for considerable variation in clinical effect. Consistent with clinical experience, Lepola et al.[28] found that roughly 25% of GSP patients experience full or substantial remission of GSP symptoms following SSRI treatment, a further 35% experience partial improvement, and 40% derive little clinical benefit from treatment. While these figures are encouraging, it is likely that a straightforward "insufficient serotonin neurotransmission" hypothesis is inadequate to explain GSP treatment response. Considerable basic research has been conducted in an attempt to identify genetic predispositions to differences in the metabolism of antidepressant medications that may account for differential effects and side effects across individuals and cultural groups.[72,73]

There is always some ambiguity in interpreting a null effect in any study. While the study design had sufficient power to detect a clinical effect of the size that is typical of SSRIs, there was insufficient power to detect a small effect. It is possible that nefazodone may be effective for a small percentage of GSP patients. Furthermore, if the clinical effect of nefazodone is for some reason delayed relative to the other SSRIs, our treatment duration of 14 weeks may have been too short (or patients may have had too short a time on an adequate dose) to permit us to detect any such late-onset effect.

This study was also limited by having the treating physicians provide the main clinical outcome measures. Because of the distinct side effect profiles of placebo and any active medication, it is quite possible that raters were not blind to experimental condition. To the extent that this was the case, we would expect estimates of clinical effect to be too large and placebo response rates to be too small. Instead, our placebo response rate of 23.5% is fairly typical of studies of this kind, and any inflation of the clinical effect of nefazodone due to bias on the part of the raters fails to threaten our main conclusion that nefazodone is not a particularly effective treatment for GSP.

Drug names: fluoxetine (Prozac and others), gabapentin (Neurontin), imipramine (Tofranil), paroxetine (Paxil, Pexeva, and others), pregabalin (Lyrica), sertraline (Zoloft), venlafaxine (Effexor).

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
2. Kessler RC, 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
3. Shields M. Social anxiety disorder: beyond shyness. Health Rep 2004; 15(suppl):45–61
4. Offord DR, Boyle MH, Campbell D, et al. One year prevalence of psychiatric disorder in Ontarians 15–64 years of age. Can J Psychiatry 1996;41:559–563
5. Stein MB, Torgrud LJ, Walker JR. Social phobia symptoms, subtypes, and severity: findings from a community survey. Arch Gen Psychiatry 2000;57:1046–1052
6. Van Ameringen M, Mancini C, Farvolden P. The impact of anxiety disorders on educational achievement. J Anxiety Disord 2003;17: 561–571
7. Liebowitz MR, Gorman JM, Fyer AJ, et al. Social phobia: review of a neglected anxiety disorder. Arch Gen Psychiatry 1985;42:729–736
8. Taylor S. Meta-analysis of cognitive-behavioral treatments for social phobia. J Behav Ther Exp Psychiatry 1996;27:1–9
9. Gelernter CS, Uhde TW, Cimbolic P, et al. Cognitive-behavioral and pharmacological treatments of social phobia: a controlled study. Arch Gen Psychiatry 1991;48:938–945
10. 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
11. Heimberg RG, Liebowitz MR, Hope DA, et al. Cognitive behavioral group therapy vs phenelzine therapy for social phobia: 12-week outcome. Arch Gen Psychiatry 1998;55:1133–1141
12. Fahlen T, Nilsson HL, Borg K, et al. Social phobia: the clinical efficacy and tolerability of the monoamine oxidase-A and serotonin uptake inhibitor brofaromine: a double-blind placebo-controlled study. Acta Psychiatr Scand 1995;92:351–358
13. van Vliet IM, den Boer JA, Westenberg HG. Psychopharmacological treatment of social phobia: clinical and biochemical effects of brofaromine: a selective MAO-A inhibitor. Eur Neuropsychopharmacol 1992;2: 21–29
14. Lott M, Greist JH, Jefferson JW, et al. Brofaromine for social phobia:

a multicenter, placebo-controlled, double-blind study. J Clin Psychopharmacol 1997;17:255–260
15. Versiani M, Nardi AE, Mundim FD, et al. The long-term treatment of social phobia with moclobemide. Int Clin Psychopharmacol 1996; 11(suppl 3):83–88
16. Davidson JR, Potts N, Richichi E, et al. Treatment of social phobia with clonazepam and placebo. J Clin Psychopharmacol 1993;13:423–428
17. Versiani M, Egidio N, Figueira I, et al. Double-blind placebo controlled trial with bromazepam in social phobia. Jornal Brasilerio de Psiquiatria 1997;46:167–171
18. van Vliet IM, den Boer JA, Westenberg HG. Psychopharmacological treatment of social phobia: a double blind placebo controlled study with fluvoxamine. Psychopharmacology (Berl) 1994;115:128–134
19. Stein MB, Fyer AJ, Davidson JR, et al. Fluvoxamine treatment of social phobia (social anxiety disorder): a double-blind, placebo-controlled study. Am J Psychiatry 1999;156:756–760
20. Davidson JR, Foa EB, Huppert JD, et al. Fluoxetine, comprehensive cognitive behavioral therapy, and placebo in generalized social phobia. Arch Gen Psychiatry 2004;61:1005–1013
21. 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
22. Van Ameringen MA, Lane RM, Walker JR, et al. Sertraline treatment of generalized social phobia: a 20-week, double-blind, placebo-controlled study. Am J Psychiatry 2001;158:275–281
23. Blomhoff S, Haug TT, Hellstrom K, et al. Randomised controlled general practice trial of sertraline, exposure therapy and combined treatment in generalised social phobia. Br J Psychiatry 2001;179:23–30
24. Liebowitz MR, DeMartinis NA, Weihs K, et al. Efficacy of sertraline in severe generalized social anxiety disorder: results of a double-blind, placebo-controlled study. J Clin Psychiatry 2003;64:785–792
25. Stein MB, Liebowitz MR, Lydiard RB, et al. Paroxetine treatment of generalized social phobia (social anxiety disorder): a randomized controlled trial. JAMA 1998;280:708–713
26. Baldwin D, Bobes J, Stein DJ, et al. Paroxetine in social phobia/social anxiety disorder: randomised, double-blind, placebo-controlled study. Paroxetine Study Group. Br J Psychiatry 1999;175:120–126
27. Allgulander C. Paroxetine in social anxiety disorder: a randomized placebo-controlled study. Acta Psychiatr Scand 1999;100:193–198
28. Lepola U, Bergtholdt B, St. Lambert J, et al. Controlled-release paroxetine in the treatment of patients with social anxiety disorder. J Clin Psychiatry 2004;65:222–229
29. Rickels K, Mangano R, Khan A. A double-blind, placebo-controlled study of a flexible dose of venlafaxine ER in adult outpatients with generalized social anxiety disorder. J Clin Psychopharmacol 2004;24: 488–496
30. Allgulander C, Mangano R, Zhang J, et al. Efficacy of venlafaxine ER in patients with social anxiety disorder: a double-blind, placebo-controlled, parallel-group comparison with paroxetine. Hum Psychopharmacol 2004; 19:387–396
31. Pande AC, Davidson JR, Jefferson JW, et al. Treatment of social phobia with gabapentin: a placebo-controlled study. J Clin Psychopharmacol 1999;19:341–348
32. Pande AC, Feltner DE, Jefferson JW, et al. Efficacy of the novel anxiolytic pregabalin in social anxiety disorder: a placebo-controlled, multicenter study. J Clin Psychopharmacol 2004;24:141–149
33. Van Ameringen M, Mancini C, Pipe B, et al. Optimizing treatment in social phobia: a review of treatment resistance. CNS Spectr 2004;9: 753–762
34. DeVane CL, Grothe DR, Smith SL. Pharmacology of antidepressants: focus on nefazodone. J Clin Psychiatry 2002;63(suppl 1):10–17
35. Trivedi MH, Rush AJ, Pan J-Y, et al. Which depressed patients respond to nefazodone and when? J Clin Psychiatry 2001;62:158–163
36. Ninan PT, Rush AJ, Crits-Christoph P, et al. Symptomatic and syndromal anxiety in chronic forms of major depression: effect of nefazodone, cognitive behavioral analysis system of psychotherapy, and their combination. J Clin Psychiatry 2002;63:434–441
37. Keller MB, McCullough JP, Klein DN, et al. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. N Engl J Med 2000;342:1462–1470
38. Marcus RN, Mendels J. Nefazodone in the treatment of severe, melancholic, and recurrent depression. J Clin Psychiatry 1996; 57(suppl 2):19–23
39. Rickels K, Schweizer E, Clary C, et al. Nefazodone and imipramine in major depression: a placebo-controlled trial. Br J Psychiatry 1994; 164:802–805
40. Cohn CK, Robinson DS, Roberts DL, et al. Responders to antidepressant drug treatment: a study comparing nefazodone, imipramine, and placebo in patients with major depression. J Clin Psychiatry 1996;57(suppl 2): 15–18
41. Feiger A, Kiev A, Shrivastava RK, et al. Nefazodone versus sertraline in outpatients with major depression: focus on efficacy, tolerability, and effects on sexual function and satisfaction. J Clin Psychiatry 1996; 57(suppl 2):53–62
42. Robinson DS, Roberts DL, Smith JM, et al. The safety profile of nefazodone. J Clin Psychiatry 1996;57(suppl 2):31–38
43. Letter. Available at: www.fda.gov/ohrms/dockets/dailys/03/Nov03/ 110303/03p-0090-sup0001-vol1.pdf. Accessibility verified January 3, 2007
44. Letter. Available at: www.fda.gov/ohrms/dockets/dailys/04/June04/ 062404/03p-0090-pdn00001-vol1.pdf. Accessibility verified January 3, 2007
45. Letter. Available at: www.fda.gov/medwatch/SAFETY/2002/ serzone_deardoc.pdf. Accessibility verified January 3, 2007
46. Table 2. Health Canada, Canadian Adverse Reaction Newsletter 2003;13. Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/ carn-bcei_v13n1_e.html. Accessibility verified January 3, 2007
47. World Health Organization. Nefazodone. WHO Pharmaceuticals Newsletter 2003;1:7–8
48. Worthington JJ, Zucker BG, Fones CS, et al. Nefazodone for social phobia: a clinical case series. Depress Anxiety 1998;8:131–133
49. Van Ameringen M, Mancini C, Oakman JM. Nefazodone in social phobia. J Clin Psychiatry 1999;60:96–100
50. Kelsey JE, Slevig AL, Knight BT, et al. Treatment of generalized social phobia with the 5-HT_2 antagonist nefazodone. Presented at the Anxiety Disorders Association of America's 20th National Conference; March 23–26, 2003; Washington, DC
51. Keller MB, Klein DN, Hirschfeld RM, et al. Results of the DSM-IV mood disorders field trial. Am J Psychiatry 1995;152:843–849
52. Guy W. ECDEU Assessment Manual for Psychopharmacoloy. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
53. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382–389
54. Liebowitz MR. Social phobia. Mod Probl Pharmacopsychiatry 1987; 22:141–173
55. Connor KM, Davidson JR, Churchill LE, et al. Psychometric properties of the Social Phobia Inventory (SPIN): new self-rating scale. Br J Psychiatry 2000;176:379–386
56. Mattick RP, Clarke JC. Development and validation of measures of social phobia scrutiny fear and social interaction anxiety. Behav Res Ther 1998;36:455–470
57. Beck AT, Ward CH, Mendleson M, et al. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561–571
58. Beck AT, Epstein N, Brown G, et al. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol 1988; 56:893–897
59. Sheehan DV. The Anxiety Disease. New York, NY: Scribner; 1983
60. Hays RD, Sherbourne CD, Mazel RM. The RAND 36-Item Health Survey 1.0. Health Econ 1993;2:217–227
61. Blanco C, Schneier FR, Schmidt A, et al. Pharmacological treatment of social anxiety disorder: a meta-analysis. Depress Anxiety 2003;18:29–40
62. Kobak KA, Greist JH, Jefferson JW, et al. Fluoxetine in social phobia: a double-blind, placebo-controlled pilot study. J Clin Psychopharmacol 2002;22:257–262
63. Clark DM, Ehlers A, McManus F, et al. Cognitive therapy versus fluoxetine in generalized social phobia: a randomized placebo-controlled trial. J Consult Clin Psychol 2003;71:1058–1067
64. DeVane CL. Differential pharmacology of newer antidepressants. J Clin Psychiatry 1998;59(suppl 2):85–93
65. Preskorn SH. Comparison of the tolerability of bupropion, fluoxetine, imipramine, nefazodone, paroxetine, sertraline, and venlafaxine. J Clin Psychiatry 1995;56(suppl 6):12–21
66. Eison AS, Eison MS, Torrente JR, et al. Nefazodone: preclinical pharmacology of a new antidepressant. Psychopharmacol Bull 1990;26:311–315

67. Owens MJ, Ieni JR, Knight DL, et al. The serotonergic antidepressant nefazodone inhibits the serotonin transporter: in vivo and ex vivo studies. Life Sci 1995;57:PL373–PL380
68. Narayan M, Anderson G, Cellar J, et al. Serotonin transporter-blocking properties of nefazodone assessed by measurement of platelet serotonin. J Clin Psychopharmacol 1998;18:67–71
69. Preskorn SH. Imipramine, mirtazapine, and nefazodone: multiple targets. J Pract Psychiatr Behav Health 2000;97–102
70. Wander TJ, Nelson A, Okazaki H, et al. Antagonism by antidepressants of serotonin S1 and S2 receptors of normal human brain in vitro. Eur J Pharmacol 1986;132:115–121
71. Richelson E. Pharmacology of antidepressants. Mayo Clin Proc 2001; 76:511–527
72. Bertilsson L. Geographical/interracial differences in polymorphic drug oxidation: current state of knowledge of cytochromes P450 (CYP) 2D6 and 2C19. Clin Pharmacokinet 1995;29:192–209
73. Meyer UA, Zanger UM, Skoda RC, et al. Genetic polymorphisms of drug metabolism. Prog Liver Dis 1990;9:307–323