THERAPEUTIC ADVANCES: PAROXETINE FOR THE TREATMENT OF SOCIAL ANXIETY DISORDER

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Data from early studies of selective serotonin reuptake inhibitors have shown that these agents are effective in the treatment of social anxiety disorder (social phobia). This review highlights the outcomes of three large clinical trials of paroxetine in patients with social anxiety disorder. In two of the studies, patients received a flexible dose of paroxetine (20–50 mg/day) or placebo; the third trial was a fixed-dose study, in which patients received paroxetine 20, 40, or 60 mg/day, or placebo. A total of 861 subjects were randomized to treatment for 12 weeks, in centers across the U.S.A., Canada, Europe, and South Africa. The primary outcome measures were the Clinical Global Impressions (CGI) Global Improvement item and Liebowitz Social Anxiety Scale (LSAS) Total Score.

In each of the studies, 45–66% of patients receiving paroxetine were rated as responders (very much or much improved on the CGI scale). Paroxetine treatment improved symptoms of social anxiety, as measured by the LSAS, compared with placebo. Differences between paroxetine and placebo groups were statistically significant and were clinically relevant within each study. In general, paroxetine was well tolerated.

Paroxetine is effective for the treatment of social anxiety disorder. Based on the findings from these studies, a starting dose of 20 mg/day is recommended. The range of efficacy appears to be 20–50 mg/day for most patients. Depression and Anxiety 11:99–104, 2000. *© 2000 Wiley-Liss, Inc.*

Key words: *social anxiety disorder; social phobia; clinical trial; randomized; placebo-controlled*

INTRODUCTION

Social anxiety disorder (social phobia) is a common, potentially crippling anxiety disorder which affects an estimated 7–13% of the general population at some point [Kessler et al., 1994; Wittchen et al., 1999; Lecrubier et al., 2000]. Most individuals (about 75%) with social anxiety disorder have the generalized subtype (the more severe form) in which most types of social situations are feared. The remainder forms a heterogeneous group that includes individuals who fear a single or several performance situations, but not most social situations (nongeneralized subtype). The pathological social fear and avoidance associated with social anxiety disorder can result in poor academic achievement, social limitations, and often financial dependence for the sufferer [Davidson, 1994; Schneier et al., 1992; Weiller et al., 1996; Wittchen and Beloch, 1996]. Table 1 shows the main features of social anxiety disorder. The lifetime prevalence rates of the disorder found in community studies range from 4% [Schneier et al., 1992] up to 14% [Magee et al., 1996]. Social anxiety disorder is complicated by a 70–80% lifetime risk of comorbid psychiatric conditions, such as depression and alcohol abuse [Merikangas and Angst, 1995].

Social anxiety disorder is amenable to both cognitive-behavioral and pharmacological treatment, as discussed in the article by Davidson [2000] and elsewhere

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TABLE 1. Key clinical features of social anxiety disorder/social phobia

Clinical feature
Fear of embarrassment in one or more or social situations
Fear of negative evaluation
Exposure to the situation reliably causes anxiety, often with panic-like symptoms
The fear is recognized as excessive or unreasonable
The social situation is often avoided, or is endured with dread
Panic attacks are associated with social situations and do not occur unexpectedly
Causes significant distress or interference with in one or more domains of functioning
Subtypes
Generalized (encompasses most social interactions)
Nongeneralized (a few discrete situations such as public speaking, eating, writing, etc. in front of others, but not most social situations)

[Jefferson, 1995; den Boer, 1997; Boerner and Möller, 1998; Davidson, 1998; Lydiard, 1998]. Recently, the International Consensus Group on Depression and Anxiety recommended selective serotonin re-uptake inhibitors (SSRIs) as the therapy of choice for social anxiety disorder [Ballenger et al., 1998].

Clinical data derived from case reports and open-label studies of SSRIs have indicated their potential for use in social anxiety disorder. Acute efficacy has been demonstrated in small-scale studies of fluvoxamine [van Vliet et al., 1994], sertraline [Katzelnick et al., 1995], and paroxetine [Stein et al., 1996] (Table 2). A relapse prevention study by Stein et al. [1996] showed that abrupt placebo substitution for paroxetine therapy following successful treatment of generalized social anxiety disorder led to relapse of symptoms, while continued paroxetine therapy was of benefit. Based on the optimistic preliminary data from these smaller studies, three large-scale studies of paroxetine in social anxiety disorder were undertaken. These studies, which represent the largest sample (n = 861) of SSRI treatment of patients with social anxiety disorder, were all intentionally structured with similar designs to allow easy comparison between studies [Stein et al., 1998; Baldwin et al., 1999] (SmithKline Beecham, unpublished). These studies are highlighted below.

TABLE 2. Early studies of SSRIs in social anxiety disorder/social phobia

SSRI[a]	Study design	n	% Responders	Reference
Paroxetine	Open	36	77	Stein et al. [1996]
Sertraline	Parallel cross-over	12	42	Katzelnick et al. [1995]
Fluvoxamine	Parallel	30	46	van Vliet et al. [1994]

[a]*SSRI, selective serotonin reuptake inhibitors.*

METHODS

GENERAL STUDY DESIGN

Flexible-dose studies. Two multicenter, double-blind, placebo-controlled, flexible-dose clinical trials of paroxetine were conducted: one in the U.S.A. and Canada (Study 382), which included 187 subjects, and one in Europe and South Africa (Study 502), which included 290 subjects. Each study employed a 1-week, single-blind, placebo run-in period followed by a 12-week treatment phase. The dose of paroxetine was 20 mg/day for the first 2 weeks. After the initial 2 weeks, the daily dosage could be increased by 10 mg daily per week to a maximum daily dose of 50 mg (Fig. 1).

Fixed-dose study. The 12-week fixed-dose study (Study 454) was conducted in the U.S.A. and Canada. A total of 384 patients were randomized to receive paroxetine 20, 40, or 60 mg/day, or placebo. A 1-week, single-blind, placebo run-in preceded random assignment to the treatment groups. Paroxetine was initiated at 20 mg/day for the first week of the trial for all patients in the active treatment groups. At week 2, the dosage was increased to 40 mg/day for the 40 or 60 mg/day treatment groups and at the start of the third week, the dosage was further increased to 60 mg/day for the 60 mg/day treatment group. For the 20 and 40 mg group, additional placebo tablets were added so that all groups took the same number of tablets (three per day) of paroxetine or placebo.

INCLUSION AND EXCLUSION CRITERIA

Inclusion and exclusion criteria were similar across all studies. Subjects were recruited by referral or from advertisements in the media. Outpatients with DSM-IV [American Psychiatric Association, 1994] criteria for social anxiety disorder (social phobia) were evaluated with the Structured Clinical Interview for the DSM-IV [First et al., 1995] or the Mini International Neuropsychiatric Interview [Sheehan et al., 1998].

Patients (men and women) with social anxiety disorder, who were at least 18 years old, and had given written informed consent were eligible for the studies. The main exclusion criteria were other Axis I disorder(s) which might interfere with assessment of efficacy in the study (e.g., major depression, panic disorder, schizophrenia, bipolar affective disorder, body dysmorphic disorder, recent alcohol, or substance abuse or dependence), or a significant risk of suicide. In Studies 454 and 502, patients with a Hamilton Depression Rating Scale (HAM-D) score of 15 or more were also excluded [Hamilton, 1967]. Patients who required other psychotropic medication (anxiolytics, antidepressants, or neuroleptics) were excluded, as were patients with a history of paroxetine intolerance. Patients with unstable medical disorders, or conditions that might interfere with study procedures were also excluded.

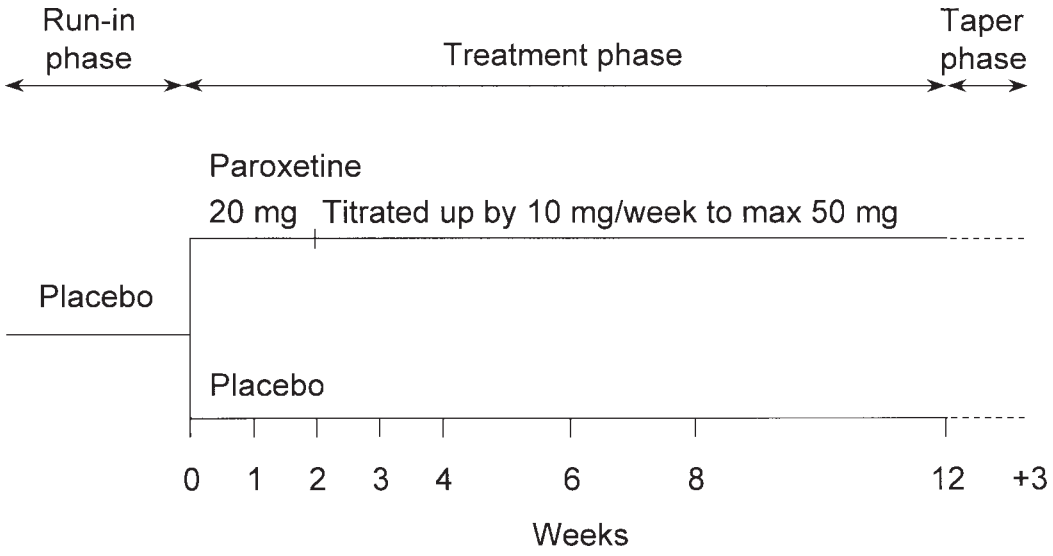

Figure 1. Design of the flexible dose studies. Adapted from Baldwin et al. [1999].

EFFICACY AND SAFETY ASSESSMENTS

All patients were assessed weekly for the first 4 weeks of the trial, then at weeks 6, 8, and 12 (end point). The primary efficacy variables were the proportion of patients with a Clinical Global Impressions (CGI) Global Improvement score of 1 (very much improved) or 2 (much improved) [Guy, 1976], and the mean change from baseline in Liebowitz Social Anxiety Scale (LSAS) Total Score [Liebowitz, 1987]. Changes in anxiety symptoms were also measured using the Social Anxiety and Distress Scale (SADS) [Watson and Friend, 1969]. Disability was assessed with the Sheehan Disability Scale (SDS) [Sheehan, 1983], which assessed patient-rated impairment of work, social life, and family-life domains. CGI Severity of Illness scores were used to assess overall disease severity (except Study 382).

A routine medical examination preceded study participation, and monitoring for adverse experiences was conducted at each visit. Standard laboratory tests were obtained at baseline and end point. Patients with clinically significant laboratory measures were excluded.

STATISTICAL ANALYSIS

In each study, the proportion of responders (defined as a CGI Global Improvement score of 1 or 2) was analyzed by logistic analysis using the categorical modeling procedure of the Statistical Analysis System with a model that included an effect for treatment. The mean change from baseline in LSAS Total Score and the secondary efficacy scales were analyzed using parametric analysis of variance. All statistical tests comparing paroxetine with placebo were two-tailed and with an overall significance level of 0.05. In Study 454, Dunett's test was used to compare each paroxetine dose with placebo to maintain an overall significance level of 0.05 and the adjusted level of significance was less than 0.019. Efficacy analyses included the intent-to-treat population (i.e., patients who took at least one dose of medication and had at least one postrandomization assessment). The primary time point of interest was end point for each study. For patients who did not complete the entire study, the last observation during treatment was carried forward to end point.

RESULTS

PATIENT CHARACTERISTICS

Patient sample characteristics were similar across the three studies (Table 3). The mean age of onset of social anxiety disorder was 15.8 years and the mean current age of the study population was 36 years (entire patient sample).

EFFICACY

Paroxetine-treated patients exhibited clinically and statistically significant improvement in the primary efficacy measures (CGI and LSAS scores), compared with placebo-treated patients.

CGI Global Improvement measures. The proportion of responders ("much improved" or "very much improved") in Study 382 was 55% in the paroxetine group compared with 24% in the placebo group, and in Study 502, the response rate was 66% vs. 32% in the paroxetine and placebo groups, respectively (Fig. 2). The mean paroxetine-placebo difference in response was similar in each study: 31% in Study 382 and 34% in Study 502.

In the fixed-dose study, similar percentages of patients in the paroxetine groups were rated as responders on the CGI-Improvement assessment (Fig. 2). However, only the 40 mg/day group was statistically different from the placebo group. Interestingly, the percentages of patients rated as responders in the three active fixed-

TABLE 3. Patient characteristics of the study populations

	Study 382[a]		Study 502[b]		Study 454[c]	
	Paroxetine N = 94	Placebo N = 93	Paroxetine n = 139	Placebo n = 151	Paroxetine n = 289[d]	Placebo n = 95
Mean age (y)	35.9	36.7	34.7	37.3	37.7	34.7
Age range (y)	18–59	18–76	18–67	18–85	20–70	18–65
Sex (%)						
Male	53	60	46	46	59	58
Female	47	40	54	54	41	42
Race (%)[e]						
Caucasian	76	86	89	90	81	83
Black	16	9	6	3	9	11
Other	8	5	6	7	10	6

[a]*Data from Stein et al. [1998].*
[b]*Data from Baldwin et al. [1999].*
[c]*SmithKline Beecham, data on file.*
[d]*Combined data from the three active treatment dose groups.*
[e]*Some totals greater than 100% due to rounding.*

dose study groups (ranging from 45%, 47%, and 43% at 20, 40, and 60 mg, respectively) was lower than in either flexible-dose study (55% and 66%), but the placebo response rates were comparable (20–30% range) across all three studies. In the fixed-dose trial, if all three active drug groups are combined, the mean proportion of responders in the paroxetine group (45%) was significantly greater than with placebo (28%) at week 12 ($P < 0.01$). Most of the difference between the paroxetine and placebo groups was due to the percentage of responders who were "very much improved": 19%, 21%, and 22% with increasing doses of paroxetine, compared with 8% in the placebo group.

LSAS rating. Across all three studies, patients receiving paroxetine experienced greater improvements in their social anxiety symptoms than placebo-treated patients, as measured by the average reduction in LSAS scores from baseline (Fig. 3). In both flexible-dose studies, the paroxetine-treated patients exhibited significantly more improvement in the LSAS score ratings than placebo recipients by week 4 and through all of the subsequent assessments to end point (week 12). At end point, the differences in LSAS score improvement between the paroxetine (Study 382, 31 points; Study 502, 29 points) and placebo groups (Study 382, 15 points; Study 502, 16 points) were statistically significant. In Study 454, the reduction in LSAS scores in the 20 mg/day dose group (31 points) was statistically greater than in the placebo group (15 points). The two higher dose groups (paroxetine 40 and 60 mg/day) both exhibited the same degree of improvement (25 points) in LSAS ratings, but this difference was not statistically significantly different from placebo (Fig. 3).

Secondary efficacy measures. Improvements in all secondary efficacy variables were greater with paroxetine than with placebo. The results from the

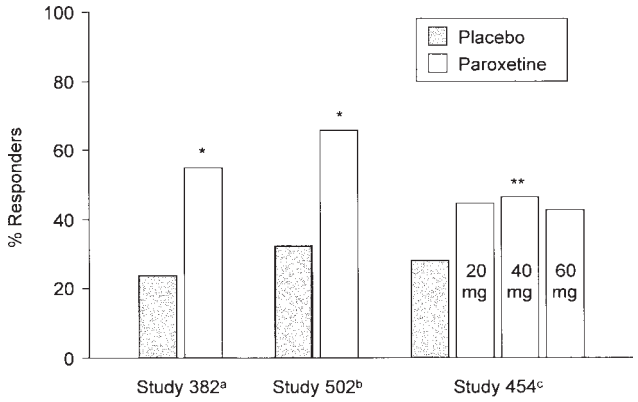

Figure 2. Proportion of patients at end point with CGI Global Improvement scores of 1 or 2 ("responders"). *$P < 0.05$, paroxetine vs. placebo.$P < 0.019$ (Dunett's test), paroxetine vs. placebo. [a]Data from Stein et al. [1998]. [b]Data from Baldwin et al. [1999]. [c]SmithKline Beecham, data on file.**

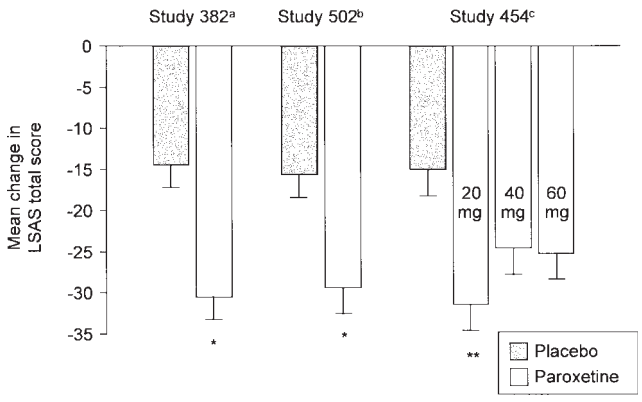

Figure 3. Social anxiety symptoms–mean reduction in Liebowitz Social Anxiety Scale (LSAS) total scores at end point. *$P < 0.05$, paroxetine vs. placebo. **$P < 0.019$ (Dunett's test), paroxetine vs. placebo. [a]Data from Stein et al. [1998]. [b]Data from Baldwin et al. [1999]. [c]SmithKline Beecham, data on file.

secondary efficacy measures of the flexible dose studies are shown in Table 4. In the fixed-dose study, several of these variables showed statistical significance for each dose level, but as might be expected, not all doses showed statistical superiority on all measures. At no time was placebo superior to paroxetine.

TREATMENT EFFECTS ON DEPRESSION

In the Europe-South Africa flexible dose study, change in HAM-D rating was determined for the two treatment groups. The mean HAM-D scores at baseline and end point, respectively, were 6.2 and 4.2 for the paroxetine group, and 6.7 and 6.5 for the placebo group. Thus, on entry to the study, subjects had low levels of depression, and little change in depressive symptoms was observed following treatment. Therefore, the overall treatment effect observed for symptoms of social anxiety disorder does not appear to be dependent on a change in any symptoms of coexistent depression. Similar results were observed in the fixed-dose study.

PAROXETINE DOSAGE

In the flexible-dose studies (20–50 mg/day), the mean dose of paroxetine at study end point was 36.6 mg/day in the U.S.A. and Canada study (Study 382) and 34.7 mg/day in the European and South Africa study (Study 502). Not surprisingly, optimal individual patient dosage varied within both studies. In the dose-finding trial (Study 454), a good response to treatment was observed with 20 or 40 mg/day paroxetine, with no added efficacy advantage of raising the dose to 60 mg/day.

TOLERABILITY

Overall, the most common treatment emergent adverse experiences in the paroxetine group were abnormal ejaculation, nausea, somnolence, insomnia, headache, and asthenia. Headache, insomnia and asthenia, however, were reported at a similar rate in the placebo groups (Table 5).Most adverse experiences in both groups were mild or moderate. The rate of adverse experiences classed as "severe" was similar for the paroxetine (9%) and placebo (6%) groups.

TABLE 4. Efficacy of paroxetine in the treatment of social anxiety disorder, data represents mean change from baseline at end point.

Secondary efficacy measure	Study 382[a]		Study 502[b]	
	Paroxetine	Placebo	Paroxetine	Placebo
CGI[d] severity of illness	ND[c]	ND	–1.4*	–0.7
LSAS[e]—fear/anxiety	–15.8*	–7.0	ND	ND
LSAS—avoidance	–14.8*	–7.6	ND	ND
SADS total score	–7.8*	–2.8	–7.2*	–3.9
SDS[f]—work	–1.4*	–0.7	–2.8*	–1.6
SDS—social life	–2.7*	–1.4	–3.2*	–2.5
SDS-family life	–1.0*	–0.6	–1.8*	–0.8

[a]*Data from Stein et al. [1998].*
[b]*Data from Baldwin et al. [1999].*
[c]*ND = not described.*
[d]*CGI, Clinical Global Impressions.*
[e]*LSAS, Liebowitz Social Anxiety Scale.*
[f]*SDS, Sheehan Disability Scale.*
**Statistically significant improvement with paroxetine compared to with placebo (P < 0.05).*

EARLY TERMINATION

For all studies combined, lack of efficacy was the most common reason for withdrawal from the placebo group (12% vs. 2% with paroxetine). However, there were more withdrawals due to adverse experiences from the paroxetine group (16% vs. 4% with placebo). Withdrawal for other reasons included: patients lost to follow-up (8% paroxetine, 6% placebo), and lack of efficacy (2% paroxetine, 12% placebo). In the individual trials, the reasons for withdrawal followed the same pattern as for the overall study population.

DISCUSSION AND CONCLUSIONS

This article has summarized three large placebo-controlled, multicenter studies of the treatment of patients with social anxiety disorder with paroxetine. As a class, SSRIs show promise for the treatment of social anxiety disorder. The three trials described in this review show consistently that paroxetine (20–50 mg/day) is an effective and well-tolerated treatment for social anxiety disorder. Paroxetine produced overall improvement, in addition to providing more specific benefits with respect to anxiety and avoidance symptoms, and social anxiety-related disability.

In the flexible-dose studies, a more robust response was seen than in the fixed-dose study. There were similar baseline sample characteristics and sample sizes in the treatment groups. This suggests that factors inherent in the differences between study designs may have reduced the rates of response in the fixed-dose study. It may be that some patients needed higher or lower doses than allowed by the fixed-dose design. Because all subjects were committed to a single dose, individual optimization was not possible. Additionally, no further improvement in efficacy in the high-dose

TABLE 5. Most common adverse experiences reported over 12 weeks of treatment, combined data for the three large-scale studies

	% Paroxetine (n = 522)	% Placebo (n = 339)
Abnormal ejaculation[a]	32	1
Nausea	25	7
Somnolence	23	5
Insomnia	23	16
Headache	22	22
Asthenia	22	14

[a]*Corrected for gender.*

(60 mg/day) group suggests that for most patients there is no advantage in prescribing doses higher than 50 mg/day. Based on the accrued evidence, a starting dose of 20 mg/day is recommended. The pattern of adverse experiences attributed to paroxetine in these studies is similar to those reported for paroxetine in previous studies [reviewed by Gunasekara et al., 1998]. Paroxetine is the first SSRI to receive approval for use in social anxiety disorder in the U.K., other European countries, and more recently in the U.S.A.

The process of development of paroxetine as a treatment for social anxiety disorder, as described in this article, is the first important step in an ongoing effort to develop effective and safe treatment for this condition. Since approximately 60–70% of patients with social anxiety disorder respond to treatment with SSRIs, there is a clear need for further expansion of the treatment armamentarium. Whether patients who are responsive or incompletely responsive to one SSRI may respond to another SSRI or a monoamine oxidase inhibitor remains an open and important clinical question. It appears that the other SSRIs, some of the newer non-SSRI antidepressant agents, high potency benzodiazepines, and the anticonvulsant gabapentin may also be effective as treatments for this prevalent and serious disorder [Lydiard, 1998; Ballenger et al., 1998; Pande et al., 1999]. Studies comparing these newer agents both with each other as well as with the other efficacious treatments are needed to provide important clinical information on their relative efficacy and tolerability.

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