Sertraline Treatment of Panic Disorder: Response in Patients at Risk for Poor Outcome

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Background: More than one third of panic disorder patients have a chronic and/or recurrent form of the disorder, accounting for much of the individual and societal cost associated with the illness. Six clinical variables have been most consistently identified as high-risk predictors of poor outcome: (1) panic severity, (2) presence of agoraphobia, (3) comorbid depression, (4) comorbid personality disorder, (5) duration of illness, and (6) female sex. No published research has systematically examined the differential antipanic efficacy of selective serotonin reuptake inhibitors in patients at high risk for poor outcome.

Method: Data were pooled (N = 664) from 4 double-blind, placebo-controlled studies of the efficacy of sertraline for the treatment of DSM-III-R panic disorder. Two of the studies were 12-week fixed-dose studies with starting daily doses of sertraline, 50 mg, and 2 were 10-week flexible-dose studies with starting daily doses of sertraline, 25 mg. All other study design features were the same, except for the exclusion of women of childbearing potential in the 2 fixed-dose studies. Exclusion of patients with marked personality disorders and depression meant that only 4 of the poor-outcome variables could be evaluated.

Results: Clinical improvement was similar for patients treated with sertraline whether or not they carried an agoraphobia diagnosis, had a duration of illness > 2 years, or were female. Patients with high baseline panic severity had significantly (p = .01) less improvement on the endpoint Clinical Global Impressions-Improvement (CGI-I) scale than patients with moderate severity, although the Clinical Global Impressions-Severity of Illness scale change score was higher in the patients with high severity (–2.00 vs. –1.31). For patients with 3 or more high-risk variables, there was a modest, but statistically significant, tendency for reduced global improvement (endpoint CGI-I score of 2.7 for the high-risk vs. 2.4 for the non–high-risk group; p = .017), although the high-risk group actually had a similar endpoint reduction in frequency of panic attacks (82%) compared with the non–high-risk group (78%).

Conclusion: Treatment of panic disorder with sertraline was generally effective, even in the presence of baseline clinical variables that have been associated with poor treatment response. The main limitations of the analysis were the reliance on pooled data from 4 studies (even if the designs were similar) and our inability to examine the impact of depression and personality disorders on response to treatment because of the exclusion criteria of the clinical trials.

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For the majority of affected patients, the course of panic disorder is characterized by the persistence of symptomatology despite treatment.[1,2] These persistent symptoms contribute to the high individual and societal cost of the illness. Examination of the predictors of treatment response is critical for the development of optimal treatment strategies.

Over the past 20 years, more than a dozen studies have been published that examine predictors of outcome in panic disorder.[3–23] Not surprisingly, given widely varying differences in patient populations and methodologies, many different patient and illness variables have been identified as predictors of poor outcome. Only 6 high-risk variables, though, have been consistently identified across sufficient studies (5 or more) that they may be considered to be predictors with any degree of validity: (1) baseline severity of panic anxiety, (2) the presence and/or baseline severity of agoraphobia, (3) comorbid depression, (4) comorbid personality disorder, (5) duration of panic illness, and (6) female sex.

These 6 clinical variables are high-risk predictors of poor outcome that have been identified in long-term naturalistic studies. Predictors of short-term treatment response in controlled, double-blind acute studies have also been identified, although the studies examining this issue are far fewer. In most instances—for example, severity of panic anxiety,[9,24–26] presence or severity of phobic avoidance,[23,25] duration of illness,[9,26] comorbid depression,[27] and comorbid personality disorder[24]—the predictors have been found to be the same as for long-term clinical outcome.

The purpose of the current investigation is to compare the efficacy of sertraline in the treatment of panic disorder patients who have 1 or more risk factors for poor outcome with panic disorder patients who lack such risk factors. To accomplish this, pooled data were analyzed from 4 double-blind, placebo-controlled studies of sertraline in the treatment of panic disorder with or without agoraphobia. Two of the studies were flexible in their dosing of sertraline, whereas the other 2 were fixed-dose studies. The flexible-dose studies were 10 weeks in duration, whereas the fixed-dose studies were 12 weeks in duration to allow for titration to different dosage levels. With the additional exception of the exclusion of women of childbearing potential in the fixed-dose studies (and some differences in secondary outcome measures), the study design and inclusion and exclusion criteria (except for the dosing) were identical for all 4 trials. Both studies excluded patients with major depression as well as patients with any personality disorder that was considered severe or likely to interfere with study participation. Therefore, these 2 clinical variables could not be included in the current high-risk analysis. Thus, we undertook to examine the efficacy of sertraline in a large sample of patients (N = 407) with 1 or more of the variables previously associated with poor clinical outcome: female sex, long duration of illness, presence of agoraphobia, and higher baseline severity.

METHOD

The present investigation reports an analysis of pooled data from 4 separate multicenter, randomized, double-blind, parallel-group studies of sertraline versus placebo in the treatment of panic disorder. Details of study methodology are presented in previous publications.[27–30]

Study Patients

All 4 studies[27–30] had similar inclusion and exclusion criteria, which required that patients be 18 years or older and meet a Structured Clinical Interview for DSM-III-R–confirmed[31] diagnosis of panic disorder with or without agoraphobia. Also required for study entry were the presence of 4 or more panic attacks during the 4 weeks prior to screening, 3 or more panic attacks during a 2-week placebo washout period, and a Hamilton Rating Scale Anxiety (HAM-A) total score ≥ 18 at baseline. Patients were excluded for any of the following: (1) current 21-item Hamilton Rating Scale for Depression (HAM-D) total score ≥ 18; (2) current diagnosis of major depression, bipolar disorder, organic mental disorder, schizophrenic disorder, or alcohol or substance abuse in the previous 6 months; (3) current principal diagnosis of obsessive-compulsive disorder, dysthymia, any other anxiety disorder, or any personality disorder; (4) use of concomitant psychotropic medication (or a positive urine drug screen); (5) any previous treatment with sertraline; and (6) pregnancy, nursing, or not practicing a medically accepted form of birth control.

Study Design

All 4 studies[27–30] used a 2-week, single-blind, placebo washout period in which patients who continued to meet entrance criteria were randomly assigned to double-blind treatment with either sertraline or placebo. Two of the studies[27,30] were fixed-dose studies of 12 weeks' duration. Both of these studies employed a starting dose of 50 mg of sertraline, with a blinded, stepwise titration of 50 mg per week up to 3 dose levels: 50, 100, and 200 mg. Two of the studies[28,29] were flexible-dose studies of 10 weeks' duration. Both of these flexible-dose studies employed a starting dose of 25 mg of sertraline, with titration of no more than 50 mg per week, based on tolerability and clinical response, to a final daily dose in the range of 50 to 200 mg. Frequency of panic attacks per week was assessed using a diary completed daily by the patient. Additional patient- and clinician-rated outcome measures, including the HAM-A,[32] the Modified Sheehan Panic and Anticipatory Anxiety Scale,[33] the Panic Disorder Severity Scale (PDSS),[34] the Clinical Global Impressions-Severity of Illness scale (CGI-S),[35] the CGI-Improvement scale (CGI-I),[35] and the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q),[36] are described in detail in published reports on the results of each individual study.

Statistical Analysis

The safety analysis included all patients who took at least 1 dose of medication during the double-blind phase and provided any follow-up data; patients included in the safety analysis who had baseline and postrandomization efficacy data were included in the efficacy analysis. All statistical tests were 2-sided.

Change from baseline in panic attack frequency at the last-observation-carried-forward (LOCF) endpoint and at weeks 1 through 12 was analyzed using an analysis of covariance (ANCOVA) model with terms for baseline number of panic attacks (the covariate), treatment, protocol, and protocol-by-treatment interaction. For sertraline-treated patients, CGI-I score and percentage reduction in panic attacks were compared between subgroups of patients with and without each of 4 high-risk variables. The 4 high-risk variables were (1) female sex, (2) presence of agoraphobia, (3) duration of illness > 2 years, and (4) CGI-S score ≥ 5. The comparison was performed using an ANCOVA model (analysis of variance [ANOVA] was used for the CGI-I) with terms for treatment, protocol, risk category, baseline, treatment-by-protocol, and treatment-by-risk category interactions. Both completers and LOCF endpoints were analyzed.

A series of multiple regression analyses were performed using the high-risk variables identified by literature review (i.e., duration of illness, presence of agoraphobia, female

Table 1. Baseline Demographic and Clinical Characteristics of Patients Pooled From 2 Flexible-Dose[28,29] and 2 Fixed-Dose[27,30] Panic Disorder Treatment Studies[a]

	Sertraline			Placebo		
Characteristic	N	Total N	%	N	Total N	%
Sex						
Male	204	407	50	126	257	49
Female	203	407	50	131	257	51
Panic disorder with agoraphobia	232	407	57	152	257	59
CGI-S score ≥ 5 (marked-to-severe)	148	405	37	98	257	38
	Mean	Total	SD	Mean	Total	SD
Age, y	38.7	405	11.4	36.4	257	10.0
Duration of illness, y	9.0	407	9.4	9.1	256	9.9
Panic attacks per week	8.3	407	17.7	7.4	257	11.0
HAM-A total score	22.8	407	4.4	22.7	257	4.0
PDSS total score[b]	13.0	167	4.1	12.8	174	3.9

[a]Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-A = Hamilton Rating Scale for Anxiety, PDSS = Panic Disorder Severity Scale.
[b]PDSS was used only in the 2 flexible-dose studies.

sex, and baseline severity), as well as other clinically relevant baseline variables (i.e., percentage of time spent worrying, HAM-A score, score on items 4 [phobic avoidance] and 5 [anxiety sensitivity] on the PDSS, Q-LES-Q score, and HAM-D score). CGI-I scores, panic attack frequency, and presence of comorbidity by both a completer and an LOCF analysis were examined separately.

If a patient reported multiple episodes of the same adverse event, the event was counted only once in the computation of incidence rates of adverse events. Treatment-emergent adverse events reported at a rate ≥ 10% in each treatment group were compared between sertraline and placebo using the Fisher exact test.

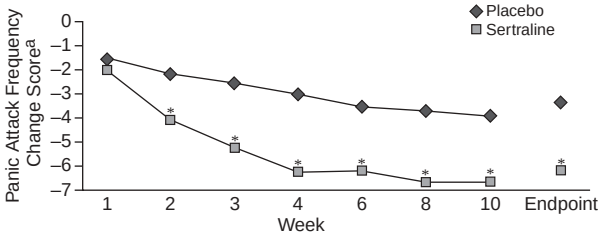
RESULTS

Patient Sample

Pooled data from the 4 double-blind studies yielded a total of 664 patients taking sertraline or placebo with evaluable data. No significant differences were found when we compared the baseline characteristics for each of the 4 panic studies by testing the treatment-by-study interaction in the ANOVA model for frequency of panic attacks, HAM-A score, mean age, duration of illness, PDSS total score, percent female, agoraphobia subtype, and CGI-S score.

Table 1 summarizes the clinical and demographic features of the combined sample. Two notable clinical features are the chronicity of panic illness in the patient sample, with 73% of patients reporting a duration of panic disorder of more than 2 years, and the high level of non-panic anxiety, with a mean HAM-A total score at baseline of approximately 22.7. For the total patient sample, 58% reported concurrent agoraphobia, and 37% reported a baseline CGI-S score ≥ 5.

Figure 1. Change in Panic Attack Frequency for 4 Pooled Fixed- and Flexible-Dose Studies[27–30]: Sertraline vs. Placebo



[a]Baseline panic attack frequency: sertraline, 8.3; placebo, 7.4.
*p < .001.

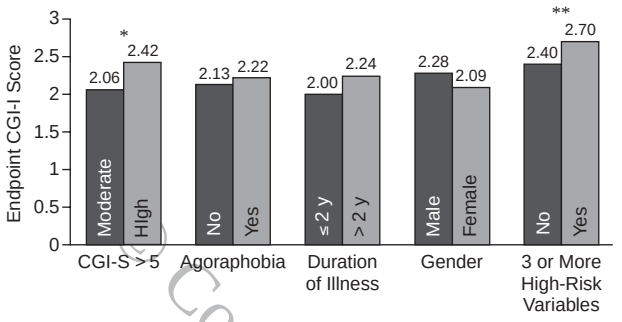
Clinical Response

Sertraline treatment, for the 4 pooled studies, was associated with a highly significant reduction in mean weekly panic attack frequency that was evident by the second week of treatment and continued to study endpoint (Figure 1). A statistically significant ($p < .001$) efficacy advantage in favor of sertraline on the CGI-I scale was evident by week 2, and that advantage continued throughout the remainder of study treatment. Sertraline treatment also yielded improvement in phobic avoidance as measured by the PDSS utilized in the 2 flexible-dose studies, an improvement that became significant at week 10. The change score on the PDSS phobic avoidance item was –1.0 for sertraline and –0.7 for placebo ($p = .006$).

Comparative efficacy was examined for subgroups of patients with or without each of the 4 high-risk variables. Figure 2 shows the results of a completer analysis of CGI-I scores. As can be seen, sertraline treatment was similarly effective in patients with or without one of the high-risk variables. The 1 exception was the tendency for patients with high baseline severity (as measured globally by the CGI-S scale) to achieve significantly ($p \leq .01$) less endpoint improvement on the CGI-I than patients with moderate baseline illness severity. However, in contrast to that finding, patients in the high illness severity group did evince significantly ($p = .0001$) greater improvement as assessed by an endpoint CGI-S change score of –2.00 compared with the moderate-illness severity group, which had an endpoint CGI-S change score of –1.31. As can also be seen from Figure 2, there was a modest but significant tendency ($p = .017$) for patients who possessed 3 or more of the high-risk variables to have a higher endpoint CGI-I score (i.e., to have less improvement).

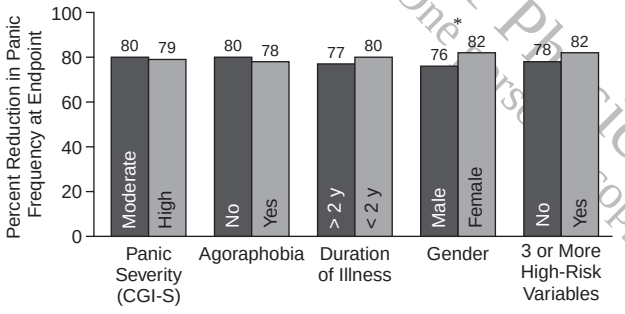
Comparative efficacy was also examined by an intent-to-treat LOCF analysis of percent reduction in panic attack frequency at study endpoint (Figure 3). Again, sertraline treatment was found to be similarly effective in both high-risk and non–high-risk patients, including those with 3 or more of the high-risk variables. In contrast to the completer analysis, the only significant difference was for

Figure 2. Sertraline Treatment of Patients at Risk for Poor Outcome: Endpoint Clinical Global Impressions-Improvement Scale (CGI-I) Score for Study Completers[a]



[a]Abbreviation: CGI-S = Clinical Global Impressions-Severity of Illness scale score.
*p = .010.
**p = .017.

Figure 3. Sertraline Treatment of Patients at Risk for Poor Outcome: Percent Reduction in Panic Attack Frequency at Treatment Endpoint[a]



[a]Abbreviation: CGI-S = Clinical Global Impressions-Severity of Illness scale.
*p < .02.

women to have a slightly greater percent reduction in panic attack frequency than men.

Prediction of Clinical Response

To determine which variables best predicted positive clinical response, a series of multiple regression analyses were performed using the high-risk variables identified by literature review (i.e., duration of illness, presence of agoraphobia, female sex, and baseline severity). In addition, several other baseline clinical variables were used as candidate predictor variables in the regression analyses, including percent of time spent worrying, HAM-A score, score on items 4 (phobic avoidance) and 5 (anxiety sensitivity) on the PDSS, Q-LES-Q score, and HAM-D score. CGI-I scores, panic attack frequency, and presence of comorbidity by both a completer and an endpoint LOCF analysis were examined separately.

The results of the regression analysis using CGI-I for 10-week completers as the outcome variable identified baseline HAM-A score as the only significant predictor variable (R^2 = .053; p = .009). The results of the regression analysis using LOCF CGI-I score as the outcome variable identified percentage of time worrying as the only significant predictor variable (model R^2 = .038; p = .012).

Table 2. Disposition of Patients Pooled From 2 Flexible-Dose[28,29] and 2 Fixed-Dose[27,30] Panic Disorder Treatment Studies

	Sertraline (N = 407)		Placebo (N = 257)	
Disposition	N	%	N	%
Completed study	284	69.8	204	79.4
Withdrew from study	123	30.2	53	20.6
Lack of efficacy	2	0.5	9	3.5
Adverse events	53	13.0	8	3.1
Protocol violation	7	1.7	2	0.8
Other	61	15.0	34	13.2

Tolerability and Discontinuation

Patients treated with sertraline had a higher tendency to withdraw during the course of study treatment (Table 2). A disproportionate contribution to premature discontinuation (70%) was made by patients in the 2 fixed-dose studies,[27,30] both of which required an initial daily dose of 50 mg with forced titration upward, compared with the flexible-dose studies,[28,29] which initiated treatment at 25 mg/day for the first week and then titrated up to 50 mg/day, with flexible dosing thereafter. Comparative rates of discontinuation for patients with or without each of the 4 high-risk variables were analyzed. The presence of agoraphobia (vs. no agoraphobia) was found to be associated with a significantly lower rate of discontinuation for sertraline (28.0% vs. 33.1%), but not for placebo (21.1% vs. 20.0%). There were no other discontinuation differences for patients with or without high-risk variables.

Sertraline treatment was well tolerated, with relatively few treatment-emergent adverse events reported (Table 3). The presence of high-risk variables was not associated with significant differences in adverse event rates, with the exception that women treated with sertraline were somewhat more likely than men to report nausea (34.5% for women vs. 25.5% for men; Fisher exact test p = .052) and diarrhea (25.6% vs. 15.2%; Fisher exact test p = .009). Sex-based differences in placebo-treated patients were less significant for both nausea (23.7% for women vs. 14.3% for men; p = .059) and diarrhea (11.5% vs. 7.9%; p = .403).

DISCUSSION

The availability of 4 placebo-controlled studies of the efficacy of sertraline for the treatment of moderate-to-severe panic disorder provided an opportunity to examine whether the response to sertraline was reduced in patients with clinical and demographic variables that have been

Table 3. Treatment-Emergent Adverse Effects Reported at a Rate of 10% or Higher by Patients Pooled From 2 Flexible-Dose[28,29] and 2 Fixed-Dose[27,30] Panic Disorder Treatment Studies

	Sertraline (N = 407)		Placebo (N = 257)		
Adverse Effect	N	%	N	%	p Value
Headache	138	34	97	38	NS
Nausea	122	30	49	19	.002
Insomnia	105	26	48	19	.04
Diarrhea	83	20	25	10	.001
Male ejaculatory dysfunction[a]	41	20	1	1	.001
Dry mouth	63	15	27	11	NS
Drowsiness	58	14	24	9	NS
Fatigue	47	12	15	6	.02
Dizziness	44	11	28	11	NS

[a]Denominator is subset of male patients (N = 204).

identified in other studies[3–27] as negative predictors of acute and long-term outcome. The results of the pooled analysis suggest that the presence of these high-risk variables (i.e., female sex, high baseline illness severity, more chronicity, and presence of agoraphobia) generally has minimal effect on the efficacy of sertraline in treating panic disorder. However, patients with high baseline panic severity had significantly higher endpoint CGI-I scores (i.e., less improvement; see Figure 2) than patients with moderate baseline severity as measured by the CGI-S, although this finding stands in contrast to the observation that endpoint CGI-S change score was greater for the high baseline illness severity subgroup. For patients with 3 or more high-risk variables, there was a modest tendency for global improvement with sertraline to be reduced (see Figure 2). Despite this, the group with multiple high-risk factors had a similar endpoint reduction in frequency of panic attacks (82%) compared with the group of patients without the high-risk factors (78%; see Figure 3). Across the 4 high-risk variables (agoraphobia, chronicity of illness, high severity, and female sex), endpoint reduction in panic attack frequency was comparable to reductions observed in non–high-risk patients. However, it should be noted that because the entry criteria for the fixed-dose studies excluded women of childbearing potential, the impact of female hormonal milieu on response to treatment may have been obscured. Additional studies directly examining this issue are warranted.

The results of regression analyses found none of the 4 clinical variables identified in the literature review to have any significant value in predicting clinical response to sertraline treatment. When CGI-I was used as the index of clinical response, a lower baseline HAM-A score was the only significant predictor of greater response to sertraline in the completer analysis; in the LOCF analysis, only baseline anticipatory anxiety was significantly correlated with response to sertraline. However, only a small fractional portion of the variance in outcome was accounted for by either of these predictor variables.

The presence of high-risk variables had minimal clinically significant effects on tolerability of study drug and patient discontinuation rates. As would be expected, the rate of dropouts due to adverse effects was higher in the fixed-dose studies,[27,30] in which the initial dose level was higher and the titration schedule did not permit dose adjustments in response to emergent adverse effects, compared with the flexible-dose studies.[28,29] Gastrointestinal symptoms were reported at a somewhat higher rate in women compared with men, whether the study drug was sertraline or placebo.

The main limitations of the current investigation were the reliance on pooled data from 4 studies (even if the designs were highly similar) and our inability to examine the impact of depression and personality disorders on response to treatment because of the exclusion criteria of the clinical trials. Nonetheless, the resultant large sample size enhances confidence in our findings, which stand in contrast to the results of several previous reports, including smaller studies with the selective serotonin reuptake inhibitors fluvoxamine and paroxetine that found 1 or more of the clinical and demographic variables examined to be correlated with reduced efficacy.[23,24,26,37]

Drug names: fluvoxamine (Luvox), paroxetine (Paxil), sertraline (Zoloft).

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