Theoretical Paper

SERTRALINE IN THE TREATMENT OF ANXIETY DISORDERS

Robert M.A. Hirschfeld, M.D.

Sertraline was first developed and approved for the treatment of depression. However, considerable research has been conducted on its use in anxiety disorders. This paper reviews the data emerging from controlled and open trials of the use of sertraline in anxiety disorders. Sertraline has been tested extensively in the treatment of panic and obsessive-compulsive disorders. Less extensive testing has been completed on social phobia and post-traumatic stress disorder. The reviewed studies show that sertraline is an effective and well-tolerated treatment of all of these disorders. A comparison of sertraline with other pharmacotherapeutic options shows it to be at least equivalent to other medications for anxiety disorders. Depression and Anxiety 11:139–157, 2000. *© 2000 Wiley-Liss, Inc.*

Key words: ***Sertraline; depression; anxiety disorders; panic disorder; obsessive-compulsive disorder; social phobia; PTSD; SSRIs; pharmacotherapy***

INTRODUCTION

Sertraline was first developed for the treatment of depression. Additionally, it has been proven effective in patients with prominent anxiety symptoms as part of their syndrome of depression and those with anxiety disorders alone. Anecdotal reports of its use in these patients fostered the design of larger controlled trials of sertraline in the treatment of patients with anxiety disorders. At this time, sertraline has been tested extensively in controlled trials in the treatment of panic disorder and obsessive-compulsive disorder. Less extensive testing has been done on patients with social phobia and with post-traumatic stress disorder, although the results are encouraging.

This article will review the accumulated research on the use of sertraline as a treatment for specific anxiety disorders, including panic disorder, obsessive-compulsive disorder, social phobia, and post-traumatic stress disorder. Key details of studies will be presented in order to give the reader an up-to-date and thorough description of all the relevant research of sertraline in the treatment of these anxiety disorders.

SERTRALINE IN THE TREATMENT OF PANIC DISORDER

A number of psychopharmacological agents have demonstrated efficacy in the treatment of panic disorder. The TCAs and the MAOIs were the first to show efficacy in panic disorder, followed by the benzodiazepines. In the 1990s, the selective serotonin reuptake inhibitors have become first line treatments [Hirschfeld, 1993].

The efficacy of sertraline in the treatment of panic disorder has been tested in four large multicenter studies: two fixed-dose [Londborg et al., 1998; Wolkow, 1996], and two flexible-dose [Pohl et al., 1998; Pollack et al., 1998]. The two fixed-dose studies had identical designs, as did the two flexible-dose studies.

FIXED-DOSE STUDIES

The fixed-dose studies were each multicenter, 12-week, double-blind studies of outpatients with a DSM-III-R diagnosis of panic disorder [Londborg et al., 1998; Wolkow, 1996]. Inclusion criteria for the study were age greater than or equal to 18 years, DSM-III-R diagnosis of panic disorder with or without agoraphobia, at least three panic attacks in a 2-

Department of Psychiatry and Behavioral Sciences, The University of Texas Medical Branch, Galveston, Texas

*Correspondence to: Dr. Robert M.A. Hirschfeld, Department of Psychiatry and Behavioral Sciences, University of Texas—Medical Branch, 1.302 Rebecca Sealy, 301 University Boulevard, Galveston, TX 77555-0188.

Received for publication 28 December 1999; Accepted 7 February 2000

week run-in phase, a Hamilton Anxiety Score ≥ 18, a 21-item Hamilton D Score ≤ 17, no significant psychiatric comorbidity, and no concomitant psychotropic medication. Women of child-bearing potential were excluded. Written informed consent was obtained in all patients.

Patients were randomly assigned to four treatment groups with sertraline doses of 50, 100, and 200 mg/day, or placebo. Initial dosing for all active medication groups was 50 mg per day. Titration to the 100 mg and 200 mg doses was accomplished by using double-blind procedures with increases of 50 mg a day on a weekly basis. Medication was taken with the evening meal as a single dose. Chloral hydrate for sleep was the only other psychotropic medication permitted. Safety and efficacy data were obtained at the end of weeks 1, 2, 3, 4, 6, 8, 10, and 12. Efficacy was assessed by changes in number of DSM-III-R defined panic attacks, number of limited symptom attacks, the percentage of time that the patient experienced anticipatory anxiety, and the Hamilton A Scale.

In the first study, 178 adult outpatients entered double-blind treatment, 177 of whom were evaluable [Londborg et al., 1998]. The study was conducted at seven sites within the United States. The other fixed-dose study involved 152 participants from eight centers in the United States [Wolkow, 1996]. Baseline demographic and clinical measures from both studies are presented in Table 1.

Since there were no significant differences between the two studies in baseline measures or in outcomes, the results from the two have been combined. Figure 1 depicts data on panic attack frequency at each week of treatment in each sertraline dosage group and placebo. At endpoint, panic attack frequency was significantly reduced in each of the sertraline dosage groups compared to placebo, $P \leq .05$. There was no dose response relationship. Figure 2 depicts the reduction in number of panic attacks for the pooled results from the two fixed-dose studies. A statistically significant decrease in number of panic attacks for the combined doses compared with placebo emerged at week 2 ($P < 0.05$), and persisted throughout the entire study. At endpoint, the combined sertraline treatment group was superior to placebo in reducing panic attacks ($P < 0.01$). There was an endpoint reduction of less than four panic attacks in the placebo group, whereas for the combined sertraline group there was a reduction of eight.

A completer analysis of the reduction of panic attack frequency at week 12 for the pooled fixed-dose studies shows a substantial reduction at all three sertraline doses, the highest at 50 mg, and a modest reduction in the placebo group (see Fig. 3). A reduction in limited-symptom attacks (those involving three or fewer panic attack symptoms) is an important clinical variable. Londborg et al. [1998] reported a significantly greater reduction in limited symptom attacks from baseline to endpoint in sertraline groups (50, 100, and 200 mg) than in placebo, both when the ANCOVAs were performed for the four treatment groups ($P < 0.02$) and for the pooled sertraline group and placebo ($P < 0.006$). There was a significantly greater reduction in limited symptom attacks at endpoint in the pooled sertraline group compared to placebo ($P < 0.05$), as demonstrated in Figure 4.

Reduction in overall anxiety was also achieved in the active medication groups. Figure 5 shows significantly greater improvement in HAM-A scores in all of the active medication groups compared with the placebo, starting at week 6. Anticipatory anxiety is the amount of time spent worrying about panic attacks. Figure 6 shows a substantial drop in anticipatory anxiety in all three active medication groups compared to a modest drop in the placebo group ($P < 0.05$ between pooled sertraline groups and placebo, as well as between sertraline 50 mg and placebo, and sertraline 100 mg and placebo).

TABLE 1. Baseline demographic and clinical variables for panic disorder fixed-dose studies*

	Londborg et al. [1998]					Wolkow [1996]	
		Sertraline					
	Placebo (N = 45)	Pooled (N = 132)	50 mg (N = 43)	100 mg (N = 44)	200mg (N = 45)	Placebo (N = 38)	Sertraline pooled[a] (N = 114)
Age (mean)	39.1	38.7	37.2	41.8	37.2	37.5	40.5
Sex (n)							
% Female	35.6	50.8	62.8	54.5	35.6	31.6	28.1
Race (n)							
Black	1	4	3	1	0	5	8
White	44	119	38	40	41	29	90
Hispanic	0	8	2	3	3	2	11
Other	0	1	0	0	1	2	5
Panic attacks (mean)	9.4	6.7	5.4	9.9	4.8		
Unexpected attacks (mean)	5.8	4.2	3.4	5.7	3.4		
Limited symptoms attacks (mean)		6.7	7.2	7.9	4.9		

**Adapted from Londborg et al. [1998] and Wolkow [1996].*

[a]Data on sertraline individual doses was not available from the Wolkow [1996] study.

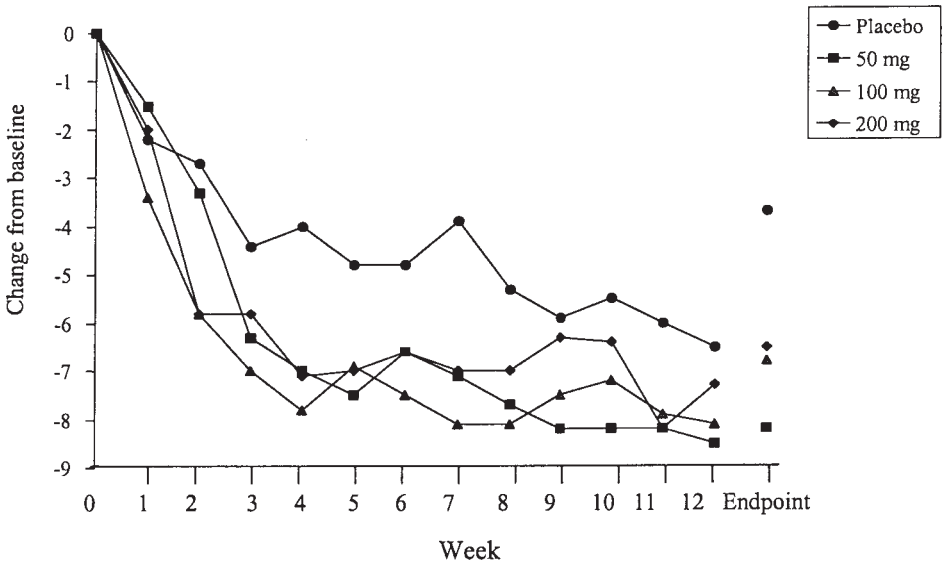

Figure 1. Reduction in panic attack frequency in sertraline 50, 100, and 200 mg/day groups and placebo, pooled from two fixed-dose studies [Londgorg et al., 1998; Wolkow, 1996]. Data on file Pfizer.

Table 2 shows the number of adverse events reported by 10% or more of the patients. Only two symptoms, dry mouth and ejaculatory delay, were reported at a significantly higher rate among the sertraline patients than the placebo in Londborg et al. [1998] study. In the other fixed-dose study [Wolkow, 1996], four symptoms were reported at a significantly higher rate among sertraline-treated patients: insomnia, somnolence, dyspepsia, and ejaculatory delay.

For the pooled sertraline groups, 63% completed the study; 56% of the 50 mg, 77% of the 100 mg, and 56% of the 200 mg patients completed the study, whereas 69% of the placebo-treated patients completed the study. The most frequent reason for early discontinuation for the sertraline patients was an adverse event (20%), whereas it was insufficient clinical response (11%) for the placebo group.

The results of the two fixed-dose studies demonstrate the efficacy of sertraline at three different doses in the treatment of panic disorder on a variety of outcome measures, including reduction in the number of full panic attacks, reduction in limited-symptom attacks, reduction in overall anxiety, and reduction in anticipatory anxiety. Only two adverse events occurred at a significantly higher rate in the sertraline than in the placebo group, suggesting its tolerability in panic disorder patients.

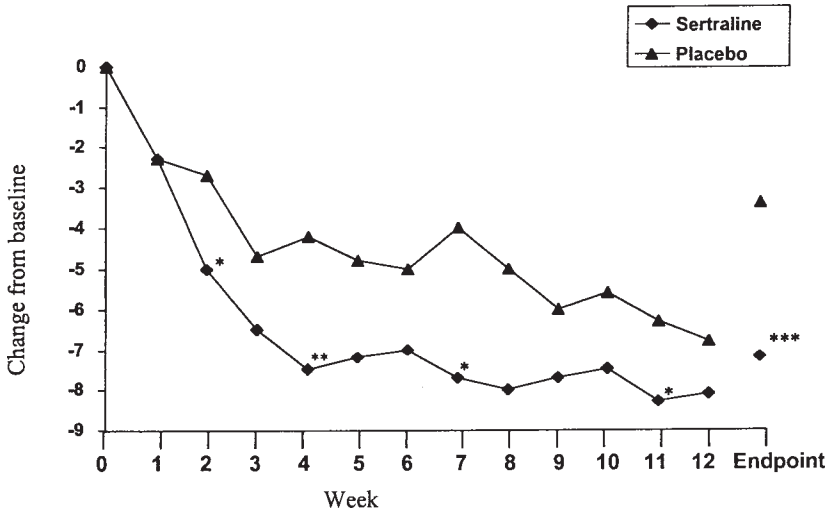

Figure 2. Reduction in panic attack frequency for the combined sertraline groups and placebo, pooled from two fixed-dose studies [Londberg et al., 1998; Wolkow, 1996]. *$P \leq 0.05$. **$P \leq 0.01$. ***$P \leq 0.001$.

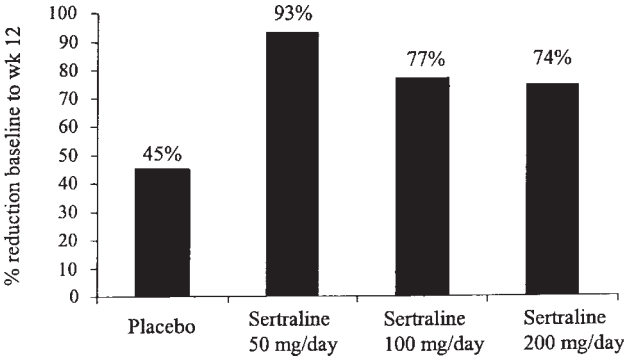

Figure 3. Pooled reduction in panic attack frequency from baseline to week 12 in the fixed-dose studies, completer analysis. Adapted from Gorman and Wolkow [1994].

FLEXIBLE-DOSE STUDIES

Two 10-week, multicenter, flexible-dose studies comparing sertraline in a dose range of 50–200 mg and placebo were conducted with patients with DSM-III-R panic disorder, with or without agoraphobia [Pohl et al., 1998; Pollack et al., 1998]. Inclusion criteria required at least four panic attacks in the 4 weeks prior to baseline and at least three panic attacks during the 2-week, single-blind, placebo lead in. Inclusion criteria also required a Ham-A Score of ≥ 18, and a 21-item Ham-D score of ≤ 17. Exclusion criteria included pregnant or nursing women or those not practicing birth control, patients with an organic mental disorder, psychotic disorder, major depression, bipolar disorder; patients with principal DSM-III-R diagnosis of dysthymia, personality disorder or anxiety disorder; patients requiring concomitant psychotropic therapy; or previous treatment with sertraline. Outcome measures included the modified Sheehan Panic Anticipatory Anxiety Scale (PAAS), the Clinical Global Impression of Improvement (CGI-I), and Patient Global Evaluations.

Pooled baseline demographics and clinical data are presented in Table 3. In general, patients were in their mid-30s, predominantly female, had been ill for nearly 10 years, and were experiencing approximately six panic attacks per week.

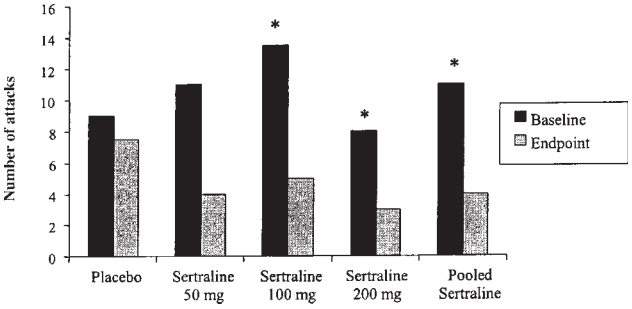

Figure 4. Pooled limited-symptom attack reduction from baseline to endpoint in fixed-dose studies. Adapted from Gorman and Wolkow [1994]. *$P < 0.05$.

The dose titration in the flexible-dose studies differed from those in the fixed-dose studies. All patients on sertraline were started at 25 mg per day for the first week, after which the dose was increased to 50 mg and increased further on a weekly basis if considered necessary to a maximum of 200 mg a day. At endpoint, the mean daily dose of sertraline in the two studies was 121.9 mg.

Figure 7 depicts the reduction in panic attacks over the course of treatment. At endpoint, the reduction in panic attacks for the placebo group was approximately 3, and it was 5 for sertraline, a statistically significant difference. The difference between sertraline and placebo reduction in panic attacks was significantly different at week 2 and continued throughout the study.

Clinical Global Impression Improvement scores reflected improvements obtained on other measures. At endpoint, the sertraline group revealed a significant improvement over placebo on clinician's CGI-Severity scores ($P < 0.001$) and global improvement scores ($P < 0.001$), as well as on patient's global assessment of improvement ($P < 0.001$).

There was also a significantly greater reduction in the number of limited-symptom attacks in the sertraline groups compared to the placebo groups. At endpoint, the number of limited-symptom attacks was reduced by approximately 3 in the placebo group and by approximately 5 in the sertraline group, a statistically significant reduction ($P = 0.007$). There were also significant reductions from baseline to endpoint in the sertraline group compared to the placebo group in anticipatory anxiety ($P = .013$), panic burden ($P < 0.001$), Hamilton Anxiety scale scores ($P = .013$), and Multicenter Panic Anxiety Score ($P < 0.001$).

With regard to discontinuations, 8% of sertraline treated patients discontinued due to adverse events, compared to 2% of placebo treated patients ($P = 0.03$). There were no significant differences in the number of patients reporting adverse experiences between the sertraline and placebo groups in either of the studies. In the Pohl et al. [1998] study, 93% of sertraline-treated patients and 94% of placebo-treated patients reported adverse experiences. Five adverse experiences occurred significantly more often in the sertraline group than in the placebo group. The incidence rates of these experiences are presented in Table 4. In the Pollack et al. [1998] study, 94% of sertraline-treated patients and 88% of placebo-treated patients experienced adverse events, the difference between the groups not being statistically significant. Only two adverse events, tremor (8% vs. 0%, $P = 0.006$) and diarrhea (27% vs. 10%, $P = 0.006$), were experienced significantly more often by the sertraline-treated patients than by placebo-treated patients. The majority of the events were rated as mild or moderate in severity in both studies.

The results of the two flexible-dose studies parallel those of the fixed-dose studies, reflecting efficacy and safety of sertraline in the treatment of panic disorder.

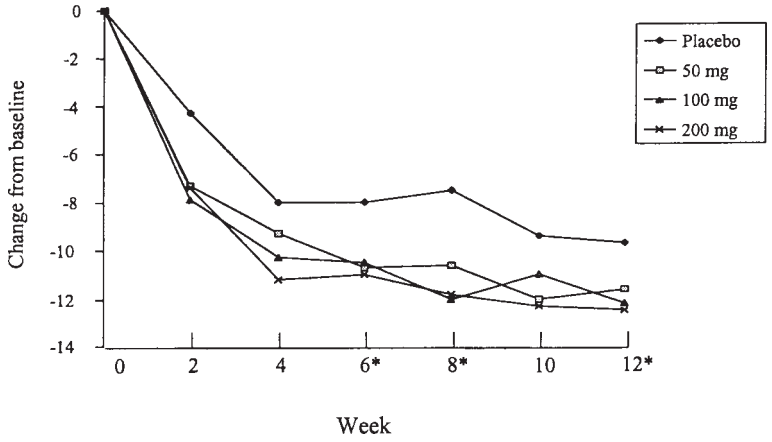

Figure 5. HAM-A scores in fixed-dose panic studies. Adapted from Gorman and Wolkow [1994]. *$P < 0.05$.

INITIAL DOSING

Table 5 lists the discontinuations in the two fixed-dose and the two flexible-dose studies during the first week. The fixed-dose studies began with the initial dose of 50 mg/day; 8.1% of the patients discontinued, with 5.9% due to jitteriness. In sharp contrast, only 1.8% of the sertraline patients in the flexible-dose studies (in which the starting dose was 25 mg per day) discontinued during the first week, with .005% due to jitteriness. These results demonstrate the desirability of an initial dose of 25 mg/day for patients with panic disorder. An initial increase in anxiety is more frequent with the higher dose and presents a considerable clinical problem, which can be avoided if started at a lower dose.

FULL REMISSION RESULTS

Full remission is defined as zero panic attacks, zero limited-symptom attacks, and a CGI-I score of 1 or 2, that is *very much* or *much* improved [Pollack et al., 1997]. This definition is much more rigorous than most commonly used outcome measures. One quarter of the sertraline patients achieved full remission, whereas only 10% on placebo did so ($P < 0.05$).

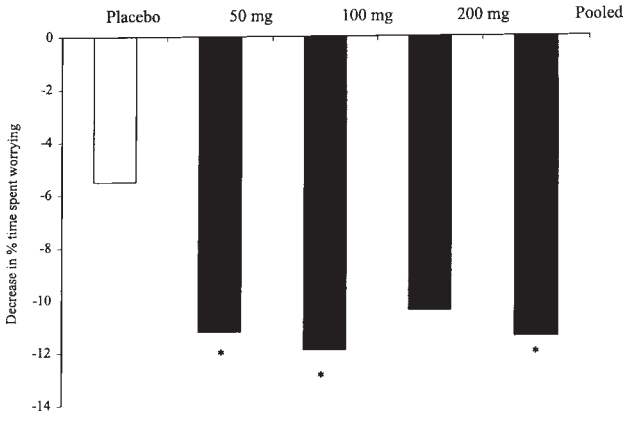

Figure 6. Pooled anticipatory anxiety for fixed-dose panic studies. Adapted from Gorman and Wolkow [1994]. *$P < .05$ vs. placebo.

QUALITY OF LIFE RESULTS

Patients with panic disorder suffer substantial and pervasive impairments in quality of life. Quality of life includes general happiness, economic status, quality of housing, physical health, and life satisfaction. Ability to function and actual functioning are also included.

Quality of life was assessed in all patients in the flexible-dose studies. Baseline assessments revealed impairments in a wide variety of areas including physical functioning, role limitation, pain, and general health. Sertraline treatment was associated with significantly better improvements in quality of life and functioning compared to placebo. Table 6 depicts the change in quality of life from baseline to endpoint. In the sertraline group there were statistically significant compared with placebo improvements in quality of life on mood, work, household activities, social and family relations, leisure time activities, ability to function in daily life, economic status, living/housing situation, ability to get around physically, overall sense of well-

TABLE 2. Adverse events reported by 10% or more of the sertraline-treated patients[†]

Adverse event	Sertraline (%)	Placebo (%)
Nausea	33	20
Headache	31	40
Insomnia	22	16
Diarrhea	15	9
Dry mouth	14*	2
Fatigue	13	4
Somnolence	11	7
Nervousness	11	7
Dyspepsia	11	11
Ejaculatory delay[a]	19*	0

[†] *Adapted from Londborg et al. [1998].*
[a] *13 of 67 males.*
*P < *0.05.*

TABLE 3. Baseline demographic and clinical data for the pooled flexible-dose panic studies*

	Sertraline (N = 168)	Placebo (N = 176)
Gender		
% Females	63.7	59.1
Race		
White	157 (93.5%)	155 (88.1%)
Black	5 (3%)	14 (8%)
Hispanic	5 (3%)	7 (4%)
Other	1 (0.67%)	0 (0%)
Panic with agoraphobia	111 (66.1%)	113 (64.2%)
Panic without agoraphobia	57 (33.9%)	63 (35.8%)
Age in years, mean (SD)	37.8 (12.2)	36.0 (9.8)
Duration of illness (years), mean (SD)	9.7 (10.1)	9.2 (10.1)
Age at onset, mean (SD)	28.1 (12.2)	26.8 (11.2)
HAM-D, mean (SD)	10.9 (4.1)	11.0 (3.5)
HAM-A, mean (SD)	22.46 (4.48)	22.84 (4.19)
CGI-Severity, mean (SD)	4.40 (0.73)	4.41 (0.7)
Mean dose (mg/day)		
Week 10	137.1	157.6
Endpoint	121.7	147.4
Number of panic attacks, mean (SD)	6.2 (7.7)	5.4 (5.9)
Number of limited-symptom attacks, mean (SD)	9.0 (0.2)	8.2 (7.9)
Percent time worrying, mean (SD)	29.9 (26.0)	29.2 (24.9)
Panic burden, mean (SD)	39.1 (54.8)	34.9 (43.1)
MC-PAS total score, mean (SD)	13.04 (4.15)	12.78 (3.88)
Q-LES-Q, mean (SD)	67.92 (12.79)	68.89 (11.25)

**None of the differences were statistically significant. Adapted from Rapaport et al. [1998].*

being, medication, and overall life satisfaction. The total score was significantly improved over placebo at the level of $P \leq .001$ [Rapaport et al., 1998].

Interesting results emerged when treatment groups were subdivided into treatment responders and nonresponders. The sertraline responders had a significantly better improvement in quality of life than the placebo responders. Among the nonresponders, there were no significant differences [Wolkow et al., 1997]. These results suggest that successful treatment for panic disorder with sertraline is more broad-based than is that attained by placebo.

SUMMARY

The results of these four large multicenter studies are consistent. In all doses, sertraline proved to be a safe and effective treatment for panic disorder. In addition, one quarter of the patients on sertraline attained full remission. A statistically significant and clinically observable improvement occurred as early as week 2 in treatment and was sustained on most measures. Of further importance is the positive effect of sertraline on overall quality of life, an issue that has received far too little attention and is of substantial importance to patients. The experience of the two flexible-dose studies leads to a recommendation of a starting dose of 25 mg per day of sertraline with an increase to 50 mg after the first week. Such a strategy will considerably reduce the risk of premature termination because of increased anxiety.

SERTRALINE IN THE TREATMENT OF OBSESSIVE-COMPULSIVE DISORDER

There have been eight controlled trials of sertraline in the treatment of OCD, including five placebo-controlled [Chouinard et al., 1990; Greist et al., 1995a,b; Kronig et al., 1999; Rasmussen et al., 1997], one clomipramine-controlled [Bisserbe et al., 1997], and two child and adolescent studies [Alderman et al., 1998; March et al., 1998].

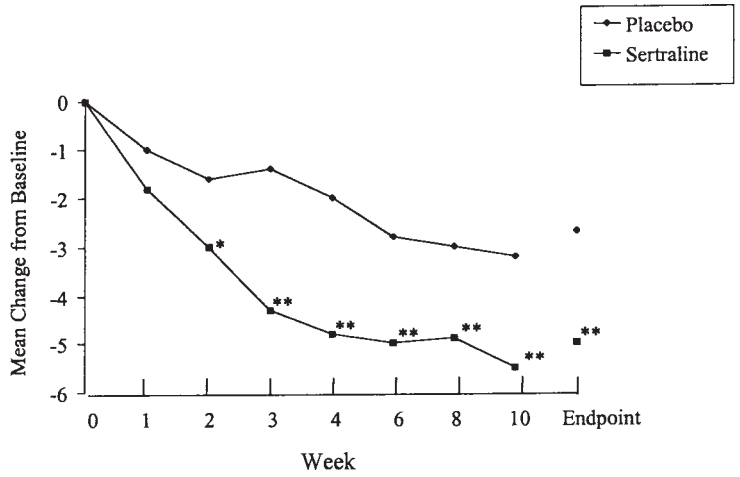

Figure 7. Reduction in panic attack frequency for the combined sertralline group and placebo, pooled from two fixed-dose studies [Pohl et al., 1998; Pollack et al., 1998]. Adapted from Pohl et al. [1997]. *P = 0.004. **P < 0.001.

TABLE 4. Adverse events experienced more frequently by patients with panic disorder taking sertraline than by those taking placebo*

Adverse event	Sertraline (N = 80)	Placebo (N = 88)	*P* (Fisher's exact test)
Nausea (%)	33	17	0.03
Diarrhea (%)	24	11	0.04
Dry mouth (%)	19	8	0.04
Ejaculation failure (%)[a]	11	0	0.001
Decreased libido (%)	10	0	0.002

**Adapted from Pohl et al. [1998].*
[a]Primary delayed ejaculation.

PLACEBO-CONTROLLED STUDIES

Fixed-dose studies. A fixed-dose, multicenter, placebo-controlled study was conducted to determine the efficacy, safety, and optimal effective dosages of sertraline in the treatment of OCD [Greist et al., 1995a]. All patients were 18 years of age or older, who met the DSM-III-R criteria for OCD. Inclusion criteria also required a score of 17 or less on the 24-item Hamilton Depression Scale and a score of 7 or more on the NIMH scale. Excluded were pregnant or nursing women, or women not practicing birth control, patients with organic mental disorders or organic brain syndromes, patients with psychiatric disorders other than OCD, patients with drug abuse (including alcohol) problems in the past 6 months, and patients with medical contradictions to a treatment with antidepressants.

Three hundred twenty-four patients were randomly assigned to treatment with one of the three dosages of sertraline (50, 100, or 200 mg/day) or placebo. Eighty-four participants were assigned to placebo, fifty to 50 mg sertraline daily, eighty-one to 100 mg/day, and eighty to 200 mg/day. The titration schedule was established so that 100 mg was obtained by day 5 and 200 mg by day 14 in the relevant groups.

The primary efficacy measures were the Y-BOCS (Yale-Brown Obsessive Compulsive Scale), NIMH-OC (National Institute of Mental Health Global Obsessive Compulsive Scale), and the CGI (Clinical Global Impression Scale). As Table 7 shows, statistical significance was achieved on all three main efficacy measures against placebo when the three sertraline dosage groups were pooled. Statistically significant differences between drug and placebo began after only 2 weeks of treatment. When the sertraline dosage groups were analyzed separately, it was found that sertraline patients exhibited significantly greater improvements at endpoint than placebo patients in all three main efficacy measures in the 50 mg and the 200 mg groups, while in the 100 mg group significance was obtained only on the NIMH scale (Fig. 8). For reasons that are not apparent, nearly twice as many patients in the 100 mg per day group dropped out because of adverse events than in any of the other groups

TABLE 5. Discontinuations in week 1 of panic disorder studies*

	Initial dose of 50 mg (Fixed-dose studies)		Initial dose of 25 mg (Flexible-dose studies)	
	Sertraline	Placebo	Sertraline	Placebo
Total discontinuations (%)	8.1	0	1.8	0.6
Discontinuations due to jitteriness (%)	5.9	0	0.005	0

**Data on file, Pfizer. Adapted from Wolkow [1996] and Pohl et al. [1997].*

TABLE 6. Changes from baseline in quality of life at endpoint*

	Sertraline (n = 167) Adjusted mean	Placebo (n = 175) Adjusted mean	*P*-value
Physical health	0.16	0.02	NS
Mood	0.68	0.16	<.001
Work	0.51	0.24	.011
Household activities	0.41	0.14	.005
Social relations	0.57	0.14	<.001
Family relations	0.48	0.02	<.001
Leisure time activities	0.53	0.21	.003
Ability to function in daily life	0.51	0.17	.002
Sexual drive and interest	0.20	0.16	NS
Economic status	0.36	0.13	.009
Living/housing situation	0.36	0.13	.008
Ability to get around physically	0.13	–0.06	.035
Ability to do work or hobbies	0.34	0.17	NS
Overall sense of well-being	0.56	0.10	<.001
Medication	0.67	0.11	<.001
Overall life satisfaction	0.60	0.11	<.001
Total	8.28	2.37	<.001

**Adapted from Rapaport et al. [1998].*

TABLE 7. Baseline and endpoint comparison of efficacy variables in patients with obsessive-compulsive disorder*

	Sertraline (N = 240)		Placebo (N = 84)	
Scale	Sertraline	Placebo	Sertraline	Placebo
Y-BOCS	23.8	18.2	23.4	20.0
NIMH	9.3	7.5	9.2	8.2
CGI-S	4.8	4.0	4.7	4.7

**Data from Greist et al. [1995a]. At baseline, none of the differences between the sertraline and placebo groups were statistically significant. At endpoint, the mean change from baseline to last visit the on Y-BOCS was significant at the* P = *0.006 level, on the NIMH at the* P = *0.002 level, and on the CGI-S at the 0.02 level.*

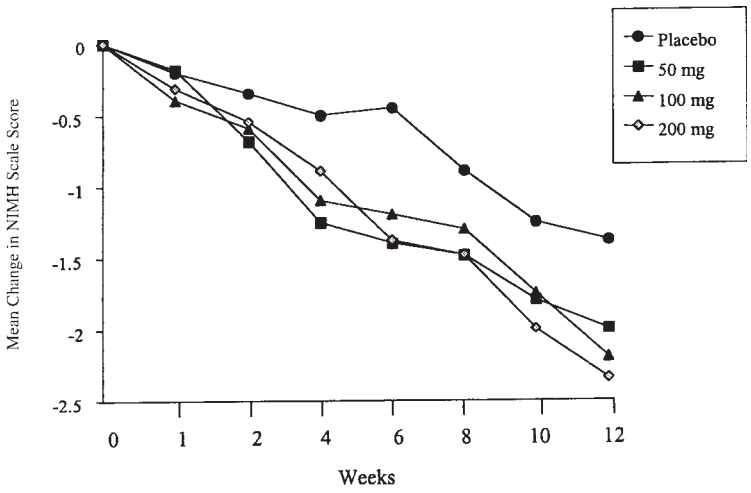

Figure 8. Change in the National Institute of Mental Health (NIMH) Global Obsessive-Compulsive Scale scores by visit. Adapted from Griest et al. [1995a].

(active medication and placebo), which probably accounted for the lack of statistical significance in this group. There were no statistically significant differences among the three sertraline dosage groups.

Consistent with other sertraline studies [Chouinard et al., 1990; Kronig et al., 1999], adverse experiences with significantly higher incidence in sertraline-treated patients than in placebo patients included diarrhea, insomnia, decreased libido, nausea, anorexia, ejaculation failure, and headaches. An analysis of adverse events incidence showed that the number of side effects increased with dose level of sertraline. However, most of the adverse experiences were characterized as mild or moderate.

The placebo response rate in this study was higher than was reported in similar trials [The Clomipramine Collaborative Study Group, 1991; Goodman et al., 1989]. This was partially due to the fact that the less severely ill patients in the placebo group showed a better treatment response compared to the more severely ill patients.

At 12 weeks in the Greist et al. [1995a] study, responders (including placebo responders) were offered an additional 40 weeks (i.e., up to a total of 1 year) of double-blind treatment [Greist et al., 1995b]. The same efficacy measures were utilized as in the acute study. Of the 324 patients who had been randomized in the acute study, 236 patients completed the 12 week treatment phase. Of these, 125 were considered responders; 118 patients participated in the extension phase, with 33 patients in the 50 mg per day, 25 in the 100 mg per day, 38 in the 200 mg per day, and 22 placebo patients.

An analysis of change from baseline at week 0 to the last visit within the 48-week period for all patients (n = 324) showed that sertraline-treated patients achieved significantly greater improvements on all major efficacy measures compared to placebo-treated patients. Significantly greater improvement appeared as early as week 2 in treatment and persisted throughout the full year. By the end of the 48-week period, the patients improved by 23% on the Y-BOCS in the pooled sertraline group and by 14.5% in the placebo group, a statistically significant difference ($P < .001$). The improvements were established in the first 12 weeks of treatment, and no significant differences were observed between week 12 and endpoint at week 48 in any of the individual dosage groups and placebo, or between combined dosage groups and placebo (see Fig. 9).

Of the 118 patients entering the extension phase, 75% of the sertraline patients and 68% of the placebo patients completed the entire 52-week study. There were no differences in discontinuation due to adverse experiences during this phase between the active medication groups and the placebo group. Rate of discontinuation due to adverse effects of treatment dropped from 10% during weeks 0–12 to 4% during weeks 12–52.

Fifty-nine patients who completed the 1-year double-blind study entered a subsequent 1-year open extension [Rasmussen et al., 1997]. Altogether, the study was extended 2 years. In the open label phase, all patients were prescribed sertraline with a starting dose of 50 mg per day and were titrated according to clinical response up to a maximum of 200 mg per day. At endpoint of this 1 year extension, there was an additional 3.6 decrease in mean Y-BOCS score to a mean of 8.5 ($P < .001$). Interestingly, those patients who had completed 1 year of treatment on placebo showed greater Y-BOCS reduction scores than those who had been on continuous sertraline treatment. This finding suggests that placebo responders will improve further if given active medication. Figure 10 shows the mean change in Y-BOCS score from week 0 in the double-blind study to week 104 in the open extension. Patients who were treated with sertraline for 2 years experienced a mean improvement of 15.6 points from the original

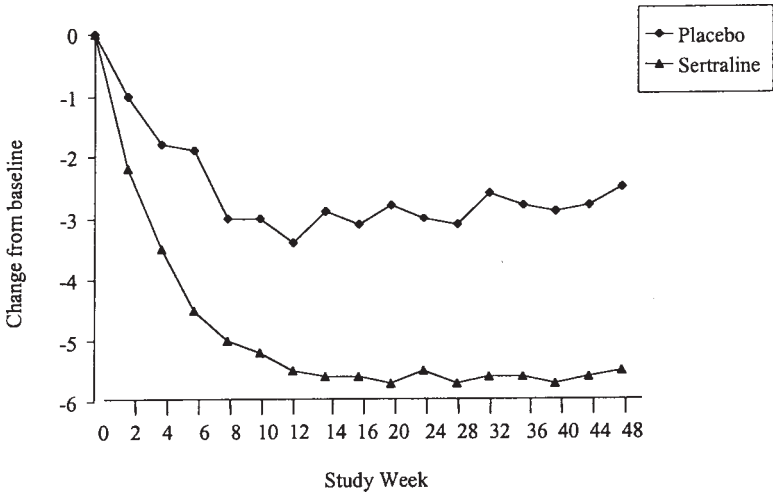

Figure 9. Change in Y-BOCS from baseline, last observation carried forward. Adapted from Griest et al. [1995b].

baseline of 23.4 on the Y-BOCS. They also experienced a mean improvement of 5.5 points on NIMH-GOCS and 2.1 points on CGI Severity scale.

Flexible-dose studies. The first of these studies was conducted with 87 patients receiving from 50 to 200 mg/day [Chouinard et al., 1990]. The study was 8 weeks in length, which was shorter in duration than subsequent trials. Nonetheless, at endpoint, significantly greater improvements were observed in sertraline-treated patients than in placebo recipients.

A 12-week, multicenter, flexible-dose, placebo-controlled study was conducted with 167 patients with OCD [Kronig et al., 1999]. All patients met the DSM-III-R criteria for OCD diagnosis, with a minimum duration of illness of 1 year. Other inclusion criteria required a score of 20 or more on the Y-BOCS, a score of 7 or more on the NIMH, and a score of 4 or worse on the CGI-Severity. Exclusion criteria were clinically significant depression, a primary diagnosis of a major affective disorder, dysthymia, a psychotic disorder, another anxiety disorder, an organic disorder, drug or alcohol abuse, or contraindication to antidepressant medication.

Eighty-six patients were randomly assigned to sertraline and eighty-one to placebo. All patients were titrated to 50 mg sertraline or placebo per day for the first 3 weeks of the study, with flexible titration up to 200 mg/day after that. At endpoint, the mean maximum dose of sertraline was 165 mg/day and 170 mg/day for placebo.

All three major measures of efficacy (Y-BOCS, NIMH, and the CGI severity and improvement subscales) showed significant improvements in sertraline-treated patients compared to placebo-treated patients starting at week 8 and through the end of the trial at week 12. It is notable that significant differences in sertraline group vs. placebo were observed as early as week 3 on the Y-BOCS and CGI Improvement Scores. No statistically significant differences were observed between the sertraline group and placebo in the incidence of blood pressure, heart rate or body weight abnormalities. Overall, sertraline was well tolerated.

These placebo-controlled studies clearly demonstrate the long-term safety, efficacy, and tolerability of sertraline in the treatment of OCD.

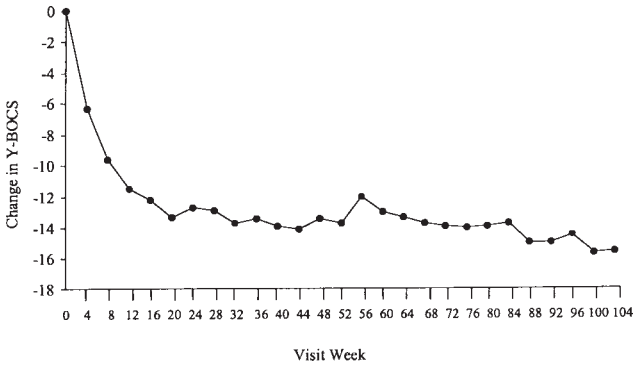

Figure 10. Decrease in Y-BOCS from baseline in 51 OCD patient who received 1 years of double-blind sertraline treatment followed by a 1-year open extension. Adapted from Rasmussen et al. [1997].

COMPARISON WITH CLOMIPRAMINE

A multicenter, double-blind, flexible-dose study of sertraline and clomipramine was conducted with DSM-III-R diagnosed OCD patients [Bisserbe et al., 1997]. Patients were required to have a score of 20 or more on the Y-BOCS, ≥ 7 on the NIMH Global OCD Scale, and ≥ 4 on the Clinical Global Impression Severity of Illness Scale, and ≤ 17 on the 17 item Hamilton Depression Scale; 86 patients were randomized to sertraline and 82 patients to clomipramine

once daily for 16 weeks. Initial dosage for each medication was 50 mg. Doses could be increased by 50 mg every 2 weeks after 4 weeks, up to a maximum of 200 mg per day on the basis of clinical judgment.

The final mean doses were 90 mg of clomipramine and 129 mg of sertraline. Treatment with both sertraline and clomipramine produced significant improvements in Y-BOCS, NIMH-OC, and CGI Severity scores. However, when the mean change from baseline to the final visit was analyzed, sertraline demonstrated significantly greater efficacy than clomipramine in the intent-to-treat patient group (Fig. 11). In the sertraline group mean baseline to final visit reductions were 50.8% for the Y-BOCS, 41.9% for the NIMH, and 37.7% for the CGIs. Mean clomipramine group reductions were 42.9% for the Y-BOCS, 33.8% for the NIMH, and 30% for the CGIs. The differences between the sertraline and clomipramine groups were statistically significant. The differences in efficacy were primarily due to the greater number of premature treatment terminations in the clomipramine group. Dropouts due to adverse events were substantially higher in the clomipramine group (26%) than in the sertraline group (11%).

The study of Bisserbe et al. [1997] demonstrated at least equal efficacy for sertraline compared with clomipramine and significantly greater tolerability than clomipramine in the treatment of OCD.

SERTRALINE IN PEDIATRIC OCD

Sertraline treatment was evaluated for pharmacokinetics, tolerability, and efficacy in a sample of children and adolescents with OCD, MDD, or both [Alderman et al., 1998]. Seventeen of the patients suffered from OCD. Two different dose schedules were evaluated: sertraline was started at either 25 mg/day and increased in 25 mg increments every 3–4 days, or at 50 mg/day and increased in 50 mg increments weekly. At the end of the study all OCD-diagnosed patients (n = 17) improved significantly on Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS), NIMH Global Obsessive Compulsive Scale, and the CGI Severity of Illness and Improvement scales. The results of the study demonstrated that sertraline was effective in the treatment of OCD in pediatric patients.

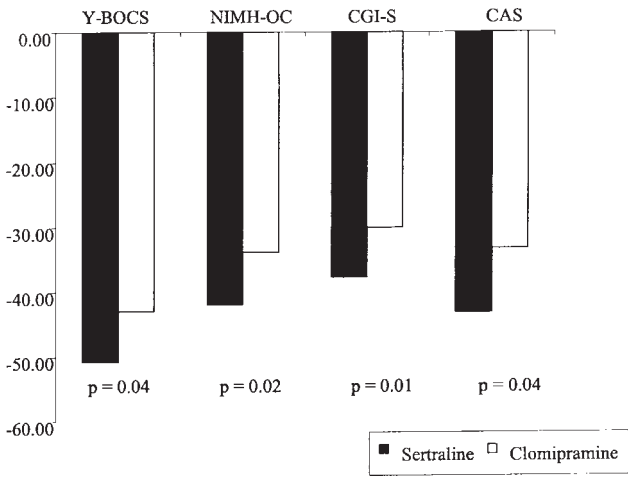

Figure 11. Change from baseline to last visit in Y-BOCS, NIMH-OC, CGI-S, and CAS scores (intent-to-treat patient sample). Adapted from Bisserbe et al. [1997].

The safety and efficacy of sertraline in the treatment of children and adolescents (age 6–17 years) with OCD was evaluated in a 12-week, multicenter, double-blind, flexible-dose, placebo-controlled trial [March et al., 1998]. The study began with 25 mg per day with an upward titration up to a maximum dose of 200 mg per day. One hundred seven 6- to 12-year-old patients, and eighty 13- to 17-year-old patients were randomized to sertraline (53 children, 39 adolescents) or placebo (54 children, 41 adolescents).

Intent-to-treat analyses showed that sertraline was associated with significantly greater improvement on the three efficacy measures compared with placebo. Figure 12 demonstrates week-by-week improvements from baseline on CY-BOCS. The differences between sertraline and placebo groups became significant at week 2 of treatment. Similar improvements were observed on NIMH-GOC Scale scores and NIMH-CGI Scale scores; 12% of the sertraline and 3.2% of the placebo-treated patients discontinued prematurely due to adverse events. There were no differences in the incidence of clinically significant vital signs, laboratory, or EKG abnormalities between the two groups. The study demonstrated that sertraline was a safe and efficacious treatment for OCD in children.

SUMMARY

These studies strongly demonstrate the efficacy and safety of sertraline in the treatment of OCD in children and adults. Sertraline is as effective as clomipramine and significantly more tolerable, and is substantially more effective than placebo. These data also demonstrate the effectiveness of sertraline at all doses, beginning with 50 mg. There is clinical lore that high doses of medication are necessary in the treatment of obsessive-compulsive disorder. These studies show that this is not true for sertraline. What is true is that response to treatment of obsessive-compulsive disorder is gradual, although indications (separation from placebo) are evident as early as week 2 or 3. Overall improvement is slow and unfortunately requires patience. In addition, psychotherapy, particularly cognitive behavioral therapy, is strongly recommended for the treatment of obsessive-compulsive disorder [Cottraux, 1993; Greist, 1996; Kobak et al., 1998].

SERTRALINE IN THE TREATMENT OF SOCIAL PHOBIA

The efficacy of sertraline in the treatment of social phobia was investigated in several small, open-label

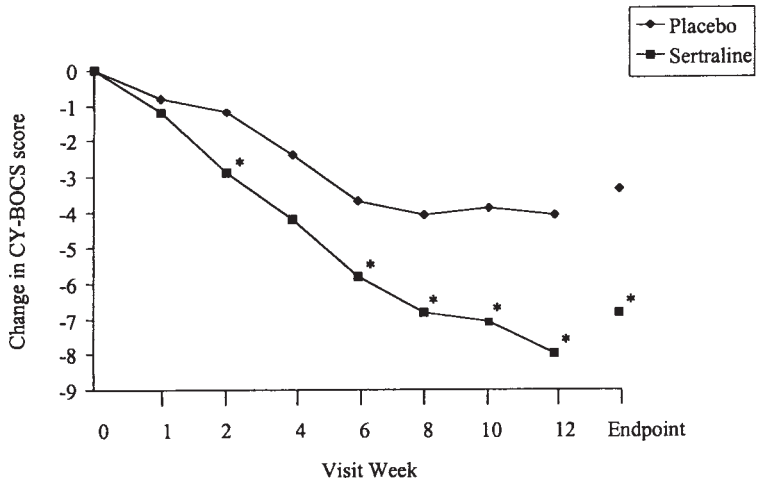

Figure 12. Mean change from baseline to endpoint in CY-BOCS (observed cases). Adapted from March et al. [1998]. *$P < 0.05$.

studies, one fixed-dose [Martins et al., 1994/1995], and three flexible-dose [Czepowicz et al., 1995; Munjack et al., 1994/1995; Van Ameringen et al., 1994]. Additionally, two placebo-controlled studies were conducted, both of which were flexible-dose design [Katzelnick et al., 1995; Van Ameringen et al., 1999].

OPEN-LABEL STUDIES

Martins et al. [1994/1995] administered sertraline (50 mg/day) in a 6-week, fixed-dose, open-label study with 19 patients. The primary efficacy measure was the Davidson Brief Social Phobia Rating Scale (DBSPS). Significant reductions from baseline in DBSPS scores were observed at weeks 4 and 6 of treatment. No serious adverse effects were associated with sertraline administration during the study.

Additionally, three open-label, flexible-dose studies of sertraline in the treatment of social phobia were conducted. Table 8 presents a summary of these studies. Van Ameringen et al. [1994] assessed the efficacy of sertraline in a 12-week, flexible-dose, open-label study with 20 patients. Sertraline was initially administered at 50 mg per day and increased every 2 weeks according to clinical response up to a maximum of 200 mg/day; 16 patients were considered responders with either markedly or moderately improved CGI (Clinical Global Impression) scores. Mean time to achieve clinical improvement was 8.5 weeks.

Czepowicz et al. [1995] reported treating 11 patients assessed to be at least moderately ill on the CGI scale. All patients were treated for at least 4 weeks with flexible dosages of sertraline starting at 50 mg/day up to a maximum of 200 mg/day, dependent on clinical response; 63% of patients were either markedly or moderately improved on CGI scale scores.

Seven patients were treated with flexible doses of sertraline (50 mg/day for 4 weeks, increasing up to 200 mg/day according to clinical response) for 12 weeks [Munjack et al., 1994/1995]. Five patients responded substantially to medication. There were no significant side effects.

PLACEBO-CONTROLLED STUDIES

Safety and efficacy of sertraline was further evaluated in two placebo-controlled studies. The first of these studies was a single-site, placebo-controlled trial of 12 outpatients who met DSM-III-R criteria for social phobia [Katzelnick et al., 1995]. Average duration of illness was 22 years. Mean baseline score on the Liebowitz Social Anxiety Scale indicated moderately severe social phobia. Patients had no co-morbid mood disorders and were relatively free from depressive symptoms. The Liebowitz Social Anxiety Scale was the primary outcome measure.

In the first 10 weeks of treatment six patients were randomized to sertraline with an initial dose of 50 mg per day and flexible dosing of up to a maximum of 200 mg per day based on clinical judgment, and six patients to placebo. After the initial 10 weeks of treatment, medication was terminated for 2 weeks. The subjects were then

TABLE 8. The efficacy of sertraline in social phobia: a summary of three open-label, flexible-dose studies

Study	Duration of study	Sertraline mean daily dose (mg)	Evaluable patients	Responders (%)
Van Ameringen et al. [1994]	12 weeks	148	20	80
Czepowicz et al. [1995]	4 weeks	110	11	63
Munjack et al. [1994/1995]	12 weeks	170	7	71

crossed over to the other treatment group for an additional 10 weeks. Patients on sertraline had statistically significant improvements in scores on the Liebowitz Social Anxiety Scale, while placebo-treated patients failed to demonstrate similar improvements; 50% of patients were considered moderately or markedly improved on the social anxiety scale of the Liebowitz Social Phobic Disorders Rating Form, compared to one patient who was rated as markedly improved on placebo. Measures of quality of life showed significant improvement on sertraline but not on placebo.

Sertraline was well tolerated by the majority of the patients. Only one patient discontinued due to adverse experiences. One other patient discontinued due to the lack of efficacy on placebo after having experienced substantial clinical improvement on sertraline. Four patients received dose reductions because of adverse side effects, the most common being headache, insomnia, anxiety, and fatigue. The mean dose of sertraline achieved was 133.5 mg per day.

While this study is small, the results, especially considering the crossover design, suggest that sertraline is a safe and effective treatment for social phobia. Clearly additional studies are necessary to evaluate this more comprehensively.

A 20-week, double-blind, placebo-controlled flexible-dose study of sertraline was conducted at ten Canadian centers [Van Ameringen et al., 1999]; 204 patients with DSM-III diagnosis of primary generalized social phobia were randomized, 135 to sertraline and 69 to placebo. The patients were started on 50 mg of medication daily, with flexible titration of up to 200 mg/daily. Mean duration of treatment was 140 days, with mean daily doses of sertraline and placebo being 146.7 and 161.1 mg, respectively. There were no statistical differences between sertraline and placebo groups at baseline.

At endpoint, sertraline-treated patients were significantly improved compared to placebo on all primary efficacy measures. On the CGI-I scale, significantly more sertraline-treated patients achieved a score of 1 (very much improved) or 2 (much improved) than placebo treated patients (53% vs. 29%, respectively, $P < 0.001$). Sertraline-treated patients were significantly improved compared to placebo on the three subscales (fear, avoidance, and physiologic) of BSPS (Physician-Rated Duke Brief Social Phobia Scale). Overall, BSPS scores were reduced by 34.8% in the sertraline group and by 16.7% in the placebo group ($P < 0.005$). Marks Fear Questionnaire (MFQ) social phobia subscale scores were reduced by 32.4% in the sertraline group and by 8.6% in the placebo group ($P < 0.005$).

Adverse events experienced by sertraline-treated patients were those generally expected with SSRI treatment. Adverse events experienced by significantly more patients in the sertraline group than in the placebo group were nausea ($P = 0.007$), insomnia ($P = 0.016$), dyspepsia ($P = 0.002$), flu syndrome ($P = 0.018$), delayed ejaculation ($P = 0.003$), and sweating ($P = 0.013$); 21% of sertraline-treated patients and 22% of placebo-treated patients discontinued the study. Significantly more sertraline-treated patients discontinued due to adverse events than placebo-treated patients (12% vs. 1%, respectively, $P < 0.003$).

SUMMARY

Overall, the one large multicenter trial of sertraline for the treatment of social phobia [Van Ameringen et al., 1999] and the smaller single-site trial [Katzelnick et al., 1995] show that sertraline is an effective and safe treatment for generalized social phobia.

SERTRALINE EFFECTIVENESS IN POST-TRAUMATIC STRESS DISORDER

The efficacy of sertraline for the treatment of PTSD was investigated in three small uncontrolled clinical trials [Brady et al., 1995; Kline et al., 1994; Rothbaum et al., 1996] and later in two large, multicenter, parallel-group, flexible-dose studies [Baker et al., 1998; Davidson et al., 1997b]. All five studies reported positive results.

OPEN-LABEL STUDIES

Sertraline in the treatment of rape victims. The efficacy of sertraline in the treatment of rape victims diagnosed with PTSD was evaluated in a small open 12-week study of seven patients who averaged 16 years post assault [Rothbaum et al., 1996]. Sertraline (average dose of 105 mg/day) reduced PTSD and related symptoms on average by 53% on the Clinician-Administered PTSD Scale (CAPS).

Sertraline in the treatment of veterans with PTSD and depression. Sertraline was evaluated in an open trial with 19 Vietnam veterans [Kline et al., 1994]. The participants were moderately to severely depressed combat veterans who failed to respond to other antidepressants. Sertraline was administered for a minimum of 3 months, with an average daily dose of 98.5 mg. Twelve of the nineteen participants (63%) were found to improve on measures of PTSD, depression, anxiety, and global functioning.

Dow and Kline [1997] also reported on their clinical experience with a variety of antidepressants (including two SSRIs, six TCAs, one MAOI, trazodone, bupropion, and lithium) in the treatment of PTSD in veterans. They found that sertraline alone accounted for 47% of all successes. Overall, success rates for sertraline was .35, and it was in the group of medications with the highest success rate.

Sertraline in the treatment of comorbid PTSD and alcohol dependence. Six patients with comorbid PTSD and alcohol dependence completed 12 weeks of open treatment with sertraline, mean dose of 110.4 mg/day [Brady et al., 1995]. Significant decreases were found in all three symptom clusters of patients (avoidant/intrusion/arousal) of the Modified PTSD Symptoms Scale (MPSS) and in Hamilton Rating Scale for

Depression (HRS-D) scores. Additionally, days of abstinence increased and average number of drinks decreased in the follow-up period. Although the study demonstrates an overall effectiveness of sertraline in the treatment of PTSD co-morbid with alcoholism, interpretation is limited by the small sample size and absence of a control group.

PLACEBO-CONTROLLED STUDIES

A double-blind placebo controlled study of sertraline in the treatment of PTSD was conducted by Davidson et al. [1997b]. The study was multi-center (12 sites), 12 weeks in duration with adult outpatients who met DSM-III-R diagnosis of PTSD and having a score of 50 or more on part 2 of the CAPS. Traumatic events leading to PTSD for most patients were physical or sexual assault (60.5% of the patients), serious accident, fire, or injury (12%), seeing someone hurt or die (11%), and being in a war or combat (5%). The average duration of illness was 12 years. Patients with a primary DSM-III-R diagnosis of any mood, anxiety, or psychotic disorder were excluded.

Two hundred eight patients were randomized, 100 to sertraline and 108 to placebo. Of these, 98 sertraline-treated and 104 placebo-treated patients were evaluable for the intent-to-treat analyses. Patients began with 25 mg of sertraline for 1 week, with a flexible dose titration of up to 200 mg according to their clinical response and tolerability. The mean daily doses of sertraline at the end of week 12 and endpoint were 146 and 125 mg per day, respectively.

Patients on the sertraline group were statistically significantly improved compared with placebo on all four efficacy measures (Table 9). Sertraline treatment was associated with statistically significant improvements in CAPS-2 Avoidance/Numbing symptom cluster ratings, as well as in the ratings for occupational functioning, overall improvements, and severity of illness, compared to placebo. Figure 13 shows improvements in DTS (Davidson Self-rating Trauma Scale) ratings in sertraline-treated patients compared to placebo from baseline to endpoint at week 12. Sertraline was well tolerated with no difference in discontinuations for adverse events between the placebo and sertraline treated groups. The adverse events that occurred significantly more frequently in sertraline treated patients were insomnia, diarrhea, nausea, fatigue, and anorexia. The study suggests that sertraline is an effective treatment for PTSD and is well tolerated.

Another double-blind, placebo-controlled, flexible-dose study of sertraline was conducted at 14 US centers with DSM-III-R diagnosed outpatients with PTSD [Baker et al., 1998]. All patients had a score of 50 or more on Part 2 of CAPS at baseline and a minimum duration of illness of 6 months. Traumatic events leading to PTSD were physical/sexual assault (61.5%), seeing someone hurt or die (8.6%), serious accident/fire/injury (8.6%), being in a war or combat (5.9%), natural disaster (0.5%), or other event (15%). Patients with a primary diagnosis of any mood, anxiety, or psychotic disorder were excluded, as were pregnant and breast-feeding women, and women not practicing birth control, patients on psychotropic medication, and nonresponders to previous treatment with sertraline.

TABLE 9. Mean (SD) change in primary efficacy ratings at endpoint in the intent-to-treat patient sample*

Scale	Sertraline mean (SD)	Placebo mean (SD)	*P*-value
CAPS-2 total	–33.0 (2.41)	–26.2 (2.33)	0.043
IES Total	–19.2 (1.53)	–14.1 (1.48)	0.018
CGI-S	–1.3 (0.12)	–1.0 (0.12)	0.037
CGI-I	2.2 (1.16)	2.8 (1.21)	0.001

**CAPS-2 total, IES total, and CGI-S means are adjusted for treatment, site, treatment-by-site, and baseline values. CGI-I means are adjusted for treatment, site, and treatment-by-site. Adapted from Davidson et al. [1997b].*

Sertraline was administered at an initial dose of 25 mg/day for 1 week, followed by flexible titration between 50 and 200 mg/day based on clinical response and tolerability. Primary efficacy rating scales included Clinician Administered PTSD Scale Part 2 (CAPS-2), Impact of Event Scale (IES), and Clinical Global Impression of Severity (CGI-S) and Improvement (CGI-I) scales. Secondary efficacy rating scales included Davidson Self-Rating Trauma Scale (DTS), Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), and 24-Item Hamilton Depression Scale (HAM-D). As Table 10 shows, sertraline treatment led to statistically significant improvements on three of the four primary measures of efficacy and on all secondary measures of efficacy. Sertraline treatment pro-

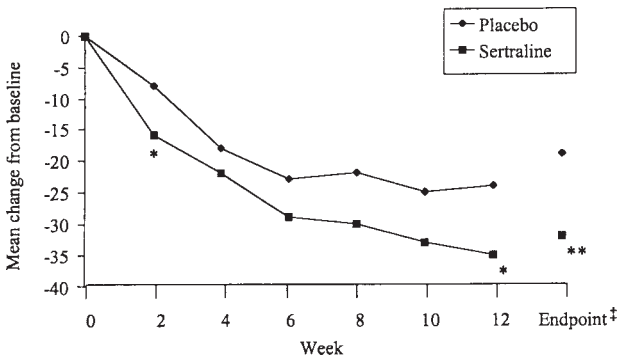

Figure 13. Change in mean Davidson Self-rating Trauma Scale (DTS) ratings at each visit in PTSD study. Adapted from Davidson et al. [1997b]. *$P < 0.05$ for sertraline versus placebo. **$P < 0.01$ for sertraline versus placebo.

TABLE 10. Mean (± SD) change in primary efficacy ratings at endpoint (intent-to-treat patient sample)*

Scale	Sertraline	Placebo	*P*-value
Primary			
CAPS-2 total severity	–33.0 (±2.82)	–23.2 (±2.86)	.016
IES total	–16.2 (±1.60)	–12.1 (±1.63)	NS
CGI-S	–1.2 (±0.13)	–0.8 (±0.13)	.012
CGI-I	–2.5 (±0.13)	3.0 (±0.14)	.016
Secondary			
DTS	–28.1 (±2.77)	–16.1 (±2.85)	.003
HAM-D	–8.6 (±1.29)	–5.0 (±1.19)	.042
Q-LES-Q	11.7 (±2.08)	3.3 (±1.90)	.004

**CAPS-2 total, IES total, and CGI-S, DTS, HAM-D, and Q-LES-Q means are adjusted for treatment, site, treatment-by-site, and baseline values. CGI-I means are adjusted for treatment, site, and treatment-by-site. Adapted from Baker et al. [1998].*

duced statistically significant improvements in the Avoidance/Numbing and Hyperarousal symptom clusters of CAPS-2 and was also associated with statistically significant improvements in all CAPS-2 global ratings (severity, improvement, occupational, and social). Sertraline treatment led to statistically significant improvements in quality of life compared to placebo as demonstrated by the Q-LES-Q total score (total score in the sertraline group was 11.7 (± 2.08) and 3.3 (± 1.9) for placebo, $P = 0.004$).

SUMMARY

The three uncontrolled studies [Brady et al., 1995; Kline et al., 1994; Rothbaum et al., 1996] initially demonstrated sertraline's efficacy in the treatment of post-traumatic stress disorder, which was later confirmed by the two multicenter placebo-controlled studies [Baker et al., 1998; Davidson et al., 1997b]. Patients receiving sertraline improved significantly over placebo, as demonstrated by both an alleviation in PTSD symptoms, as well as in quality of life improvements observed in the sertraline-treated group. Sertraline was also well tolerated.

DISCUSSION

The efficacy and safety of sertraline in the treatment of panic disorder and in the treatment of obsessive-compulsive disorder have been demonstrated in multiple placebo-controlled, double-blind trials. Follow-ups extending to 2 years have demonstrated its sustained effect. In both disorders, the best results were obtained when starting sertraline at 25 mg per day and titrating upward. Fixed-dose studies have demonstrated the effectiveness of sertraline in several doses at or above 50 mg (i.e., 50 mg, 100 mg, and 200 mg per day).

Two placebo-controlled studies have been conducted with sertraline in the treatment of social phobia. Both trials had encouraging results in terms of safety and efficacy. There have been two multicenter, placebo-controlled studies of sertraline in the treatment of post-traumatic stress disorder. Significant improvement in a variety of relevant measures support sertraline's efficacy and safety in PTSD.

How does the performance of sertraline in the treatment of these anxiety disorders compare with other pharmacological options? A brief discussion of the issue follows.

PANIC DISORDER

Several classes of medications, including TCAs, MAOIs, benzodiazepines, and SSRIs, have demonstrated utility in the treatment of panic disorder. Overall there is little difference among these classes of drugs in terms of efficacy, as assessed by improvements in panic attacks (see Table 11). With the exception of one fluoxetine study [Michelson et al., 1998], all report over a 50% reduction in the total number of panic attacks from baseline to endpoint. These differences are all significantly better than placebo. In general there is significant improvement for all agents in other efficacy measures, such as percent panic-free at endpoint, reduction in anticipatory anxiety, reduction in general anxiety, and reduction in phobic avoidance.

The agents can be distinguished in other ways, including speed of onset, efficacy in comorbid disorders, and in safety and tolerability profiles (see Table 12).

TABLE 11. Percentage of patients free from panic attacks at endpoint, and number of panic attacks at baseline and endpoint in acute studies

Agent	Patients achieving panic-free status (%)	Number of panic attacks		
		Baseline	Endpoint	Percent improvement
TCAs				
Clomipramine[b]	37	16.0	3.9	76
Imipramine[c]	44	4.3	1.3	70
MAOIs				
Brofaromine[d]	NA[a]	8.5	2.8	58
Benzodiazepines				
Alprazolam[c]	57	3.6	0.9	75
Clonazepam[e]	62	4.2	1.5	64
SSRIs				
Citalopram[f]	43–58	NA	NA	NA
Fluvoxamine[g]	61–73	3.8	0.9	76
Fluoxetine[h]	17–23	8.9	4.8	46
Paroxetine[i]	84	9.6	1.3	86
Sertraline[j]	57	6.4	1.5	77

[a]NA, not available.
[b]Lecrubier et al. [1997a], and Lecrubier et al. [1997b].
[c]Schweizer et al. [1993].
[d]Bakish et al. [1993].
[e]Moroz and Rosenbaum [1999].
[f]Wade et al. [1997].
[g]Hoehn-Saric et al. [1993].
[h]Michelson et al. [1998].
[i]Ballenger et al. [1998].
[j]Londborg et al. [1998] and Pohl et al. [1998].

TABLE 12. Comparison of the effective therapeutic classes by agent, based on published data[†]

Area of comparison	TCAs	MAOIs	BZDs	SSRIs
Efficacy in panic disorder	***	***	***	***
Efficacy in comorbid conditions				
Depression	***	***	*	***
Other anxiety disorders	**	**	***	***
Safety				
In overdose	*	*	***	***
Lack of dependence	***	***		***
Ease of withdrawal	***	***	*	***

[†]***, *well established;* **, *moderately established;* *, *not established;* blank, *not meeting criteria.*

The benzodiazepines clearly have a more rapid onset of action (less than 2 weeks) than any of the other agents, but have concerns about withdrawal and dependence, and lack of efficacy in co-morbid conditions. TCAs and MAOIs have broad-spectrum efficacy but have considerable safety and tolerability concerns. The SSRIs have emerged as the first line agents in recent years because of the combination of efficacy in panic disorder and comorbid disorders, as well as attractive safety and tolerability profiles.

Among the SSRIs, there are no apparent differences in efficacy but some in dosing and in side effect profiles. Sertraline has shown efficacy at all tested dose levels (50, 100, and 200 mg/day), whereas paroxetine, fluoxetine, fluvoxamine, and citalopram have not. Paroxetine has shown efficacy significantly superior to placebo at doses of 40 mg/day and above [Ballenger et al., 1998]. Citalopram is effective in the doses of 20, 30, 40, and 60 mg/day. The higher doses of citalopram (40–60 mg/day) were less effective than 20–30 mg/day [Wade et al., 1997]. Fluoxetine produced significant reductions in the total number of panic attacks compared to placebo in the 10 mg/day dose but not in 20 mg/day dose. The 20 mg/day dose of fluoxetine did produce significant improvements in anxiety, phobia, and depression [Michelson et al., 1998]. Sertraline appears to have a more rapid onset of action (in 2–3 weeks) compared to some of the other SSRIs. Significant improvements were observed at week 4 of treatment with paroxetine [Ballenger et al., 1998], fluoxetine [Michelson et al., 1998], and citalopram [Wade et al., 1997], while fluvoxamine became significantly superior to placebo at week 3 [Hoehn-Saric et al., 1993]. Unfortunately, no head-to-head trials of the SSRIs have been conducted to test this issue directly.

OBSESSIVE-COMPULSIVE DISORDER

Several classes of medication including MAOIs, benzodiazepines, TCAs, and SSRIs have been studied in the treatment of OCD. Average reductions in Y-BOCS are presented in Table 13. Although some studies show the efficacy of MAOIs and benzodiazepines in the treatment of OCD, it is generally acknowledged that serotonergic agents (clomipramine and the SSRIs) are the most effective treatment options. One MAOI, phenelzine, has been found to be as effective as clomipramine in one small trial lacking a placebo control [Vallejo et al., 1992]. However, in a study comparing phenelzine with fluoxetine and placebo, fluoxetine was found to be more effective than both phenelzine and placebo [Jenike et al., 1997]. Only one study reported the efficacy of a benzodiazepine, clonazepam, but the drop-out rate was the highest for clonazepam compared to two other active agents, clomipramine and clonidine, and diphenhydramine, which acted as control [Hewlett et al., 1992].

Among the TCAs, clomipramine is the most effective drug in the treatment of OCD. For example, in a comparative trial clomipramine was found to be superior to desipramine in significantly reducing obsessive-compulsive symptoms [Leonard et al., 1989]. Additionally, the SSRIs were also more effective than TCAs other than clomipramine in reducing OCD symptomatology. In a trial of fluvoxamine vs. desipramine, fluvoxamine was significantly more effective than desipramine in reducing the severity of OCD symptoms as measured by the Y-BOCS, as well as in the global response rate [Goodman et al., 1990].

TABLE 13. Average reduction in Y-BOCS in OCD trials

Agent	Reduction in Y-BOCS (%)
TCAs	
Clomipramine[b]	40[a]
Desipramine[c]	1
MAOIs	
Phenelzine[d]	9
Benzodiazepines	
Clonazepam[e]	2.22[a]
SSRIs	
Fluoxetine[d,f]	
20 mg/day	20[a]
40 mg/day	22[a]
60 m g/day	27[a]
Fluvoxamine[g]	
249 mg/day (mean dose)	20[a]
Paroxetine[h]	
20 mg/day	17
40 mg/day	25[a]
60 mg/day	29[a]
Sertraline[i]	
50 mg/day	24[a]
100 mg/day	19
200 mg/day	28[a]

[a]*Significantly different from placebo.*
[b]*Clomipramine Collaborative Study Group [1991].*
[c]*Goodman et al. [1990].*
[d]*Jenike et al. [1997].*
[e]*Hewlett et la. [1992].*
[f]*Tollefson et al. [1994].*
[g]*Rasmussen et al. [1999].*
[b]*Wheadon et al. [1993].*
[i]*Greist et al. [1995a,b].*

TABLE 14. Double-blind comparisons of selective serotonin reuptake inhibitors (SSRIs) and clomipramine (CMI) in obsessive-compulsive disorder*

Study	Duration (weeks)	N	Treatment groups	Efficacy results	Side-effects profile
Pigott et al. [1990]	26	11	CMI (≤250 mg) vs. FLX (≤80 mg)	FLX = CMI	CMI > FLX
Freeman et al. [1994]	10	66	CMI (≤250 mg) vs. FLV (≤250 mg)	FLV = CMI	FLV = CMI
Zohar et al. [1996]	12	406	CMI (≤250 mg) vs. PAR (≤60 mg)	PAR = CMI	CMI > PAR
Bisserbe et al. [1997]	16	168	CMI (≤200 mg) vs. SER (≤200 mg)	SER > CMI	CMI > SER

**CMI, clomipramine; FLX, fluoxetine; FLV, fluvoxamine; PAR, paroxetine; SER, sertraline.*

The agents most effective in the treatment of OCD are the SSRIs and clomipramine. Direct comparisons of these agents are summarized in Table 14. As Table 14 demonstrates, studies directly comparing clomipramine with several SSRIs (fluoxetine, fluvoxamine, and paroxetin) showed equal efficacy of these medications in the treatment of OCD, except for the study by Bisserbe et al. [1997], which showed sertraline to be more effective than clomipramine in the treatment of OCD.

To decide on the preferred treatment, a consideration of side effects and tolerability becomes important because it affects the ability of patients to continue treatment and consequently the chances of recovery. At present, clomipramine and the SSRIs show equal efficacy; however, the SSRIs show better tolerability and therefore should be considered first-choice medication in the treatment of OCD.

SOCIAL PHOBIA

Several drug classes, including beta-blockers, benzodiazepines, MAOIs, and SSRIs have been studied in the treatment of social phobia in large placebo-controlled trials. The response rates to active medications compared to placebo are presented in Table 15.

TABLE 15. Response rate to active medication compared with placebo in acute placebo-controlled trials of patients with social phobia*

	Response rate (%)	
Classes of medication	Active agent	Placebo
Beta-blockers		
Atenolol	30	23
MAOIs		
Phenelzine	63–70[a]	20
Brofaromine	50[a]	19
Benzodiazepines		
Alprazolam	38[a]	20
Clonazepam	78[a]	20
SSRIs		
Paroxetine	45–65[a]	23–32
Sertraline	50[a]	10
Fluvoxamine	46[a]	7

**Data adapted from Davidson [1998] and Pollack and Gould [1996].*
[a]Significantly different from placebo.

Although β-blockers have shown efficacy in an open trial in both generalized and performance types of social phobia [Gorman et al., 1985], a subsequent placebo-controlled trial with atenolol and phenelzine demonstrated that atenolol was less effective than phenelzine and not significantly different from placebo [Liebowitz et al., 1992]. Placebo-controlled studies with monoamine oxidase inhibitors (phenelzine and brofaromine) have demonstrated them to be significantly more effective than placebo. However, the clinical use of phenelzine is compromised by the need for a restricted diet and the risk of hypertensive crisis. The efficacy of benzodiazepines (alprazolam and clonazepam) has been established in two placebo-controlled studies [Davidson et al., 1993; Gelernter et al., 1991]. Although the response to clonazepam appears to be more robust than the response to alprazolam, both drugs were significantly more effective than placebo. Among the main advantages of benzodiazepine treatment are efficacy and rapid onset of improvements. The disadvantages include adverse side effects, difficulties with discontinuation, and risk of abuse of benzodiazepines, particularly by patients with comorbid alcohol abuse problems [Pollack, 1996].

Among the SSRIs, paroxetine, sertraline, and fluvoxamine have been shown to be superior to placebo in controlled trials. The most studied drug so far has been paroxetine. Although there have been no head-to-head comparisons between paroxetine and sertraline in the treatment of social phobia, controlled studies of both drugs produce comparable efficacy and safety profiles (see Table 16).

TABLE 16. Rating scale scores on CGI-I and LSAS for paroxetine and sertraline studies[†]

Scale	Paroxetine	Placebo	Sertraline	Placebo
% responders on CGI-I	55*	24	53*	29
% change in LSAS[a]	39*	17	32*	10

[†]Data from Katzelnick et al. [1995], Stein et al. [1998], and van Ameringen et al. [1999].
[a]LSAS, Liebowitz Social Anxiety Score.
**P < 0.001.*

The main advantages of the SSRIs in the treatment of social phobia over other classes of medication are efficacy, favorable side effects profile, lack of dietary restrictions, and usefulness in comorbid depression and other anxiety disorders. Based on these results, therefore, SSRIs as a class may be considered as first-line treatment for social phobia.

POST-TRAUMATIC STRESS DISORDER

Three classes of medication are effective in the treatment of posttraumatic stress disorder: TCAs, MAOIs, and SSRIs [Davidson, 1997]. Response rates are presented in Table 17. Of the MAOIs and TCAs, amitriptyline and brofaromine were not found significantly different from placebo. Both studies were conducted with combat veterans.

Among the SSRIs, sertraline, fluoxetine, fluvoxamine, and paroxetine were found effective. In two placebo-controlled studies of fluoxetine, it was found to be more effective than placebo in the treatment of civilian patients but not in combat veterans (with more severe symptomatology than the civilian population) [Davidson, 1997; van der Kolk et al., 1994]. These results are consistent with research in tricyclic antidepressants, which also shows an inverse relationship between the severity of symptoms and response to medication [Davidson, 1997]. An open trial of paroxetine demonstrated its efficacy in chronic PTSD in civilian population [Marshall et al., 1998]. The efficacy of fluvoxamine has been demonstrated in an open trial with combat veterans [Marmar et al., 1996]. The present review demonstrated the efficacy and tolerability of sertraline in two placebo-controlled trials with civilians, as well as in an open trial with combat veterans. The efficacy of SSRIs, as well as their favorable side-effects profile, makes them first-line treatment for PTSD.

TABLE 17. Response rate to MAOIs, TCAs, and SSRIs compared with placebo in acute placebo-controlled trials of patients with PTSD

		Response rate (%)[a]	
Classes of medication	Population	Active agent	Placebo
MAOIs			
Phenelzine[c]	Combat	68[b]	28
Brofaromine[d]	Civilian	52[b]	29
Brofaromine[e]	Combat	60	40
TCAs			
Amitriptyline[f]	Combat	50	17
Imipramine[c]	Combat	65[b]	28
SSRIs			
Fluoxetine[g]	Civilian	85[b]	62
Fluoxetine[g]	Combat	17	33
Sertraline[h]	Civilian	56[b]	35

[a] *Response rates indicate improvements on CGI-I.*
[b] *Active agent significantly superior to placebo.*
[c] *Kosten et al. [1991].*
[d] *Katz et al. [1995].*
[e] *Baker et al. [1995].*
[f] *Davidson et al. [1990].*
[g] *Davidson et al. 1997a].*
[h] *Baker et al. [1998].*

Acknowledgments. The author received an honorarium from Pfizer Pharmaceuticals, Inc. to prepare this manuscript. The author would like to thank Kimberly M. Berry, M.A., and Lana A. Vornik, M.Sc., for their invaluable assistance in the preparation of the manuscript.

REFERENCES

Alderman J, Wolkow R, Chung M, Johnston HF. 1998. Sertraline treatment of children and adolescents with obsessive-compulsive disorder or depression: pharmacokinetics, tolerability, and efficacy. J Am Acad Child Adolesc Psychiatry 37:386–394.

American Psychiatric Association. 1980. Diagnostic and statistical manual of mental disorders, 3rd edition. Washington, DC: American Psychiatric Association.

American Psychiatric Association. 1987. Diagnostic and statistical manual of mental disorders, 3rd edition, revised. Washington, DC: American Psychiatric Association.

Baker D, Brady K, Goldstein S, Farfel G. 1998. Double-blind flexible dose multicenter study of sertraline and placebo in outpatients with post-traumatic stress disorder. [Poster]. Presented at 11th European College of Neuropsychopharmacology Congress, Paris, France; October 31–November 4, 1998.

Baker DG, Diamond BI, Gillette G, Hamner M, Katzelnick D, Keller T, Mellman TA, Pontius E, Rosenthal M, Tucker P, et al. 1995. A double-blind, randomized, placebo-controlled, multi-center study of brofaromine in the treatment of post-traumatic stress disorder. Psychopharmacology 122:386–389.

Bakish D, Saxena R, Bowen R, D'Souza J. 1993. Reversible monoamine oxidase-A inhibitors in panic disorder. Clin Neuropharmacol 16:S77–S82.

Ballenger JC, Wheadon DE, Steiner M, Bushnell W, Gergel IP. 1998. Double-blind, fixed-dose, placebo-controlled study of paroxetine in the treatment of panic disorder. Am J Psychiatry 155:36–42.

Bisserbe JC, Lane RM, Flament MF, and the Franco-Belgian OCD study group. 1997. A double-blind comparison of sertraline and clomipramine in outpatients with obsessive-compulsive disorder. Eur Psychiatry 12:82–93.

Brady KT, Sonne SC, Roberts JM. 1995. Sertraline treatment of comorbid post-traumatic stress disorder and alcohol dependence. J Clin Psychiatry 56:502–505.

Couinard G, Goodman W, Greist J, Jenike M, Rasmussen S, White K, Hackett E, Gaffney M, Bick PA. 1990. Results of a double-blind placebo controlled trial of a new serotonin uptake inhibitor, sertraline, in the treatment of obsessive-compulsive disorder. Psychopharmacol Bull 26:279–284.

Clomipramine Collaborative Study Group. 1991. Clomipramine in the treatment of patients with obsessive-compulsive disorder. Arch Gen Psychiatry 43:730–738.

Cottraux J, Mollard E, Bouvard M, Marks I. 1993. Exposure therapy, fluvoxamine, or combination treatment in obsessive-compulsive disorder: one-year followup. Psychiatry Res 49:63–75.

Czepowicz VD, Johnson MR, Lydiard RB, Emmanuel NP, Ware MR, Mintzer OB, Walsh MD, Ballenger JC. 1995. Sertraline in social phobia. J Clin Psychopharmacol 15:372–373.

Davidson JRT. 1997. Biological therapies for posttraumatic stress disorder: an overview. J Clin Psychiatry 58:29–32.

Davidson JRT. 1998. Pharmacotherapy of social anxiety disorder. J Clin Psychiatry 59:47–51.

Davidson J, Kudler H, Smith R, Mahorney SL, Lipper S, Hammett E, Saunders WB, Cavenar JO Jr. 1990. Treatment of posttraumatic stress disorder with amitriptyline and placebo. Arch Gen Psychiatry 47:259–266.

Davidson JRT, Malik ML, Sutherland SN. 1997a. Response characteristics to antidepressants and placebo in post-traumatic stress disorder. Int Clin Psychopharmacol 12:291–296.

Davidson JR, Potts N, Richichi E, Krishnan R, Ford SM, Smith R, Wilson WH. 1993. Treatment of social phobia with clonazepam and placebo. J Clin Psychopharmacol 13:423–428.

Davidson J, van der Kolk B, Brady K, Rothbaum B, Sikes C, Farfel G. 1997b. Double-blind comparison of sertraline and placebo in patients with post-traumatic stress disorder. [Poster]. Presented at 10th European College of Neuropsychopharmacology Congress, Vienna, Austria; September 13–17, 1997.

Dow B, Kline N. 1997. Antidepressant treatment of posttraumatic stress disorder and major depression in veterans. Ann Clin Psychiatry 9:1–5.

Freeman CPL, Trimble MR, Deakin JFW, Stokes TM, Ashford JJ. 1994. Fluvoxamine or clomipramine in the treatment of obsessive-compulsive disorder: a multicenter, randomised, double-blind, parallel group comparison. J Clin Psychiatry 55:301–305.

Gelernter CS, Uhde TW, Cimbolic P, Arnkoff DB, Vittone BJ, Tancer ME, Bartko JJ. 1991. Cognitive-behavioral and pharmacological treatments of social phobia. A controlled study. Arch Gen Psychiatry 48:938–945.

Goodman WK, Price LH, Delgado PL, Palumbo J, Krystal JH, Nagy LM, Rasmussen SA, Heninger BG, Charney DS. 1990. Specificity of serotonin reuptake inhibitors in the treatment of obsessive-compulsive disorder: comparison of fluvoxamine and desipramine. Arch Gen Psychiatry 47:577–585.

Goodman WK, Price LH, Rasmussen SA, Delgado PL, Heninger GR, Charney D. 1989. Efficacy of fluvoxamine in obsessive-compulsive disorder: a double-blind comparison with placebo. Arch Gen Psychiatry 46:36–44.

Gorman JM, Liebowitz MR, Fyer AJ, Campeas R, Klein DF. 1985. Treatment of social phobia with atenolol. J Clin Psychopharmacol 5:298–301.

Gorman J, Wolkow R. 1994. Sertraline as a treatment for panic disorder. Presented at the XIXth CINP, Washington, D.C.; June 27–July 1, 1994.

Greist JH. 1996. New developments in behaviour therapy for obsessive-compulsive disorder. Int Clin Psychopharmacol 11:63–73.

Greist J, Chouinard G, DuBoff E, Halaris A, Kim SW, Koran L, Liebowitz M, Lydiard RB, Rasmussen S, White K, Sikes C. 1995a. Double-blind parallel comparison of three dosages of sertraline and placebo in outpatients with obsessive-compulsive disorder. Arch Gen Psychiatry 52:289–295.

Greist JH, Jefferson JW, Kobak KA, Chouinard G, DuBoff E, Halaris A, Kim SW, Koran L, Liebowitz MR, Lydiard B, McElroy S, Mendels J, Rasmussen S, White K, Flicker C. 1995b. A 1-year double-blind placebo-controlled fixed dose study of sertraline in the treatment of obsessive-compulsive disorder. Int Clin Psychopharmacol 10:57–65.

Hewlett WA, Vinogradov S, Agras WS. 1992. Clomipramine, clonazepam, and clonidine treatment of obsessive-compulsive disorder. J Clin Psychopharmacol 12:420–430.

Hirschfeld RMA. 1993. Panic anxiety and its treatment. Report of the World Psychiatric Association Presidential Education Program Task Force. Klerman GL, Hirschfeld RNA, Weissman MM, Pelicier Y, Ballenger JC, Costa e Silva JA, Judd LL, Keller MB, editors. Washington, D.C.: American Psychiatric Press, Inc.

Hoehn-Saric R, McLeod DR, Hipley PA. 1993. Effect of fluvoxamine on panic disorder. J Clin Psychopharmacol 13:321–326.

Jenike MA, Baer L, Minichiello WE, Rauch SL, Buttolph ML. 1997. Placebo-controlled trial of fluoxetine and phenelzine for obsessive-compulsive disorder. Am J Psychiatry 154:1261–1264.

Katz RJ, Lott MH, Arbus P, Crocq L, Herlobsen P, Lingjaerde O, Lopez G, Loughrey GC, MacFarlane DJ, McIvor R, et al. 1995. Pharmacotherapy of post-traumatic stress disorder with a novel psychotropic. Anxiety 1:169–174.

Katzelnick DJ, Kobak KA, Greist JH, Jefferson JW, Mantle JM, Serlin RC. 1995. Sertraline for social phobia: a double blind, placebo-controlled crossover study. Am J Psychiatry 152:1368–1371.

Kline NA, Dow BM, Brown SA, Matloff JL. 1994. Sertraline efficacy in depressed combat veterans with post-traumatic stress disorder (letter). Am J Psychiatry 151:621.

Kobak KA, Greist JH, Jefferson JW, Katzelnick DJ, Henk HJ. 1998. Behavioral versus pharmacological treatments of obsessive compulsive disorder: a meta-analysis. Psychopharmacol 136:205–216.

Kosten TR, Frank JB, Dan E, et al. 1991. Pharmacotherapy for posttraumatic stress disorder using phenelzine or imipramine. J Nerv Ment Dis 179:336–370.

Kronig MH, Apter J, Asnis G, Bystritsky A, Curtis G, Ferguson J, Landbloom R, Munjack D, Riesenberg R, Robinson D, Roy-Byrne P, Phillips K, Du Pont IJ. 1999. Placebo-controlled, multicenter study of sertraline treatment for obsessive-compulsive disorder. J Clin Psychopharmacol 19:172–176.

Lecrubier Y, Bakker A, Dunbar G, Judge R. 1997a. A comparison of paroxetine, clomipramine and placebo in the treatment of panic disorder: collaborative Paroxetine Panic Study Investigators. Acta Psychiatrica Scandinavica 95:145–152.

Lecrubier Y, Judge R, the Collaborative Paroxetine Panic Study Investigators. 1997b. Long-term evaluation of paroxetine, clomipramine and placebo in panic disorder. Acta Psychiatrica Scandinavica 95:153–160.

Leonard HL, Swedo SE, Rapoport JL, Koby EV, Lenane MC, Chesow DL, Hamburger SD. 1989. Treatment of obsessive-compulsive disorder with clomipramine and desipramine in children and adolescents: a double-blind crossover comparison. Arch Gen Psychiatry 46:1088–1092.

Liebowitz MR, Schneier F, Campeas R, Hollander E, Hatterer J, Fyer A, Gorman J, Papp L, Davies S, Gully R, et al. 1992. Phenelzine vs atenolol in social phobia: a placebo-controlled comparison. Arch Gen Psychiatry 49:290–300.

Londborg PD, Wolkow R, Smith WT, DuBoff E, England D, Ferguson J, Rosenthal M, Weise C. 1998. Sertraline in the treatment of panic disorder: a multisite, double-blind, placebo-controlled fixed dose investigation. Br J Psychiatry 173:54–60.

March JS, Bierderman J, Wolkow R, Safferman A, Mardekian J, Cook EH, Cutler NR, Dominguez R, Ferguson J, Muller B, Riesenberg R, Rosenthal M, Sallee FR, Wagner KD. 1998. Sertraline in children and adolescents with obsessive-compulsive disorder: a multicenter randomized controlled trial. JAMA 280: 1752–1756.

Marmar CR, Schoenfeld F, Weiss DS, Metzler T, Zatzick D, Wu R, Smiga S, Tecott L, Neylan T. 1996. Open trial of fluvoxamine treatment for combat-related posttraumatic stress disorder. J Clin Psychiatry 57:66–70.

Marshall RD, Schneier FR, Fallon BA, Knight CB, Abbate LA, Goetz D, Campeas R, Liebowitz MR. 1998. An open trial of paroxetine in patients with noncombat-related, chronic posttraumatic stress disorder. J Clin Psychopharmacol 18:10–18.

Martins EA, Pigott TA, Bernstein SE, Doyle BB, Sunderland B, Smolka VM, Dubbert B. 1994/1995. Sertraline in the treatment of patients with social phobia. Anxiety 1:291–297.

Michelson D, Lydiard RB, Pollack MH, Tamura RN, Hoog SL, Tepner

R, Demitrack MA, Tollefson GD, the Fluoxetine Panic Disorder Study Group. 1998. Outcome assessment and clinical improvement in panic disorder: evidence from a randomized controlled trial of fluoxetine and placebo. Am J Psychiatry 155:1570–1577.

Moroz G, Rosenbaum JF. 1999. Efficacy, safety, and gradual discontinuation of clonazepam in panic disorder: a placebo-controlled, multicenter study using optimized dosages. J Clin Psychiatry 60:604–612.

Munjack DJ, Flowers C, Eagan TV. 1994/1995. Sertraline in social phobia. Anxiety 1:196–198.

Pigott TA, Pato MT, Bernstein SE, et al. 1990. Controlled comparison of clomipramine and fluoxetine in the treatment of obsessive-compulsive disorder. Arch Gen Psychiatry 47:926–932.

Pohl RB, Clary CM, Wolkow R. 1997. Sertraline treatment of panic disorder: combined results from two placebo-controlled trials. [Poster]. Presented at Vith World Congress of Biological Psychiatry, Nice, France; June 22–27, 1997.

Pohl RB, Wolkow RM, Clary CM. 1998. Sertraline in the treatment of panic disorder: a double-blind multicenter trial. Am J Psychiatry 155:1189–1195.

Pollack MH. 1996. Social anxiety disorder: Designing a pharmacologic treatment strategy. J Clin Psychiatry 60:20–26.

Pollack MH, Gould RA. 1996. The pharmacotherapy of social phobia. Int Clin Psychopharmacol 11:71–75.

Pollack MH, Otto MW, Worthington JJ, Manfro GG, Wolkow R. 1998. Sertraline in the treatment of panic disorder: a flexible-dose multicenter trial. Arch Gen Psychiatry 55:1010–1016.

Pollack MH, Wolkow R, Clary C. 1997. Multi-dimensional outcome and quality of life in panic disorder: the effects of sertraline treatment. [Poster]. Presented at APA, San Diego, CA; May, 1997.

Rapaport MH, Wolkow RM, Clary CM. 1998. Methodologies and outcomes from the sertraline multicenter flexible-dose trials. Psychopharmacol Bull 34:183–189.

Rasmussen SA, Goodman W, Greist J, et al. 1999. Fluvoxamine in the treatment of OCD: a multicenter double-blind, placebo-controlled study in outpatients. Am J Psychiatry. In press.

Rasmussen S, Hackett E, DuBoff E, Greist J, Halaris A, Koran LM, Liebowitz M, Lydiard RB, McElroy S, Mendels J, O'Connor K. 1997. A 2-year study of sertraline in the treatment of obsessive-compulsive disorder. Int Clin Psychopharmacol 12:309–316.

Rothbaum BO, Ninan PT, Thomas L. 1996. Sertraline in the treatment of rape victims with post-traumatic stress disorder. J Traum Stress 9:865–871.

Schweizer E, Rickels K, Weiss S, Zovodnick S. 1993. Maintenance drug treatment of panic disorder. I. Results of a prospective placebo-controlled comparison of alprazolam and imipramine. Arch Gen Psychiatry 50:51–60.

Stein MB, Liebowitz MR, Lydiard RB, Pitts CD, Bushnell W, Gergel I. 1998. paroxetine treatment of generalized social phobia (social anxiety disorder): a randomized controlled trial. JAMA 280:708–713.

Tollefson GD, Birkett M, Koran L, Genduso L. 1994. Continuation treatment of OCD: double-blind and open-label experience with fluoxetine. J Clin Psychiatry 55:69–76.

Vallejo J, Olivares J, Marcos T, Bulbena A, Menchon JM. 1992. Clomipramine versus phenelzine in obsessive-compulsive disorder: a controlled clinical trial. Br J Psychiatry 161:665–670.

Van Ameringen MA, Lane RM, Walker JR, Bowen RC, Chokka PR, Goldner E, Johnston DC, Lavallie Y-L, Nandy S, Pecknold JC, Hadrava V, Swinson R. 1999. Sertraline treatment of social phobia: a 20-week, double-blind, placebo-controlled study. [Poster]. Presented at APA, Washington DC; May 15–20, 1999.

Van Ameringen M, Mancini C, Streiner D. 1994. Sertraline in social phobia. J Affect Dis 31:141–145.

Van der Kolk BA, Dreyfuss D, Michaels M, Shera D, Berkowitz R, Fisler R, Saxe G. 1994. Fluoxetine in posttraumatic stress disorder. J Clin Psychiatry 55:517–522.

Wade AG, Lepola U, Koponen HJ, Pedersen V, Pedersen T. 1997. The effect of citalopram in panic disorder. Br J Psychiatry 170:549–553.

Wheadon DE, Bushell WD, Steiner M. 1993. A fixed-dose comparison of 20, 40, or 60 mg paroxetine or placebo in the treatment of obsessive-compulsive disorder. Presented at the 32nd annual meeting of the American College of Neuropsychopharmacology; December 13–17; Honolulu, Hawaii.

Wolkow RM. 1996. A double-blind, parallel, 12-week comparison of sertraline and placebo in patients with panic disorder [Poster]. presented at Xth World Congress of Psychiatry, Madrid, Spain; August 23–28, 1996.

Wolkow RM, Judd LL, Rapaport MH, Clary CM. 1997. Quality of life differences in sertraline and placebo responsive panic disorder patients. [Poster]. Presented at ACNP, Hawaii, 1997.

Zohar J, Judge R, OCD Paroxetine Study Investigators. 1996. Paroxetine versus clomipramine in the treatment of obsessive-compulsive disorder. Br J Psychiatry 169:468–474.