

# Sertraline in the Treatment of Panic Disorder

## A Flexible-Dose Multicenter Trial

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**Background:** The serotonin selective reuptake inhibitors are increasingly being used for the treatment of panic disorder. We examined the efficacy and safety of the serotonin selective reuptake inhibitor sertraline hydrochloride in patients with panic disorder.

**Methods:** One hundred seventy-six nondepressed outpatients with panic disorder, with or without agoraphobia, from 10 sites followed identical protocols that used a flexible-dose design. After 2 weeks of single-blind placebo, patients were randomly assigned to 10 weeks of double-blind, flexible-dose treatment with either sertraline hydrochloride (50-200 mg/d) or placebo.

**Results:** Sertraline-treated patients exhibited significantly greater improvement ( $P = .01$ ) at end point than did patients treated with placebo for the primary out-

come variable, panic attack frequency. Significant differences between groups were also evident for clinician and patient assessments of improvement as measured by the Clinical Global Impression Improvement ( $P = .01$ ) and Severity ( $P = .009$ ) Scales, Panic Disorder Severity Scale ratings ( $P = .03$ ), high end-state function assessment ( $P = .03$ ), Patient Global Evaluation rating ( $P = .01$ ), and quality of life scores ( $P = .003$ ). Adverse events, generally characterized as either mild or moderate, were not significantly different in overall incidence between the sertraline and placebo groups.

**Conclusion:** Results support the safety and efficacy of sertraline for the short-term treatment of patients with panic disorder.

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**P**ANIC DISORDER is a common illness with a typically chronic course and substantial attendant morbidity and disability.<sup>1-4</sup> A number of psychopharmacological agents, as well as cognitive-behavioral therapies, have demonstrated efficacy for the treatment of patients with panic disorder.<sup>5,6</sup> Increasing clinical experience, as well as a consensus of expert clinical researchers,<sup>7</sup> has encouraged the use of serotonin selective reuptake inhibitors (SSRIs) as first-line treatments for panic disorder because of a generally favorable side-effect profile and broad spectrum of efficacy.<sup>8</sup> To date, this clinical opinion has been supported by results of double-blind trials demonstrating the effectiveness of paroxetine<sup>9,10</sup> and fluvoxamine maleate<sup>11-13</sup> for panic disorder. In addition, results from a multicenter, fixed-dose study demonstrated a significant reduction in panic frequency for sertraline hydrochloride relative to placebo.<sup>14</sup> Sertraline is a potent SSRI that has established efficacy in the treatment of depression,<sup>15</sup> obsessive-compulsive disorder,<sup>16</sup> and the prevention of depression relapse.<sup>17</sup> The lack of major anticholinergic,  $\alpha$ -adrenergic, or cardio-

toxic effects and the absence of marked induction of physiological dependence represents a potential therapeutic advantage for SSRIs such as sertraline<sup>18</sup> over the tricyclic antidepressants or benzodiazepines used to treat panic disorder.

This study assessed the effectiveness and safety of sertraline in a 10-center, random-assignment, flexible-dose, placebo-controlled study in patients with panic disorder, with and without agoraphobia. With 176 patients, this is one of the largest clinical trials with an SSRI for the treatment of panic disorder reported to date.<sup>19</sup> As a flexible-dose study, with a dosing range for sertraline hydrochloride of 50 to 200 mg/d and an initial 25-mg/d titration dose during the first week of treatment, the results provide useful information regarding the efficacy of doses typically used in clinical practice.

## RESULTS

### PATIENT DISPOSITION

One hundred seventy-eight patients were randomized and dispensed double-blind medication. Two patients treated with

## PATIENTS AND METHODS

### PATIENTS

Participants were men and women, 18 years of age and older, who met criteria for panic disorder,<sup>20</sup> with or without agoraphobia, as determined by the Structured Clinical Interview for *DSM-III-R*.<sup>21</sup> Patients needed to have a minimum of 4 panic attacks, at least 1 of which was unanticipated, during the 4 weeks before initiation of the placebo washout, and between 3 and 100 panic attacks during the 2-week placebo washout before double-blind treatment. At the end of the washout (ie, at baseline), patients needed to score at least 18 on the Hamilton Anxiety Scale and be free of substantial depression (ie, score of  $\leq 17$  on the 21-item Hamilton Depression Rating Scale).<sup>22</sup> Patients entering the study had to have a negative result for a urinary screen for benzodiazepines and a negative result for a serum screen for alprazolam (or the presence of only trace amounts of these substances) on days 1 and 8 of the placebo washout.

Women of childbearing potential who were not practicing an effective method of birth control, and pregnant or nursing women, were excluded from participation, as were patients who met *DSM-III-R* criteria for major depression, bipolar disorder, obsessive-compulsive disorder, schizophrenia, delusional or psychotic disorders, organic brain syndrome, or substance abuse or dependence (during the last 6 months). Patients with comorbid dysthymic, personality, or other anxiety disorders could be included if the panic disorder was judged to be the principal diagnosis. Other reasons for exclusion included unstable medical conditions; hypersensitivity or other medical contradictions to antidepressant therapy; participation in an investigational drug study within 1 month of study entry; previous treatment with sertraline; concomitant treatment with any psychotropic drug (with the exception of chloral hydrate for sleep) or psychotherapy during the study; administration of a monoamine oxidase inhibitor or any regular neuroleptic, antidepressant, or nonbenzodiazepine anxiolytic medication within 2 weeks, regular benzodiazepine therapy within 4 weeks, or fluoxetine within 5 weeks of the first administration of double-blind study medication; or the presence of substantial suicidal risk. Each site obtained study approval from its institutional review board and written informed consent from all patients.

### DRUG ADMINISTRATION

Patients were randomly assigned by computer-generated numbers to 10 weeks of double-blind treatment with either sertraline or placebo. Study capsules contained either 25 mg (for doses of 25-50 mg/d) or 50 mg (for doses of 100-200 mg/d) of sertraline hydrochloride or placebo. Patients were instructed to take the study capsules once daily with the evening meal; those randomized to sertraline hydrochloride received 25 mg/d for 1 week followed, in the absence of dose-limiting adverse experiences, by at least 1 week of 50 mg/d. Patients who failed to respond satisfactorily to the 50-mg/d capsules could have their dosage titrated in weekly 50-mg increments to a maximum dose of 200 mg/d. Patients responding well at lower doses continued taking that dose until the end of the study. Dosage could be decreased because of limiting adverse experiences.

### EFFICACY ASSESSMENTS

Patients were seen for evaluation at the end of weeks 1, 2, 3, 4, 6, 8, and 10. The principal efficacy instrument in this study was the Sheehan Panic and Anticipatory Anxiety Scale,<sup>23</sup> from which the principal efficacy measure—number of panic attacks—was obtained. Throughout the study, participants maintained a daily diary, from which the weekly Panic and Anticipatory Anxiety Scale scores, including frequency of panic and limited-symptom panic attacks and duration of anticipatory anxiety, were derived after investigator review. Baseline Panic and Anticipatory Anxiety Scale scores were based on the 2-week placebo washout period. Anticipatory anxiety was recorded as the percentage of time in each 24 hours spent worrying about having a panic attack.

Clinicians rated global severity by means of the Clinical Global Impression Severity Scale (CGI-S, ranging from 1 [not at all ill] to 7 [extremely ill]). Global change from the baseline assessment was rated by means of the Clinical Global Impression Improvement Scale (CGI-I, ranging from 1 [very much improved] to 7 [very much worse]).<sup>24</sup>

The frequency of full panic attacks, along with the CGI-S score,<sup>24</sup> were examined both as continuous variables and as markers of panic-free status and high end-state functioning. Consistent with previous studies,<sup>25,26</sup> *panic-free status* at end point was defined as 2 weeks with no full panic attacks, and *high end-state functioning* was defined as a CGI-S score of 1 or 2 occurring at end point in conjunction with panic-free status.

Clinicians also rated the overall severity of the panic disorder by means of the 7-item Panic Disorder Severity Scale,<sup>27</sup> assessing frequency of attacks, degree of distress during attacks, anticipatory anxiety, phobic avoidance of situations, phobic avoidance of sensations, impairment or interference with work functioning, and impairment or interference with social functioning. Severity of anxiety was assessed with the 14-item Hamilton Anxiety Rating Scale.<sup>28</sup>

Participants provided Patient Global Evaluation ratings of improvement at every visit after baseline (ranging from 1 [very much improved] to 7 [very much worse]). Patients also completed the Quality of Life Enjoyment and Satisfaction Questionnaire,<sup>29</sup> rating 16 aspects of quality of life, including physical health, mood, activities of daily living, and overall life satisfaction. The quality of life scale was completed by the patient at baseline and at the end of week 10 of the double-blind period (or at study discontinuation).

### SAFETY ASSESSMENTS

A physical examination was performed on day 1 of washout and at the end of week 10 of the double-blind period (or at study discontinuation). Blood pressure and heart rate were measured at every visit. A 12-lead electrocardiogram and laboratory tests (ie, hematology, chemistry, urinalysis, pregnancy test) were obtained on day 1 of the placebo washout and at the end of weeks 2 and 10. In addition, triiodothyronine uptake ratio and thyroxine level were measured on day 1 of the placebo washout. A serum alprazolam screen and a urine drug screen (for benzodiazepines and drugs of abuse) were done at days 1 and 8 of placebo washout and at the end of weeks 2 and 10 of the double-blind period.

Continued on next page

Observed or volunteered adverse experiences were recorded (including onset, duration, severity, cause in the investigator's judgment, action taken, and outcome). Adverse experiences were characterized by the *World Health Organization Dictionary—Preferred Terminology*.<sup>30</sup> All adverse experiences were tabulated regardless of their assessed severity or relationship to study drug. Multiple episodes of the same complaint were counted only once, although rated at the greatest level of severity.

#### DATA ANALYSIS

Patients who took at least 1 dose of double-blind medication and completed any additional assessment were included in the analysis for safety and efficacy. Differences between treatment groups (placebo or sertraline) and site were first examined at baseline by means of analysis of variance with terms for site and treatment for continuous variables, and Cochran-Mantel-Haenszel tests stratified by site for categorical variables. Subsequently, outcome was examined for all continuous variables by means of a 2 (treatment group) × 10 (treatment site) factorial analysis of variance. Differences between treatment groups in categorical measures were examined with Cochran-Mantel-Haenszel and Fisher exact tests. Primary analyses examined the last outcome for all patients entered in the trial (end-point analysis; using the last available observation forward) and all patients who completed 10 weeks of treatment (completer analysis). Secondary analyses examined the time course of changes by examining differences between treatment groups at weeks 1, 2, 3, 4, 6, 8, and 10. With the exception of the CGI-I and Patient Global Evaluation improvement measures, the dependent variable submitted for all analyses was the change in outcome from baseline. In addition, because the ratio to baseline Panic and Anticipatory Anxiety Scale variables—number of full or limited-symptom panic attacks and percentage of time in anticipatory anxiety—were not normally distributed, these variables were log-transformed before analysis. Before logarithmic analyses of the data, the value 0.5 (to eliminate 0 values) was added to each baseline and end-point count for numbers of panic attacks and limited symptom attacks; similarly, 1% was added to each baseline and end-point measurement of percentage of anticipatory anxiety.

Mean changes in values from laboratory tests from day 1 of the placebo washout period to the end of week 10 (or patient discontinuation) in the sertraline and placebo groups were compared with the Wilcoxon rank sum test.

All *P* values are 2 tailed, and statistical significance was set at the 5% level (*P* < .05).

placebo did not return for follow-up; these patients were excluded from further analyses. Hence, a total of 176 patients, 88 treated with placebo and 88 treated with sertraline, were available for analyses of safety and efficacy data. No significant differences between group

**Table 1. Baseline Comparison of Demographic and Severity Variables\***

	Sertraline Hydrochloride (n = 88)	Placebo (n = 88)	<i>P</i>
Sex, No. (%) F	61 (69)	54 (61)	.25
Race, No. (%) white	85 (97)	80 (91)	.09
Agoraphobia, No. (%)	62 (70)	61 (69)	.89
Age, y	37.8 ± 11.6	34.9 ± 9.6	.06
Duration of illness, y	9.9 ± 10.2	9.9 ± 11.8	.99
HAM-D score	10.9 ± 4.0	10.6 ± 3.1	.59
CGI-S	4.5 ± 0.8	4.5 ± 0.8	.91
Panic Disorder Severity Scale	13.1 ± 3.7	12.8 ± 4.0	.68
HAM-A score	22.7 ± 4.8	22.9 ± 4.0	.73
Quality of life score	46.8 ± 8.8	48.7 ± 8.2	.17
	(n = 87)	(n = 86)	
Panic attacks, No.	3.5 (2.2-6.2)	3.2 (2.0-6.1)	.99
Limited-symptom panic attacks, No.	6.4 (3.1-11.0)	6.5 (2.3-12.8)	.87
Anticipatory anxiety, % of time worrying	24.4 (9.5-46.3)	21.2 (6.2-40.6)	.25

\*Data are presented as number (percentage), mean ± SD, or median (interquartile range, 25th-75th percentile). HAM-D indicates Hamilton Depression Rating Scale; CGI-S, Clinical Global Impression Severity Scale; and HAM-A, Hamilton Anxiety Rating Scale.

**Table 2. Reasons for Treatment Discontinuation\***

Reason	No. (%)	
	Sertraline Hydrochloride (n = 88)	Placebo (n = 88)
Insufficient clinical response	1 (1)	4 (4)
Adverse event	7 (8)	3 (3)
Protocol violation	3 (3)	1 (1)
Unavailable for follow-up	4 (4)	5 (6)
Withdrew consent	1 (1)	1 (1)
Other	1 (1)	1 (1)
<b>Total</b>	<b>17 (19)</b>	<b>15 (17)</b>

\*All differences between treatment groups were nonsignificant by Fisher exact test.

or site were evident for demographics or severity measures (**Table 1**).

Seventy-one (81%) of the 88 sertraline-treated patients and 73 (83%) of the 88 placebo-treated patients completed the 10-week comparative phase of the study (Cochran-Mantel-Haenszel statistic = 0.378, *P* = .54).

**Table 2** summarizes reasons for study discontinuation. The most frequent reason for discontinuation in the sertraline group was adverse events (8% vs 3% in the placebo group), whereas the most common reason for discontinuation in the placebo-treated group was unavailability for follow-up (6% vs 4% in the sertraline group). Differences between groups on any of these variables were not significant (all *P* > .19 by Fisher exact test).

At end point, the mean (±SD) daily dose of sertraline hydrochloride was 118.1 ± 62.9 mg vs 147.5 ± 55.5 mg for placebo. For completers, the mean daily dose of sertraline hydrochloride was 131.4 ± 58.1 mg vs 156.7 ± 47.3 mg for placebo. The mean duration of therapy was 63.1 days (range, 2-77 days) for patients in

**Table 3. Summary of Efficacy Variables at End Point\***

Efficacy Variable	Sertraline Hydrochloride		Placebo		F Statistic (df Numerator, df Denominator)	P
	No.	Mean ± SD	No.	Mean ± SD		
Full panic attacks (ratio: end point–baseline)	87	0.21 ± 0.57	88	0.41 ± 0.73	$F_{1,155} = 6.23$	.01
CGI-S (change from baseline)	88	-1.56 ± 1.31	87	-1.04 ± 1.30	$F_{1,154} = 7.01$	.009
CGI-I (rating at end point)	88	2.26 ± 1.21	87	2.74 ± 1.21	$F_{1,155} = 6.73$	.01
Patient Global Evaluation (rating at end point)	88	2.23 ± 1.40	88	2.75 ± 1.39	$F_{1,155} = 6.19$	.01
Panic Disorder Severity Scale (change from baseline)	88	-0.88 ± 0.69	87	-0.64 ± 0.72	$F_{1,154} = 4.98$	.03
Anticipatory anxiety (change from baseline)	88	-0.98 ± 1.13	88	-0.65 ± 1.04	$F_{1,155} = 3.73$	.06
HAM-A score (change from baseline)	88	-9.50 ± 8.21	87	-8.32 ± 8.53	$F_{1,154} = 0.86$	.36
Quality of life score (change from baseline)						
Total	79	7.75 ± 13.03	77	1.29 ± 13.52	$F_{1,135} = 9.15$	.003
Overall satisfaction	79	0.60 ± 0.88	77	0.13 ± 0.91	$F_{1,135} = 10.55$	.002

\*CGI-S indicates Clinical Global Impression Severity Scale; CGI-I, Clinical Global Impression Improvement Scale; and HAM-A, Hamilton Anxiety Rating Scale.

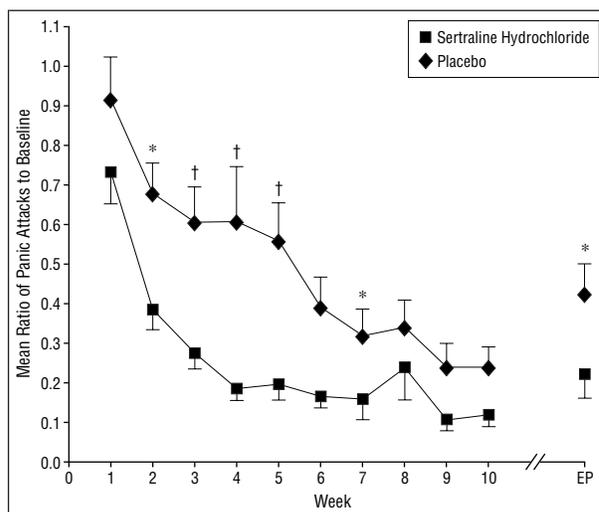
the sertraline group and 63.9 days (range, 1-77 days) for those taking placebo.

### TREATMENT OUTCOME

Changes in outcome for the treatment groups are presented in **Table 3**. Relative to baseline levels, patients treated with sertraline achieved a significantly greater reduction in (log) panic attacks ( $P = .01$ ) at end point. As shown in **Figure 1**, significant reduction in panic attacks in sertraline-treated patients compared with placebo-treated patients was achieved by the end of week 2 ( $P = .04$ ) and continued at the level of a trend or at significance for the remainder of the trial. Site effects were included in all analyses of variance that included site as a variable. Specifically, there were no significant site effects for the primary outcome variable, panic attack frequency at end point ( $F_{1,155} = 0.93$ ,  $P = .50$ ).

Patients treated with sertraline also achieved a significantly greater reduction in CGI-S scores relative to those in patients taking placebo ( $P = .009$ ) (**Figure 2**). Consistent significant differences between groups for the CGI-S measure emerged by week 4. Although end-point differences in panic-free status did not reach significance, with 57% of patients (50 of 88) treated with sertraline being panic free vs 47% of patients (41 of 88) treated with placebo (Fisher exact test,  $P = .23$ ), significant differences between groups were evident for high end-state functioning. At end point, 35% of patients (31 of 88) treated with sertraline met criteria for high end-state functioning compared with 19% (17 of 88) taking placebo (Fisher exact test,  $P = .03$ ).

These significant findings were reflected by similar results at end point for CGI-I ratings ( $P = .01$ ), Patient Global Evaluation improvement ratings ( $P = .01$ ), changes in Panic Disorder Severity Scale score ( $P = .03$ ; see also **Figure 3**), and quality of life scores ( $P = .003$ ) scores. Changes in anticipatory anxiety also approached but did not reach significance ( $P = .06$ ). No significant differences were evident at end point for changes in Hamilton Anxiety Rating Scale scores ( $P = .36$ ) or limited-symptom panic attacks ( $F_{1,155} = 0.42$ ,  $P = .52$ ); patients treated in both cells did experience a reduction in limited-symptom attacks, indicating that the reduction in full at-

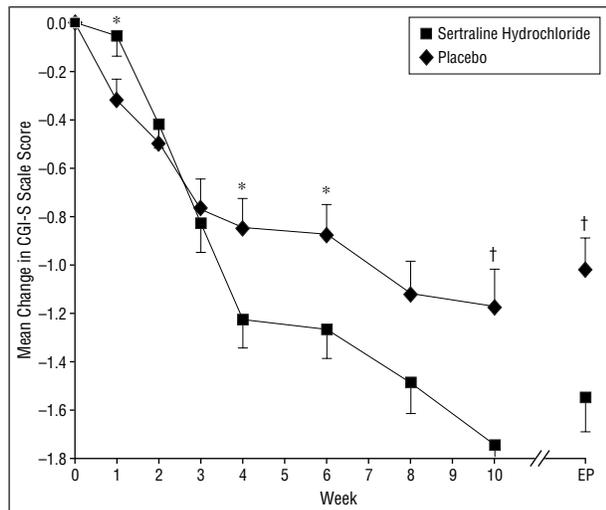


**Figure 1.** Ratio of panic attacks to baseline by visit. Bars indicate SE. Asterisk indicates  $P < .05$ ; dagger,  $P < .01$ . The non-log-adjusted data are graphed here for visual clarity. By week, the F statistic with numerator df and denominator df and the P value are as follows: week 1:  $F_{1,154} = 1.35$ ,  $P = .25$ ; week 2:  $F_{1,146} = 4.47$ ,  $P = .04$ ; week 3:  $F_{1,143} = 7.96$ ,  $P = .006$ ; week 4:  $F_{1,141} = 11.94$ ,  $P = .001$ ; week 5:  $F_{1,137} = 8.97$ ,  $P = .003$ ; week 6:  $F_{1,136} = 3.34$ ,  $P = .07$ ; week 7:  $F_{1,128} = 5.56$ ,  $P = .02$ ; week 8:  $F_{1,126} = 2.59$ ,  $P = .11$ ; week 9:  $F_{1,126} = 3.84$ ,  $P = .05$ ; week 10:  $F_{1,122} = 3.39$ ,  $P = .07$ ; and end point (EP):  $F_{1,155} = 6.23$ ,  $P = .01$ .

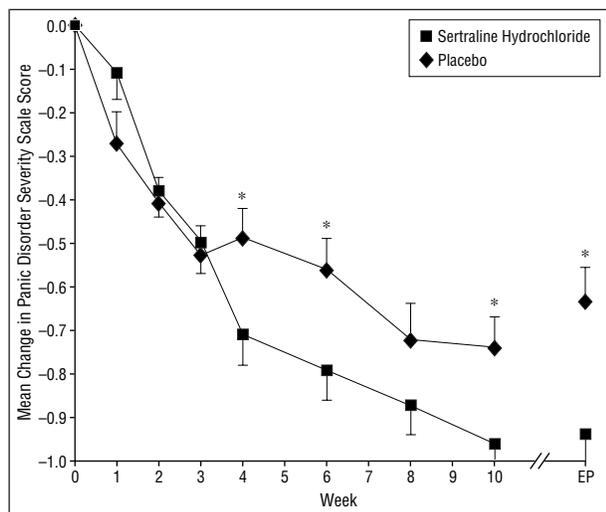
tacks did not reflect a conversion to limited-symptom attacks.

Findings were similar for analyses of patients who completed the full treatment trial (week 10 completer data). A significant advantage was evident for sertraline treatment in reduction in CGI-S scores ( $F_{1,124} = 7.40$ ,  $P = .008$ ) and was evident at the level of a trend for reduction in full panic attacks ( $F_{1,122} = 3.39$ ,  $P = .07$ ). A significant advantage for sertraline treatment was also evident for CGI-I scores ( $F_{1,122} = 7.83$ ,  $P = .007$ ), Patient Global Evaluation improvement scores ( $F_{1,127} = 9.27$ ,  $P = .004$ ), Panic Disorder Severity Scale scores ( $F_{1,124} = 4.83$ ,  $P = .03$ ), and anticipatory anxiety ( $F_{1,122} = 4.93$ ,  $P = .03$ ). No significant differences were evident for Hamilton Anxiety Rating Scale scores or limited-symptom attacks.

Previous studies have demonstrated relatively high rates of surreptitious benzodiazepine use by patients with



**Figure 2.** Mean change in Clinical Global Impression Severity (CGI-S) Scale scores by visit. Bars indicate SE. Asterisk indicates  $P < .05$ ; dagger,  $P < .01$ . By week, the  $F$  statistic with numerator df and denominator df and the  $P$  value are as follows: week 1:  $F_{1,149} = 5.00$ ,  $P = .03$ ; week 2:  $F_{1,146} = 0.32$ ,  $P = .57$ ; week 3:  $F_{1,137} = 0.15$ ,  $P = .70$ ; week 4:  $F_{1,138} = 5.01$ ,  $P = .03$ ; week 6:  $F_{1,136} = 5.08$ ,  $P = .03$ ; week 8:  $F_{1,128} = 3.42$ ,  $P = .07$ ; week 10:  $F_{1,124} = 7.40$ ,  $P = .008$ ; and end point (EP):  $F_{1,154} = 7.01$ ,  $P = .009$ .



**Figure 3.** Mean change in Panic Disorder Severity Scale scores by visit. Bars indicate SE. Asterisk indicates  $P < .05$ . By week, the  $F$  statistic with numerator df and denominator df and the  $P$  value are as follows: week 1:  $F_{1,150} = 3.11$ ,  $P = .08$ ; week 2:  $F_{1,147} = 0.17$ ,  $P = .68$ ; week 3:  $F_{1,140} = 0.04$ ,  $P = .84$ ; week 4:  $F_{1,139} = 4.99$ ,  $P = .03$ ; week 6:  $F_{1,138} = 6.06$ ,  $P = .02$ ; week 8:  $F_{1,129} = 1.87$ ,  $P = .17$ ; week 10:  $F_{1,124} = 4.83$ ,  $P = .03$ ; and end point (EP):  $F_{1,154} = 4.98$ ,  $P = .03$ .

panic disorder in controlled trials, particularly among those receiving placebo.<sup>31</sup> One each of the placebo- and sertraline-treated patients tested positive for benzodiazepines, suggesting that surreptitious benzodiazepine use was not a major issue in this trial.

#### SAFETY ASSESSMENTS

There were no significant differences in the overall incidence of adverse events between patients treated with placebo and those treated with sertraline (Fisher exact test,  $P = .18$ ). In the placebo group, 88% (77 of 88) re-

**Table 4.** Incidence of Adverse Experiences Occurring in 10% or More of Patients or With Significantly Greater Frequency in 1 Treatment Group

	No. (%)		$P$
	Sertraline Hydrochloride (n = 88)	Placebo (n = 88)	
Patients with adverse experiences	83 (94)	77 (88)	.19
Patients discontinuing because of adverse experiences	7 (8)	3 (3)	.33
Incidence of specific adverse events			
Insomnia	30 (34)	19 (22)	.08
Nausea	29 (33)	20 (23)	.15
Headache	29 (33)	30 (34)	.82
Diarrhea	24 (27)	9 (10)	.005*
Malaise	17 (19)	21 (24)	.35
Ejaculation failure†	4 (15)	1 (3)	.16
Somnolence	12 (14)	9 (10)	.47
Fatigue	12 (14)	5 (6)	.08
Dry mouth	11 (13)	17 (19)	.26
Tremor	7 (8)	0 (0)	.006*
Respiratory disorder	6 (7)	11 (13)	.26

\*Significantly different between treatment groups according to Cochran-Mantel-Haenszel test.

†Men only (sertraline,  $n = 27$ ; placebo,  $n = 34$ ).

ported at least 1 adverse event, in comparison with 94% of patients (83 of 88) in the sertraline group. **Table 4** presents the incidence of adverse events in 10% or more of patients or with significantly greater frequency in 1 treatment group. Among all adverse events, there was a significant difference (Fisher exact tests,  $P < .05$ ) in incidence between sertraline- and placebo-treated groups for only 2: tremor (8% vs 0%) and diarrhea (27% vs 10%). The majority of adverse events were characterized as mild or moderate.

Eight percent ( $n = 7$ ) of sertraline-treated patients vs 3% ( $n = 3$ ) of placebo-treated patients discontinued the study protocol because of adverse events, a nonsignificant difference ( $P = .32$ , Fisher exact test). Adverse experiences associated with discontinuation of sertraline use included agitation, impaired concentration, diarrhea, nausea, hypertension, dry mouth, urticaria, dizziness, abnormal vision, tachycardia, and hyperventilation, with some patients discontinuing because of more than 1 adverse effect. None of these adverse events was associated with discontinuation of more than 1 patient.

A total of 25 notable laboratory abnormalities (as defined by Food and Drug Administration-mandated threshold values) were reported, distributed among 11% of the sertraline group (10 of 88 patients) and 15% of the placebo group (13 of 88). None of the abnormalities was serious or resulted in discontinuation of treatment. There were no significant differences between treatment groups in the incidence of laboratory, electrocardiogram, or body weight abnormalities; incidence of intercurrent illness; or concomitant medication.

The results of this study indicate that sertraline is an effective, safe, and well-tolerated treatment for patients with panic disorder, with or without agoraphobia. At end point, patients receiving sertraline exhibited significantly greater reductions in panic attack frequency and global severity of illness than did patients treated with placebo.

Although there was significantly greater reduction in full panic attacks for sertraline-treated patients compared with those taking placebo, differences between groups on panic-free status and limited-symptom attacks did not reach significance. Although panic attacks are an important component of the panic disorder syndrome, their episodic nature makes them subject to substantial intrinsic variability; thus, a consensus conference on assessment of panic disorder emphasized the importance of considering multiple symptom domains when assessing outcome.<sup>32</sup> Consistent with this recommendation, outcome evaluation with the Panic Disorder Severity Scale (assessing multiple domains of symptoms and function) as well as clinician and patient ratings of global improvement, quality of life indexes, and high end-state function, demonstrate significant advantage for treatment with sertraline over placebo.

More than a third of patients achieved high end-state function and were considered to be in remission at the end of the short-term treatment trial with sertraline. This proportion is consistent with reports of other effective treatments for panic disorder but does underscore that, while most patients improve with effective short-term treatment, many remain at least somewhat symptomatic and may require additional time or adjunctive interventions to achieve full remission.<sup>6,33</sup>

Advantages over placebo on most efficacy measures generally emerged between weeks 2 and 4 of treatment. Consistent with other studies in panic disorder,<sup>34</sup> drug-placebo differences in efficacy were more robust in the end-point than the completer analysis; differences in panic frequency between the treatment groups did not reach significance for patients who completed the full trial, although significant differences were still observed for global improvement, severity of illness, and a number of other efficacy measures.

Sertraline was generally well tolerated, with most side effects being mild to moderate; relatively few patients discontinued sertraline because of adverse effects. Initiation of treatment with a low starting dose of sertraline hydrochloride of 25 mg/d appears to be a useful strategy to minimize early treatment discontinuation secondary to adverse events. The dropout rate for sertraline in the present study is consistent with the overall greater tolerability associated with SSRIs relative to older antidepressant treatments.<sup>34</sup>

The flexible-dose design used in this study did not permit assessment of the comparative efficacy of different dose levels of sertraline, although fixed-dose studies indicated no dose-response relationship within the effective dosage range of 50 to 200 mg/d.<sup>14</sup> The present study also excluded patients with major depression or marked

depressive symptoms, thereby ensuring that the patients' improvement was not the result of amelioration of depression but preventing estimation of the efficacy of sertraline for patients with panic disorder who had comorbid depression.

Follow-up studies would be useful to examine the ability of sertraline to maintain treatment benefits over time. We anticipate that, similar to other pharmacological interventions for panic disorder,<sup>1,33</sup> ongoing treatment with sertraline will be necessary to maintain clinical benefits. As such, its favorable side-effect profile should make sertraline suitable for the longer-term management of panic disorder. Our study also did not examine the efficacy of combining cognitive-behavioral therapy and sertraline. Studies suggest that cognitive-behavioral therapy interventions can enhance the efficacy of pharmacological treatment for panic disorder in both the short and long term<sup>34,35</sup>; as such, combined treatment also may extend the clinical benefits of sertraline for panic disorder.

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