Predictors of Response to Pharmacotherapy in Social Anxiety Disorder: An Analysis of 3 Placebo-Controlled Paroxetine Trials

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Background: There is increasing evidence that patients with social anxiety disorder (social phobia) respond to treatment with selective serotonin reuptake inhibitors (SSRIs). Response rates to SSRIs in social anxiety disorder have ranged from at least 50% in controlled trials to up to 80% in open trials. To date, however, there has been little information available about predictors of response to treatment in this disorder.

Method: Data from 3 placebo-controlled multicenter trials of paroxetine in DSM-IV social anxiety disorder (N = 829) were analyzed using logistic regression to determine predictors of response. Demographic (age, sex), physiologic (baseline heart rate, baseline mean arterial pressure), clinical (baseline social anxiety symptom severity, baseline disability, duration of illness), and trial variables (paroxetine dose, treatment duration) were included.

Results: Only duration of treatment was a statistically significant predictor of treatment response. Further analysis demonstrated that, in paroxetine-treated patients in particular, many nonresponders at week 8 (46/166; 27.7%) were responders at week 12.

Conclusion: These data demonstrate that paroxetine is a reasonable choice of treatment in a broad spectrum of patients with social anxiety disorder. An optimal trial of medication should continue beyond 8 weeks.

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Social anxiety disorder (also known as social phobia) is increasingly recognized to be a highly prevalent disorder[1–4] with significant morbidity.[4–6] There is also growing evidence that social anxiety disorder may be accompanied by demonstrable neurobiological dysfunction.[7,8] Although the disorder continues to remain underdiagnosed in clinical practice, there have been important advances in its pharmacotherapy[9,10] and psychotherapy.[11,12]

Early work on the pharmacotherapy of social anxiety disorder demonstrated the efficacy of the monoamine oxidase inhibitor (MAOI) phenelzine.[13] Given the disadvantageous side effect profile of this agent and the need for strict dietary precautions, later research has moved toward other agents. High-potency benzodiazepines, for example, may be useful for some patients,[14] although the risk of dependency should be noted. Reversible MAOIs may also be useful,[15–17] although other studies have been negative.[18]

Introduction of the selective serotonin reuptake inhibitors (SSRIs) provides another possible avenue for the pharmacotherapy of social anxiety disorder. Early open trials proved encouraging, with response rates ranging from 50% to 80% in work on fluoxetine, sertraline, fluvoxamine, and citalopram.[19–27] Small controlled trials have also been extremely encouraging,[28,29] and, most recently, 3 large, placebo-controlled, multicenter trials have demonstrated efficacy of paroxetine in social anxiety disorder.[30–32]

Despite the growing evidence that a substantial proportion of patients with social anxiety disorder respond to treatment with paroxetine, there is little information available about predictors of response to SSRIs in this disorder. In other anxiety disorders, there is evidence that earlier age at onset and certain comorbid disorders may be negative predictors of response to pharmacotherapy.[33,34] In this study, data from the multicenter trials of paroxetine in social anxiety disorder were analyzed to determine the pre-

Table 1. Logistic Regression Analysis: The Effects of Duration of Treatment

Group	Parameter Estimate	Odds Ratio	95% Confidence Interval
All treatment groups combined (N = 820)	0.041	1.04	1.03 to 1.05
All paroxetine groups combined (N = 491)	0.046	1.05	1.04 to 1.06
All placebo groups combined (N = 329)	0.036	1.04	1.02 to 1.06

dictors of response to treatment. Demographic, physiologic, clinical, and trial variables were included in the analysis.

METHOD

Data from 3 randomized, placebo-controlled, multicenter trials[30–32] of paroxetine in DSM-IV social anxiety disorder were combined to provide a large sample of patients (N = 829). Two studies used the same flexible-dose design; 1 was conducted in North America and 1 was conducted in Europe and South Africa. The third study was a fixed-dose study in North America. Taken together, 499 patients were randomly assigned to paroxetine and 330 were randomly assigned to placebo.

Response was defined in terms of a rating of 1 (very much improved) or 2 (much improved) on the global improvement item of the Clinical Global Impressions scale (CGI)[35] at endpoint (week 12, last observation carried forward). At endpoint, 43.2% of the subjects (358/829), including 52.7% (263/499) of paroxetine patients and 28.8% (95/330) of placebo patients, were responders. Additional clinical measures employed during the trials included the Liebowitz Social Anxiety Scale (LSAS)[36] to measure social anxiety symptom severity and the Sheehan Disability Scale (SDS)[37] to measure disability.

Forward stepwise logistic regression was conducted using the LOGISTIC procedure of SAS. Analyses were run on 3 groups of data: all patients given treatment, paroxetine-treated patients, and placebo-treated patients. Demographic (age, sex), physiologic (baseline heart rate, baseline mean arterial pressure), clinical (baseline symptom severity on the LSAS, baseline disability on the SDS, duration of illness), and trial variables (paroxetine dose [in the analysis of paroxetine-treated patients], treatment duration) were included.

Nine patients had incomplete data and were therefore excluded from the analysis. Data were available for only 529 patients (64.5%) on age at onset of social anxiety disorder, but as this variable was found not to statistically predict response, regression analyses were repeated without its inclusion. Similarly, results from the first (N = 529) and second (N = 820) set of regression analyses were very similar, and only the latter are reported.

Table 2. Response on CGI at 12 Weeks Given Response Rate at 4 and 8 Weeks[a]

	Week 4			Week 8		
		Proportion Responding at Week 12			Proportion Responding at Week 12	
Group	Total N	N	%	Total N	N	%
All treatment groups combined						
Responders	188	151	80.3	302	265	87.7
Nonresponders	521	170	32.6	349	61	17.5
All paroxetine groups combined						
Responders	132	111	84.1	212	191	90.1
Nonresponders	275	122	44.4	166	46	27.7
All placebo groups combined						
Responders	56	40	71.4	90	74	82.2
Nonresponders	246	48	19.5	183	15	8.2

[a]Abbreviation: CGI = Clinical Global Impressions scale.

RESULTS

When all treated patients were included, univariate comparison and the subsequent logistic regression model demonstrated that only duration of treatment in the trial predicted response (Table 1). A 2-tailed t test including all subjects (N = 829) showed that treatment duration was significantly longer in responders than in nonresponders at endpoint, with a mean difference of 20 days (95% confidence interval [CI] = 17 to 23; $p < .001$). If there were 2 patients whose treatment duration differed by a week, the odds of a favorable response to treatment for the one with the longer treatment period would be expected to be just under $1^1/_2$ times the odds expected for the other patient.

Repeating the logistic regression in paroxetine-treated patients and then in placebo-treated patients again yielded duration of treatment as the only significant predictor of response (see Table 1). T tests showed that mean treatment duration in paroxetine-treated subjects (N = 499) at endpoint was 28 days longer in responders than nonresponders (95% CI = 24 to 33; $p < .001$), while mean treatment duration in placebo-treated subjects was only 12 days longer in responders than nonresponders (95% CI = 7 to 17; $p < .001$).

In each of the 3 trials, rates of withdrawal because of adverse effects did not differ between paroxetine and placebo groups, but rates of withdrawal because of lack of efficacy were higher in placebo-treated subjects. To explore treatment duration further, CGI response at 12 weeks given response at weeks 4 and 8 was tabulated (Table 2). In paroxetine-treated patients, of nonresponders at week 8, 46 (27.7%) of 166 were responders at week 12, whereas in placebo-treated patients, of nonresponders at week 8, only 15 (8.2%) of 183 were responders at week 12. Conversely, in paroxetine-treated patients, of responders at

week 4, most (111/132; 84.1%) remained responders at week 12, whereas in placebo-treated patients, 40 of 56 or 71.4% of responders at week 4 continued to be responders at week 12.

DISCUSSION

Analysis of demographic, physiologic, clinical, and trial variables in a large group of patients with social anxiety disorder demonstrated that only duration of treatment significantly predicted treatment response. At endpoint, the mean difference in days treated between responders and nonresponders was particularly high (28 days) in paroxetine-treated patients. Thus, despite the variability in patients with social anxiety disorder, paroxetine given for an adequate period of time is an effective intervention across a broad spectrum of cases. Patients who are nonresponders at week 8 may well go on to become treatment responders at week 12, a finding that was again particularly apparent in the paroxetine-treated group (in which 27.7% of week-8 nonresponders became week-12 responders). Thus, an optimal trial of paroxetine in social anxiety disorder must continue beyond 8 weeks. This conclusion is certainly consistent with current expert consensus opinions.[38] Although medication dose was not significantly predictive of response in the analysis of paroxetine-treated patients, only 1 of the included trials was a fixed-dose study.[32]

The conclusion that an optimal trial of paroxetine should continue beyond 8 weeks raises the important clinical question of how to increase patient engagement with the treatment process and ensure appropriate use of medications. A growing awareness of the relevance of psychoeducation in psychiatric practice, the importance of correcting cognitive distortions about medication, and the role of advocacy groups in promoting increased knowledge of and engagement with appropriate treatments would seem relevant.[39]

The analysis here is limited by the strict inclusion criteria for this series of trials. For example, patients with major depression and substance abuse were excluded. It is possible that these disorders have an influence on response to treatment in social anxiety disorder; Versiani et al.,[40] for example, found that alcohol abuse was associated with poor outcome in a 1-year study of tranylcypromine in social phobia, while Chambless et al.[41] found that higher depression, more avoidant personality traits, and lower treatment expectancy were related to poorer response to cognitive-behavioral therapy for social phobia on 1 or more outcome measures.

We are not aware of large studies exploring predictors of response to other serotonin reuptake inhibitors in social anxiety disorder. In a previous analysis of some of these paroxetine data, but focusing primarily on symptom severity, Montgomery[42] reported that both patients with more severe and less severe symptoms reponded to medication, but that the effect was more clear-cut in the more severe patients. In contrast, Sutherland et al.[43] found that, 2 years after a placebo-controlled trial of clonazepam, patients with less severe baseline symptoms (whether of social anxiety disorder, depression, or anxiety) and patients who received clonazepam rather than placebo showed a better outcome. This contrast in findings may point to the different psychobiological mechanisms effected by paroxetine and clonazepam.

Slaap et al.[44] found that certain personality disorders (borderline, passive-dependent) as well as particular biological markers (higher systolic blood pressure and heart rate) were negative predictors of response to treatment with brofaromine and fluvoxamine. We were unable to replicate these physiologic data in a much larger sample of subjects.

Clearly, further work is necessary to explore the heterogeneity of social anxiety disorder (including differences between pharmacotherapy responders and nonresponders) and its implications for treatment. A number of cognitive-behavioral studies have attempted to match patients and procedures (for example, using applied relaxation in physiologic reactors and social skills training in behavioral reactors), but further empirical support for such strategies is still needed.[11]

In the interim, however, it is encouraging to note that a substantial proportion of a large sample of social anxiety disorder patients can respond to a particular intervention. Certainly, it would seem that paroxetine given for an adequate period of treatment is a reasonable choice of medication in a broad range of patients with this disorder. Given the high prevalence and significant morbidity of social anxiety disorder, steps to increase its clinical recognition and appropriate management are paramount.

Drug names: citalopram (Celexa), clonazepam (Klonopin and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft), tranylcypromine (Parnate).

REFERENCES

1. Regier DA, Narrow WE, Rae DS. The epidemiology of anxiety disorders: the Epidemiological Catchment Area (ECA) experience. J Psychiatr Res 1990;24(suppl 2):3–14
2. Magee WJ, Eaton WW, Wittchen H-U, et al. Agoraphobia, simple phobia, and social phobia in the National Comorbidity Survey. Arch Gen Psychiatry 1996;53:159–168
3. Weissman MM, Bland RC, Canino GJ, et al. The cross-national epidemiology of social phobia: a preliminary report. Int Clin Psychopharmacol 1996;3(suppl 11):9–14
4. Weiller E, Bisserbe JC, Boyer P, et al. Social phobia in general health care: an unrecognized undertreated disabling disorder. Br J Psychiatry 1996; 168:169–174
5. Schneier FR, Heckelman LR, Garfinkel R, et al. Functional impairment of social phobia. J Clin Psychiatry 1994;55:322–331
6. Wittchen H-U, Beloch E. The impact of social phobia on quality of life. Int Clin Psychopharmacol 1996;3(suppl 11):15–23
7. Potts NLS, Book S, Davidson JRT. The neurobiology of social phobia. Int Clin Psychopharmacol 1996;3(suppl 11):43–48
8. Nutt DJ, Bell CJ, Malizia AL. Brain mechanisms of social anxiety disorder. J Clin Psychiatry 1998;59(suppl 17):4–9

9. Pollack MH, Gould RA. The pharmacotherapy of social phobia. Int Clin Psychopharmacol 1996;3(suppl 11):71–75
10. Davidson JRT. Pharmacotherapy of social anxiety disorder. J Clin Psychiatry 1998;59(suppl 17):47–53
11. van Dyk R. Non-drug treatment for social phobia. Int Clin Psychopharmacol 1996;3(suppl 11):65–70
12. Shear MK, Beidel DC. Psychotherapy in the overall management strategy for social anxiety disorder. J Clin Psychiatry 1998;59(suppl 17):39–46
13. 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
14. Davidson JRT, Potts N, Richichi E, et al. Treatment of social phobia with clonazepam and placebo. J Clin Psychopharmacol 1993;13:423–428
15. Versiani M, Nardi AE, Mundim FD, et al. Pharmacotherapy of social phobia: a controlled study with moclobemide and phenelzine. Br J Psychiatry 1992;161:353–360
16. van Vliet IM, den Boer JA, Westenberg HGM. Psychopharmacologic treatment of social phobia: clinical and biochemical effects of brofaromine, a selective MAO-A inhibitor. Eur Neuropsychopharmacol 1992;2: 21–29
17. The International Multicenter Clinical Trial Group on Moclobemide in Social Phobia. Moclobemide in social phobia: a double-blind, placebo controlled study. Eur Arch Psychiatry Clin Neurosci 1997;247:71–80
18. Schneier FR, Davies SO, Goetz D, et al. A controlled trial of moclobemide in social phobia. Presented at the 149th annual meeting of the American Psychiatric Association; May 4–9, 1996; New York, NY
19. Schneier FR, Chin SJ, Hollander E, et al. Fluoxetine in social phobia. J Clin Psychopharmacol 1992;12:62–64
20. Black B, Uhde TW, Tancer ME. Fluoxetine for the treatment of social phobia. J Clin Psychopharmacol 1992;12:293–295
21. Van Ameringen M, Mancini C, Streiner DL. Fluoxetine efficacy in social phobia. J Clin Psychiatry 1993;54:27–32
22. Van Ameringen M, Mancini C, Streiner DL. Sertraline efficacy in social phobia. J Affect Disord 1994;31:141–145
23. Munjack DJ, Flowers C, Eagan TV. Sertraline in social phobia. Anxiety 1994/1995;1:196–198
24. Martins EA, Piggott TA, Bernstein SE, et al. Sertraline in the treatment of patients with social phobia. Anxiety 1994/1995;1:291–297
25. Mancini C, Van Ameringen M. Paroxetine in social phobia. J Clin Psychiatry 1996;57:519–522
26. Stein MB, Chartier MJ, Hazen AL, et al. Paroxetine in the treatment of generalized social phobia: open-label treatment and double-blind placebo-controlled discontinuation. J Clin Psychopharmacol 1996;16: 218–222
27. Bouwer C, Stein DJ. Use of the selective serotonin reuptake inhibitor citalopram in the treatment of generalized social phobia. J Affect Disord 1998;49:79–82
28. 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
29. 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
30. Stein MB, Liebowitz MR, Lydiard B, et al. Paroxetine treatment of generalized social phobia (social anxiety disorder). JAMA 1998;280: 708–713
31. Baldwin D, Bobes J, Stein DJ, et al. Paroxetine in the treatment of social phobia/social anxiety disorder: randomized, double-blind, placebo-controlled study. Br J Psychiatry 1999;175:120–126
32. Lydiard RB, Bobes J. Therapeutic advances: paroxetine for the treatment of social anxiety disorder. Depress Anxiety 2000;11:99–104
33. Ackerman DL, Greenland S, Bystritsky A, et al. Predictors of treatment response in obsessive-compulsive disorder: multivariate analysis from a multicenter trial of clomipramine. J Clin Psychopharmacol 1994;14: 247–254
34. Davidson JRT, Kudler HS, Saunders WB, et al. Predicting response to amitriptyline in posttraumatic stress disorder. Am J Psychiatry 1993;150: 1024–1029
35. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
36. Liebowitz MR. Social phobia. Mod Probl Pharmacopsychiatry 1987;22: 141–173
37. Sheehan DV, Harnett-Sheehan R, Raj BA. The measurement of disability. Int Clin Psychopharmacol 1996;11(suppl 3):89–95
38. Ballenger JC, Davidson JRT, Lecrubier Y, et al. Consensus statement on social anxiety disorder from the International Consensus Group on Depression and Anxiety. J Clin Psychiatry 1998;59(suppl 17):54–60
39. Stein DJ, Wessels C, Zungu-Dirwayi N, et al. Value and effectiveness of consumer advocacy groups: a survey of the anxiety disorders support group in South Africa. Depress Anxiety 2001;13:105–107
40. Versiani M, Mundim FD, Nardi AE, et al. Tranylcypromine in social phobia. J Clin Psychopharmacol 1988;8:279–283
41. Chambless DL, Tran GQ, Glass CR. Predictors of response to cognitive-behavioral group therapy for social phobia. J Anxiety Disord 1997;11: 221–240
42. Montgomery SA. Implications of the severity of social phobia. J Affect Disord 1998;50(suppl 1):17–22
43. Sutherland SM, Tupler LA, Colket JT, et al. A 2-year follow-up of social phobia: status after a brief medication trial. J Nerv Ment Dis 1996;184: 731–738
44. Slaap BR, van Vliet IM, Westenberg HG, et al. Responders and non-responders to drug treatment in social phobia: differences at baseline and prediction of response. J Affect Disord 1996;39:13–19