Sertraline in the treatment of panic disorder

A multi-site, double-blind, placebo-controlled, fixed-dose investigation

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Background This study compared the efficacy and safety of sertraline to placebo in treating panic disorder.

Method 178 out-patients with panic disorder who exhibited at least four panic attacks during the four weeks prior to screening and three during the two weeks of lead-in were randomly assigned to 12 weeks of double-blind treatment with sertraline (50, 100 or 200 mg) or placebo.

Results Sertraline was superior to placebo in reducing the number of panic attacks, situational attacks, unexpected attacks, limited symptom attacks, and time spent worrying (all $P<0.01$) and the Hamilton Anxiety Scale ($P<0.05$), although Clinical Global Impression (Improvement) did not significantly differentiate groups at 12 weeks and at end-point. No serious adverse events were associated with sertraline. No dose relationship was found for adverse events; overall drop-out rates were not different for sertraline or placebo, although more sertraline-treated subjects discontinued for adverse events, typically early in the study. Only dry mouth and ejaculation failure (primarily ejaculation delay) were associated significantly with sertraline.

Conclusions Sertraline was effective and safe in reducing panic attacks. Higher doses were no more effective than the 50 mg dose.

Declaration of interest R.W. is a Senior Associate Medical Director at Pfizer Inc.

Panic disorder is a relatively common disorder with a lifetime prevalence estimated at between 1.5 and 3.5% (Weinstein, 1995). It is distressing and potentially disabling, and is often accompanied by significant functional and economic costs and psychiatric comorbidity (depression, suicide; Weissman, 1988; Pounds, 1992). Tricyclic antidepressants are effective for panic disorder, but anticholinergic side-effects have limited the acceptance of this class of drugs (Rosenberg, 1993). Need for high doses, sedation, and acute re-emergence of symptoms following discontinuation have weighed against the choice of benzodiazepines for this syndrome (Salzman, 1993; Pecknold, 1993).

RECENT INVESTIGATIONS

Recent controlled investigations support selective serotonin reuptake inhibitors in treating panic disorder: fluvoxamine has been supported by Den-Boer *et al* (1995), Black *et al* (1993) and Hoehn-Saric *et al* (1993), while Oehrberg *et al* (1995) reported that paroxetine plus cognitive therapy was significantly more effective than placebo plus cognitive therapy for panic disorder. More recently, Wade *et al* (1997) found citalopram to be superior to both placebo and clomipramine in reducing number of panic attacks. The present report describes the first controlled study of sertraline in treating panic disorder.

METHOD

Research design

The study utilised a double-blind, parallel, fixed-dose design and was conducted in seven treatment sites, six in the western US and one in West Virginia; subjects were enlisted through advertising in local media. A two-week single-blind placebo lead-in period ensured an adequate number of panic attacks prior to randomisation upon which improvement could be compared, and allowed washout of prior medications. Subjects who continued to meet entry criteria at the end of the lead-in phase were randomly assigned by site, with a blocking factor of four, to 12 weeks of treatment with sertraline 50 mg/day, 100 mg/day, 200 mg/day, or placebo. Titration to the 100 mg and 200 mg doses was accomplished by double-blind increases of 50 mg/day each week. Study medication was taken with the evening meal as a single dose of two capsules contained in a blister pack. Safety and efficacy data were obtained at the end of weeks 1, 2, 3, 4, 6, 8, 10 and 12. Clinicians were instructed to give support and reassurance designed to promote compliance with the protocol; they did not provide directive advice, psychotherapeutic interpretation or cognitive therapy.

Sample selection

One hundred and seventy-eight male and surgically sterilised or post-menopausal female out-patients aged 18 or older with a DSM–III–R (American Psychiatric Association, 1987) diagnosis of panic disorder, with or without agoraphobia, entered double-blind treatment; as one subject was lost to follow-up without safety data, there were 177 subjects who were evalued for safety. The diagnosis of panic disorder was determined by the Structured Clinical Interview for DSM–III–R (SCID; Spitzer *et al*, 1990). Subjects with a psychiatric syndrome or history that might cloud the primary diagnosis (e.g. psychosis, organic brain syndrome or substance misuse) were excluded. Subjects with a secondary diagnosis of an affective disorder, anxiety states including generalised anxiety disorder, social or simple phobia, obsessive–compulsive disorder or post-traumatic stress disorder, or personality disorder were permitted to participate.

All the subjects in the study had a minimum of four panic attacks during the four weeks prior to screening, at least one classified as 'unanticipated', and at least three panic attacks during the two-week lead-in phase prior to randomisation. A minimum score of 18 or higher on the Hamilton Anxiety Scale (HAM–A; Hamilton, 1959) and 17 or lower on the first 21 items of the 24-item Hamilton Depression Scale (HAM–D; Hamilton, 1967) were also required. Medical history, physical examination, laboratory tests and electrocardiograms (ECGs) were used to exclude subjects with unstable medical conditions. Subjects

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were required to have a negative urinary drug screen (including benzodiazepines), and negative serum screen for alprazolam during the placebo lead-in phase. No regular daily therapy with any benzodiazepine was permitted during the month before entry into the study. History of drug or alcohol misuse or dependency during the six months before screening led to exclusion. Chloral hydrate for sleep was the only psychotropic drug permitted at baseline or during the study. After complete description of the study to the subjects, written informed consent was obtained in accordance with the Helsinki Declaration of 1975, as revised in 1983.

Efficacy assessment

The Sheehan Panic and Anticipatory Anxiety Scale (PAAS; Sheehan, 1989) provided the primary efficacy measure, number of panic attacks. The PAAS was completed by the investigator after reviewing the subject's daily diary with the subject. A 'panic attack' was an episode with four or more of the following DSM–III–R symptoms: shortness of breath; dizziness, unsteady feelings or faintness; palpitations or increased heart rate; trembling or shaking; sweating; choking; nausea or upset stomach; feeling unlike yourself, detached from a situation and/or like things happening around you are strange and unreal; numbness or tingling; hot flashes or chills; chest pain or discomfort; fear of dying; fear of going crazy or doing something uncontrolled. An episode manifesting one to three of these symptoms was a 'limited symptom attack'. 'Anticipatory anxiety' was defined as the percentage of time spent in each 24-hour period worrying about panic attacks. Panic attacks and limited symptom attacks were further categorised as 'unexpected' or 'situational' depending on the absence or presence of perceived situational provocation. Other outcome measures based on the clinical interview were the HAM–A, and the Clinical Global Impression (CGI; Guy, 1976) severity of illness and global improvement scales. Sertraline plasma concentrations were obtained at the start of placebo lead-in and at the end of Weeks 4 and 12 of the double-blind treatment phase.

Safety and tolerability assessment

Adverse events, volunteered or observed, were recorded and classified in respect to onset, duration, severity, cause (as judged by the investigator), action taken, and outcome. Safety was assessed by means of vital signs and body weight (Day 1 and 8 of lead-in and each week of treatment), laboratory tests including haematology and urinalysis and microscopic evaluation (Day 1 of the placebo lead-in and at the end of Weeks 2, 4, 8, and 12 of the double-blind treatment period or at end-point), and 12-lead ECG (Day 1 of lead-in and Weeks 2, 6 and 12 or at end-point). A serum alprazolam screen and a urine drug screen (for benzodiazepines or drugs of abuse) were carried out on Day 1 and at the end of Weeks 2, 4 and 12 or at end-point.

Sample characteristics at baseline

Of the 178 subjects who entered double-blind treatment, 177 provided safety data and 171 provided efficacy data. The sample was predominantly White (>90%). The average age of subjects was 38.8 years (range=18.9–74.5): 39.1, 37.2, 41.8, and 37.2 year in the placebo, 50, 100 and 200 mg sertraline groups respectively. Gender distribution was almost evenly split (53% male, 47% female). The sample had an average score of 22.5 on the HAM–A and 12.7 on the HAM–D; there were no significant differences among the treatment groups for this instrument nor for CGI severity. Subjects had been suffering from panic disorder for almost eight years on average and they experienced a mean of 10.1 (median=5) panic episodes per week during the lead-in to baseline. The number of panic attacks reported showed wide variability: 50% of the subjects (n=89) had 5.5 or fewer panic attacks per week while 12 subjects (7%) had 28 or more, and four subjects had at least 70 (n=172, min=0, max=103). There were no significant differences among the treatment groups for any sample characteristics at baseline except for gender distribution between the sertraline 50 mg and placebo treatment groups (63% females in the 50 mg sertraline group v. 36% females in the placebo group, $P<0.02$, Fisher's exact test). The treatment groups did not differ significantly for the main efficacy parameters.

A separate analysis of equivalency of treatment groups was performed for the 114 subjects who completed the full 12 weeks of treatment. No significant differences among treatment groups were noted on any variables at baseline for this sample, including gender distribution.

Although secondary diagnoses were permitted, there were few, 9 of 10 being generalised anxiety or phobia. None of the subjects had a concurrent diagnosis of major depression, although one subject in the 50 mg group was listed as having unspecified depression. One subject in the placebo group had a secondary diagnosis of generalised anxiety disorder, as did two subjects in each of the sertraline groups; one subject in the placebo group was diagnosed with social phobia; and one subject in each of the placebo, 50 mg and 200 mg sertraline group was diagnosed with simple phobia.

Statistical analyses

Age, weight, HAM–D, duration of illness, and baseline PAAS and HAM–A were compared among the treatment groups at baseline using analysis of variance (ANOVA) with terms for treatment group and site. Gender and ethnicity were compared using χ^2 tests. Parallel analyses of efficacy parameters were performed both for end-point with last observation carried forward, and weekly analyses including only those data actually collected. The PAAS measures (number of panic attacks, number of limited symptom attacks, number of episodes of anticipatory anxiety, and the percentage of time spent having anticipatory anxiety) were not normally distributed, owing to marked between-patient variability in the frequency and intensity of attacks; therefore, values were expressed as a ratio to individual baseline values, and were log-transformed prior to analysis. Although these ratios adjust for baseline severity, their means can be distorted by very large values for which reason the geometric mean (defined as the nth root of the product of n values) was also used to estimate central tendencies for the four treatment groups; this parameter is more appropriate for log-transformed data than is the arithmetic mean. Analyses of panic attacks were performed using Analysis of Covariance (ANCOVA) models with log of the baseline as the co-variate. Pair-wise comparisons among the treatment groups were performed at end-point, using Fisher's protected least significant difference method. The Kruskal–Wallis test was applied to confirm analyses of the three main efficacy parameters. Changes in HAM–A scores from baseline were compared between treatments by ANCOVA. Scores for CGI global improvement were directly compared

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between treatment groups by ANOVA and pair-wise comparisons at end-point were performed using Fisher's protected least significant difference method. Concentrations of sertraline were analysed for proportionality to treatment dose and for relationship to reduction in panic attacks at Week 4 and Week 12 or end-point. Dose proportionality was assessed using one-way ANOVA on dose-normalised concentrations by dose and the relationship between plasma concentration and efficacy was examined by multiple regression analysis.

RESULTS

Disposition of subjects

Of 177 safety-evaluable subjects, 63 (36%) withdrew from the study, 28 due to adverse experiences and 12 because of insufficient clinical response (Table 1). Discontinuations for the 50 mg, 100 mg, 200 mg, and placebo groups were 44, 23, 44, and 31% respectively; the difference among the groups was not statistically significant by χ^2 nor was the difference statistically significant when subjects in the placebo group were compared with pooled subjects taking sertraline (31 and 37%).

Efficacy

Sertraline was significantly superior to placebo at end-point in reducing the number of weekly panic attacks, the primary measure of efficacy in this research. In the pooled sertraline treatment group (n=127) panic attacks were reduced 65% from baseline compared to a 39% reduction in the placebo group (n=44). Reductions among the sertraline dose groups favoured lower doses (71% and 83% for 50 mg and 100 mg respectively compared to 42% for 200 mg). Figure 1 displays weekly improvement in panic attacks expressed as a ratio to baseline. An estimate of effect size is afforded by 'relative rate', the rate of panic attacks at end-point of each treatment group relative to the rate of panic attacks for placebo: the 50 mg group had a relative rate of 0.58, confidence interval (CI) 0.35–0.95; P=0.036; for 100 mg the value was 0.41, CI 0.25–0.67, P=0.0006); and for 200 mg, 0.60, CI=0.37–1.00, P=0.0505. No significant differences were noted among the sertraline groups.

Geometric means of the ratios between end-point and baseline are listed in Table 2 for all forms of attacks; actual means and standard deviations are shown in Table 3.

Table 1 *Disposition of subjects*

Reason for discontinuation	Sertraline				
	50 mg n (%)	100 mg n (%)	200 mg n (%)	Pooled n (%)	Placebo n (%)
Adverse experience	8 (19)	6 (14)	12 (27)	26 (20)	2 (4)[1]
Insufficient clinical response	6 (14)	0 (0)	1 (2)	7 (5)	5 (11)
Lost to follow-up	2 (5)	2 (5)	3 (7)	7 (5)	1 (2)
Poor compliance	2 (5)	0 (0)	1 (2)	3 (2)	2 (4)
Other	0 (0)	1 (2)	2 (4)	3 (2)	0 (0)
Protocol violation	0 (0)	1 (2)	0 (0)	1 (1)	2 (4)
Intercurrent illness	0 (0)	0 (0)	1 (2)	1 (1)	1 (2)
Laboratory or ECG abnormality	1 (2)	0 (0)	0 (0)	1 (1)	1 (2)
Completed study	24 (56)	34 (77)	25 (56)	83 (63)	31 (69)
Total number of subjects	43	44	45	132	45

1. Although P=0.589 when comparing overall discontinuation rate between pooled sertraline and placebo (Fisher's exact test), a result-guided comparison of adverse experience discontinuation results in a Fisher's exact P of 0.017.

Table 2 Reduction in number of attacks at end-point (geometric means of the ratio of the number of attacks between end-point and baseline)

	Sertraline				Placebo (n=44)	P	
	50 mg (n=42)	100 mg (n=41)	200 mg (n=44)	Pooled (n=127)		Overall	Pooled
Panic attacks	0.20	0.14	0.21	0.18	0.35	0.007	0.002
Situational panic attacks	0.33	0.32	0.40	0.35	0.64	0.002	<0.001
Unexpected panic attacks	0.28	0.19	0.27	0.24	0.39	0.015	0.006
Limited symptom attacks	0.39	0.26	0.27	0.31	0.56	0.014	0.006

Table 3 Percentage of subject reporting zero panic attacks, by week

Visit	Pooled sertraline	Placebo	P (χ^2)
1	21% (27/127)	23% (10/44)	0.839
2	42% (47/113)	23% (10/43)	0.034
3	50% (53/107)	36% (15/42)	0.128
4	60% (61/102)	41% (17/41)	0.046
5	68% (67/98)	36% (14/39)	0.001
6	70% (67/96)	46% (17/37)	0.011
7	70% (62/89)	49% (17/35)	0.028
8	70% (62/89)	41% (14/34)	0.004
9	71% (61/86)	69% (22/32)	0.818
10	74% (64/86)	66% (21/32)	0.344
11	75% (62/83)	61% (19/31)	0.160
12	76% (63/83)	58% (18/31)	0.062
End-point	57% (72/127)	41% (18/44)	0.071

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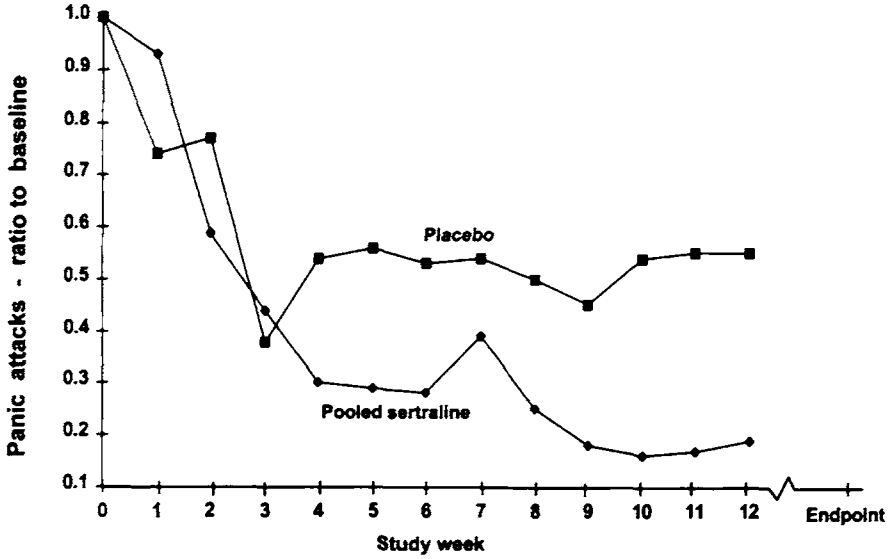

Fig. 1 Mean weekly frequency of panic attacks by group, expressed as a per cent of frequency at baseline. Weekly means reflect reducing *n* based on attrition; end-point provides the mean values obtained for the total efficacy sample, with the last value carried forward for patients not completing the study (pooled sertraline, $n=127$; placebo, $n=44$).

Overall four-group ANCOVA for these scores demonstrated significant treatment effect ($F=4.16$, d.f.=3, $P<0.01$) as did each pair-wise comparison with placebo ($P<0.05$) but there were no significant differences among the sertraline dose groups. The pooled sertraline treatment group was also superior to placebo in decreasing panic attacks, established by ANCOVA ($F=9.99$, d.f.=1, $P<0.01$) and confirmed by non-parametric Kruskal–Wallis ($\chi^2=7.67$, d.f.=1, $P<0.006$). Subjects taking sertraline showed significantly greater reductions in panic attacks than the placebo subjects at Week 2, Weeks 4–8, and Week 12. The median panic attacks per week at the end-point was 0.0 for sertraline compared to 1.0 for the placebo. End-point analysis of pooled sertraline *v.* placebo groups showed significant reduction in both situational panic attacks ($F=15.27$, d.f.=1, $P<0.001$) and unexpected panic attacks ($F=7.67$, d.f.=1, $P<0.007$).

Over 60% of the subjects in the pooled sertraline groups were free of panic attacks from Week 4 of the study onward (Table 4) and over 70% were panic-free after Week 6; these values were significantly superior to the placebo group at Week 2 and Weeks 4–8. At end-point 57% of the pooled sertraline sample were panic-free as compared to 41% of the placebo subjects. A large increase in the placebo response beginning at Week 9, and only gradually reducing, partially masks the treatment effect after that point.

The reduction in limited symptom attacks from baseline to end-point was significantly greater for sertraline than for placebo when ANCOVA was performed for the four treatment groups ($F=3.68$, d.f.=3, $P<0.02$) as well as ANCOVA for the pooled sertraline group *v.* placebo ($F=7.89$, d.f.=1, $P<0.006$). At end-point, the placebo group was suffering five times as many limited symptom attacks than the pooled sertraline subject groups (median 2.5 compared to 0.5).

The number of episodes of anticipatory anxiety at end-point were also reduced significantly in subjects taking sertraline as compared with placebo subjects on the four treatment group analysis, with median number of episodes as follows: 50 mg sertraline, 1.3, 100 mg sertraline 2.0, 200 mg sertraline, 3.5, pooled sertraline 2.0, and placebo, 4.8 ($F=5.88$, d.f.=3, $P<0.009$). Additionally, treatment with sertraline showed a significantly greater reduction in the percentage of time spent worrying about having a panic attack when ANCOVA was performed on the four treatment groups ($F=4.73$, d.f.=3, $P<0.004$)

Table 4 Panic and Anticipatory Anxiety Scale mean, s.d. and maximum values at baseline and end-point (last observation carried forward, LOCF) and Week 12 (subjects who completed study only)

	Placebo				Sertraline 50 mg				Sertraline 100 mg				Sertraline 200 mg				Pooled sertraline			
	n	Mean	s.d.	Max.[1]	*n*	Mean	s.d.	Max.	*n*	Mean	s.d.	Max.	*n*	Mean	s.d.	Max.	*n*	Mean	s.d.	Max.
Panic attacks																				
Baseline	44	9.4	15.6	92	42	5.4	6.5	29	41	9.9	15.8	71	44	4.8	5.8	28	127	6.6	10.5	71
End-point (LOCF)	44	8.8	20.9	125	42	1.7	3.3	16	41	2.5	8.9	53	44	2.3	4.7	20	127	2.2	6.1	53
Week 12	31	3.1	6.4	30	24	0.6	1.3	5	34	2.9	10.6	59	25	0.5	1.6	8	83	1.5	6.9	59
Unexpected attacks																				
Baseline	44	5.8	8.7	45	42	3.4	4.9	28	41	5.7	9.8	37	44	3.4	4.7	22	127	4.1	6.9	37
End-point (LOCF)	44	4.8	10.3	54	42	1.2	2.4	12	41	0.9	2.7	15	44	1.5	4.0	19	127	1.2	3.1	19
Week 12	31	2.4	3.9	15	24	0.3	0.8	3	34	0.9	2.8	15	25	0.2	0.4	1	83	0.5	1.8	15
Limited symptom attacks																				
Baseline	44	6.3	8.3	32	42	7.2	10.8	59	41	7.9	13.0	69	44	4.9	7.2	42	127	6.6	10.5	69
End-point (LOCF)	44	6.4	16.4	107	42	3.9	6.4	30	41	3.6	9.9	57	44	2.6	5.4	23	127	3.3	7.4	57
Week 12	31	2.8	4.0	16	24	3.3	7.0	33	34	3.5	10.3	56	25	2.7	7.3	35	83	3.2	8.5	56

1. *Minimum for all variables is zero*

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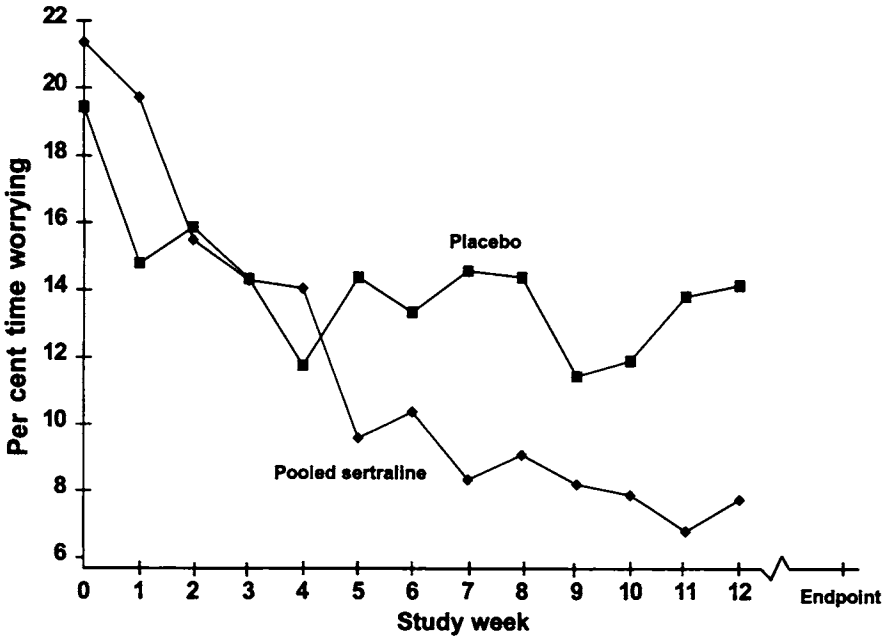

Fig. 2 Percentage time spent in anticipatory anxiety per week. Weekly averages are based on actual observations with decreasing numbers due to attrition; end-point shows averages for the total efficacy sample.

and the pooled sertraline group *v.* placebo (F=8.99, d.f.=1, P<0.004; Fig. 2).

The pooled sertraline groups exhibited significantly greater improvement on the CGI global improvement scale at the end of Weeks 2, 3, 4, 6, and 8 but not at end-point; CGI severity of illness showed a similar pattern of superiority at Weeks 4, 6 and 8. Other clinician rated measures of efficacy also revealed significantly greater improvement in sertraline-treated subjects as compared with placebo subjects. HAM–A changed −10.0 for the pooled sertraline group and −7.1 for placebo at end-point (F=4.65, d.f.=−1, P<0.04). Statistically significant HAM–A differences were observed as early as Week 2.

Although there was an imbalance in males and females in the treatment groups, overall significance was maintained for all efficacy variables when the analyses were controlled for gender.

Plasma concentrations of sertraline were proportional to sertraline dose at Week 4 and Week 12, with no significant change in mean plasma levels between the two timepoints; however, no relationship existed between efficacy and sertraline plasma concentration. Plasma levels provided an estimate of compliance: at Week 4, 97% of the subjects taking sertraline were judged compliant; even at Week 12, 91.5% of the sertraline subjects were compliant by this standard (two each in the 50 mg and 100 mg, and three in the 200 mg groups, were judged to be possible non-compliers).

Adverse experiences

Two serious adverse events occurred during the study, both in placebo-treated subjects (a 45-year-old male with history of partial complex seizure disorder experienced a single severe grand mal seizure; a 50-year-old woman suffered head trauma in a motor vehicle accident, suicidality was ruled out). The drop-out rate for adverse experiences overall was 20% (26/132) of sertraline-treated subjects and 4% (2/45) of placebo-treated subjects (Table 1). This difference was statistically significant when a *post hoc* test was performed (P=0.017, Fisher's exact test; pooled sertraline groups *v.* placebo group); however overall analysis of differences among groups does not reveal statistically significant differences (P=0.589, Fisher's exact test). Eight subjects in active treatment groups discontinued due to adverse experiences during the first week of treatment, when all the sertraline subjects were receiving 50 mg/day, most for typical serotonergic side-effects such as nausea, insomnia and agitation, but not exacerbation of panic attacks. None of the subjects in the placebo group dropped out in the first week.

Table 5 Adverse events reported by ⩾10% of sertraline-treated subjects

Adverse event	Sertraline (%)	Placebo (%)
Nausea	33	20
Headache	31	40
Insomnia	22	16
Diarrhoea	15	9
Dry mouth	14*	2
Fatigue	13	4
Somnolence	11	7
Nervousness	11	7
Dyspepsia	11	11
Ejaculatory delay[1]	19*	0

*P<0.05 *v.* placebo.
1. 13 of 67 males.

A total of 84% of the subjects treated with sertraline experienced at least one adverse event compared to 73% of the placebo group; this difference is not statistically significant. Again no significant dose relationship was found. The only adverse events that occurred with a significantly higher incidence in sertraline-taking subjects as compared with the placebo-taking subjects were dry mouth (P<0.05, Fisher's exact test, 2-tail) and ejaculation failure (P<0.05, Fisher's exact test, 2-tail). Ejaculation failure was coded as occurring in 20% of sertraline-treated male subjects but consisted primarily of ejaculatory delay rather than anorgasmia (1/16, 6/20, 6/29 in the 50 mg, 100 mg, and 200 mg groups respectively). The most common adverse events recorded during the study (>10%) are listed in Table 5. The vast majority of adverse experiences were mild or moderate in severity and the severity did not differ between treatment groups. No dose–response relationship was noted for the incidence of any individual adverse event. No statistically significant differences were found in the incidence of clinically significant laboratory abnormalities or vital sign or weight abnormalities between the pooled-sertraline and placebo groups. No clinically significant ECG abnormalities were noted.

DISCUSSION

Response to treatment

In this study, sertraline was shown to be significantly superior to placebo for the treatment of panic disorder across a wide

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spectrum of panic symptoms assessed by a variety of outcome measures. All three sertraline dosage groups were found to be significantly superior to placebo in reducing panic attacks. There were no significant differences in the efficacy of 50, 100 and 200 mg doses, although plasma levels were greater for the higher doses. Sertraline not only decreased panic attacks but also significantly reduced limited symptom attacks, the amount of anticipatory anxiety, and general anxiety (HAM–A). At end-point the pooled sertraline treatment group showed a 65% reduction in the ratio of episodes to baseline compared to a 39% reduction in the placebo group. The efficacy of sertraline, based on the CGI global improvement scale or the percentage of subjects completely free of panic attacks, was significantly superior to placebo at several points during the 12-week treatment programme but not at end-point. Overall, these findings are consistent with earlier research (Black, 1993; Hoehn-Saric *et al*, 1993; Oehrberg *et al*, 1995; Wade *et al*, 1997) which has demonstrated the effectiveness of selective serotonin reuptake inhibitors in reducing the symptoms of panic disorder.

Adverse events

Sertraline is reasonably well tolerated, with side-effects consistent with those seen with this class of drugs. There were no serious adverse events for subjects treated with sertraline. Two adverse events were found to be statistically associated with this compound – dry mouth and ejaculation failure, the latter consisting primarily of ejaculatory delay rather than anorgasmia. Additionally, a higher rate of early terminations associated with adverse events occurred in the sertraline treatment groups than in the placebo group, although this result may in part be anticipated with a fixed-dose design. A number of early terminations in the first week or two were noted due to serotonergic side-effects although not associated with the exacerbation of panic symptoms that has been previously reported with fluoxetine (Pecknold *et al*, 1995), imipramine (Cassano *et al*, 1994; Yeragani *et al*, 1992), or tricyclic antidepressants in general (Noyes *et al*, 1989). In the present investigation, no panic-like side-effects occurred with a significantly higher incidence in subjects taking sertraline as compared with placebo taking subjects. Further, the significant reduction in HAM–A by Week 2 supports the conclusion that sertraline is not associated with an increase in anxiety symptoms. However, there was decreased tolerance in this sample of subjects with panic disorder for the initial dose of sertraline (50 mg) which is well tolerated by people with depression (Svebak *et al*, 1990; Louie *et al*, 1993), post-traumatic stress disorder (Nagy *et al*, 1993), or obsessive–compulsive disorder (Greist *et al*, 1995) including paediatric subjects (Wolkow *et al*, 1996). The higher rate of side-effects in the sertraline-treated subjects did not lead to a lower completion rate: 63% (83/132) of subjects taking sertraline completed the study compared with 69% (31/45) of the subjects in the placebo group, a difference which is not statistically significant.

Although the 50 mg dose was demonstrated to be effective in pair-wise comparisons with placebo, a lower starting dose might improve tolerability in the panic disorder subject population.

Completion rates

Completion rates for this sertraline study, 64% for 12 weeks or 70% for 8 weeks, may have been depressed by the fixed-dose design. Nevertheless, they are comparable to findings of other investigations of panic disorder. After 8 weeks, open-label flexible-dose fluoxetine treatment produced a completion rate of 64% (Pecknold *et al*, 1995) and citalopram yielded a 67% rate in a flexible dose within a fixed-dose design (Wade *et al*, 1997). Oehrberg *et al* (1995) reported an exceptionally high 92% of subjects completing 12 weeks of treatment for panic disorder when paroxetine was combined with the additional clinical support of standardised cognitive therapy (again in a flexible-dose design).

Design considerations

The research design required a high current rate of panic attacks to eliminate mild cases of panic disorder and extended the lead-in phase to two weeks in an attempt to screen out placebo responders. Despite these standards, the results show quite high placebo rates, which have been noted in other research with this disorder (e.g. Oehrberg *et al*, 1995); this may reflect non-specific treatment effects including receiving a diagnosis, investigator attention, and systematic recording of symptoms in the daily diary. Apparently a two-week lead-in is of little value except for reassurance that subjects are not showing side-effects of discontinuation of previous psychotropic medication. Using the index of freedom from any panic attacks, the placebo rate was 41% at 4 weeks, 8 weeks and end-point. After 12 weeks of treatment this placebo rate was 58% for the subjects who completed the study, who represented 70% of the placebo subjects who started. The sudden improvement at Week 9 for placebo-taking subjects is demonstrated across several measures including ratio of panic attacks to baseline, the number of subjects who were panic-free and the percentage of time spent worrying about panic attacks; all dimensions subsequently reverse, whereas subjects on sertraline continued to show improvement.

The subject selection and lead-in requirements did not reduce the marked variability in panic disorder severity noted in most studies of this syndrome: a substantial minority of subjects reported extremely high frequencies of attacks, rendering the distribution of dependent variables non-normal and potentially obscuring significant clinical benefit. Expressing PAAS values as a ratio to the subject's baseline, and log-transforming the results, may allow a clearer picture of clinical benefit.

Although the research design limited the level of depression such that no subject met the criteria for major depression, no systematic monitoring of depression was carried out during the treatment programme itself; doing so would shed more light on this disorder and perhaps on the heterogeneity of the population. An additional limitation of the design is the absence of data regarding response to discontinuation of sertraline.

The current study was affected by gender selection issues that may limit its generalisability to women of child-bearing age. Women in this sample tended to respond better than men in all treatment groups, although there was no interaction between gender and treatment.

Future use of sertraline

The results of this investigation demonstrated the safety and efficacy of sertraline for the treatment of panic disorder. The 50 mg dose was no less effective than were the higher doses for subjects with panic disorder. A 25 mg initial dose would probably be even better for these subjects to ensure a high rate of compliance with treatment.

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CLINICAL IMPLICATIONS

- Sertraline is more effective than placebo in the treatment of panic disorder.
- A dose of 50 mg may be the most effective.
- Sertraline is safe and reasonably well-tolerated in this dose range.

LIMITATIONS

- Females of child-bearing age are under-represented in this sample.
- The study did not address avoidance behaviours and self-reporting measures were not utilised.
- This study did not assess the impact of discontinuation of sertraline.

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