Sertraline Versus Paroxetine in the Treatment of Panic Disorder: An Acute, Double-Blind Noninferiority Comparison

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Objective: Several classes of medications have demonstrated efficacy in panic disorder, but direct comparison of 2 proven treatments is still uncommon. The purpose of this study was to compare sertraline and paroxetine in the acute treatment of panic disorder.

Method: Adult outpatients with panic disorder with or without agoraphobia (DSM-IV and ICD-10 criteria) were randomly assigned in double-blind fashion to 12 weeks of treatment with flexible doses of sertraline (titrated up to 50–150 mg/day; N = 112) or paroxetine (titrated up to 40–60 mg/day; N = 113). Patients were then tapered off medication over 3 weeks. The primary analysis was a noninferiority analysis of Panic and Agoraphobia Scale (PAS) scores. Secondary measures included panic attack frequency and the Clinical Global Impressions-Improvement scale (CGI-I) (with responders defined as those with a CGI-I score ≤ 2). Data were collected from January 2000 to June 2001.

Results: Sertraline and paroxetine were associated with equivalent levels of improvement on the PAS total score, as well as on all secondary outcome measures. Eighty-two percent of patients taking sertraline versus 78% of those taking paroxetine were CGI-I responders at endpoint. Numerically more patients on paroxetine treatment compared with sertraline treatment discontinued due to adverse events (18% vs. 12%; NS), and a significantly higher proportion of paroxetine patients showed ≥ 7% weight gain (7% vs. < 1%; $p < .05$). During the taper period, the proportion of panic-free patients increased by 4% with sertraline but decreased by 11% with paroxetine ($p < .05$).

Conclusion: Sertraline and paroxetine had equivalent efficacy in panic disorder, but sertraline was significantly better tolerated and was associated with significantly less clinical worsening during taper than paroxetine.

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Panic disorder is a common anxiety diagnosis with a lifetime prevalence in the range of 3% to 4%.[1] Panic disorder is associated with a chronic course of illness and a great deal of distress, as well as impairment in quality of life and marked social and occupational disability.[2,3] Though patients suffering from panic disorder exhibit high rates of medical help-seeking, less than 50% receive appropriate treatment.[3,4]

Tricyclic antidepressants (TCAs) and benzodiazepines were for many years the mainstay of panic disorder treatment, but problems with tolerability and safety in overdose with TCAs and the potential for dependence and withdrawal with long-term benzodiazepine therapy have led to the consideration of selective serotonin reuptake inhibitors (SSRIs) as first-line treatment.[5,6] Double-blind, placebo-controlled trials have demonstrated the efficacy of paroxetine[7–9] and sertraline[10–13] in the treatment of panic disorder.

Although the SSRIs are similar as a group, there are differences in receptor binding affinities[14,15] and pharmacokinetic profiles[16] that suggest differences in the potential tolerability and effectiveness of individual SSRIs

in clinical practice. These findings are consistent with smaller, double-blind, comparator studies of depressed patients that have indicated that treatment with paroxetine is associated with lower tolerability,[17,18] higher withdrawal symptoms during discontinuation,[19–21] and increased ejaculatory dysfunction when compared with sertraline.[22–24] Cross-study comparisons and postmarketing surveillance provide important clinical information on the comparative efficacy and tolerability of 2 treatments. Nonetheless, the gold standard of evidence-based medicine is the double-blind, randomized clinical trial.

Approximately a decade after their introduction, double-blind comparisons of the SSRIs in the treatment of anxiety disorders are very rare. We were unable to identify a single comparison of sertraline and paroxetine in panic disorder. The aim of this study, therefore, was to compare the efficacy and tolerability of sertraline and paroxetine in the acute treatment of panic disorder.

METHOD

Study Design

The study was designed as a randomized, double-blind, parallel-group study of the efficacy and tolerability of 12 weeks of treatment with sertraline or paroxetine in patients with panic disorder. Data were collected from January 2000 to June 2001. Patients completing study treatment underwent a gradual taper from study medication over 3 weeks. The study was conducted at 5 centers in Denmark, 22 centers in Germany, 2 centers in the Netherlands, 2 centers in Switzerland, and 2 centers in Turkey. The study was approved by the institutional review boards/ethics committees of all participating centers. Study procedures were carried out in accordance with the Declaration of Helsinki, 1964, and its amendments and with the International Conference on Harmonization (ICH) guidelines for Good Clinical Practice. After a complete description of the study was given, written informed consent was obtained from all patients.

Study Sample

Patients who met the following inclusion criteria were eligible for study entry: (1) male or female outpatients between the ages of 18 and 65 years, inclusive; (2) primary DSM-IV and ICD-10 diagnosis of panic disorder with or without agoraphobia; (3) minimum of 4 panic attacks during the 4 weeks prior to screening; and (4) total score ≥ 18 at baseline on the clinician-rated version of the Panic and Agoraphobia Scale (PAS).[25,26] Patients were not eligible for study entry if they met any of the following exclusion criteria: (1) primary diagnosis other than panic disorder; (2) a Montgomery-Asberg Depression Rating Scale (MADRS)[27] total score (excluding item 3, inner tension) ≥ 14; (3) clinically significant and unstable medical illness; (4) current diagnosis of bipolar disorder, schizophrenic disorder, delusional disorder, epilepsy, major depressive disorder, obsessive-compulsive disorder, or social phobia; (5) history of alcoholism or drug abuse (within the past 3 years); (6) serious risk for suicide; (7) pregnancy or lactation or not using reliable contraceptive methods; (8) concomitant use of psychotropic drugs; (9) known intolerance or hypersensitivity to sertraline or paroxetine, or use of drugs with known contraindications or interactions (daily use of benzodiazepines required a 2-week drug-free period prior to baseline); and (10) need for structured psychotherapy or cognitive-behavioral therapy during the study.

Study Procedures

Patients underwent a screening evaluation followed by a washout period of up to 4 weeks, if needed. Patients who continued to meet all study entry criteria were randomly assigned to 12 weeks of double-blind treatment with either sertraline or paroxetine. Sertraline treatment was started at a daily dose of 25 mg in the first week, then increased to 50 mg from the second week onward. Titration to a dose of 100 mg was permitted from week 5 onward and a dose of 150 mg from week 7 onward. Paroxetine treatment was started at a daily dose of 10 mg in the first week and then increased weekly by 10 mg to an effective dose of 40 mg at week 4. Titration to a dose of 60 mg was permitted from week 5 onward. At the end of 12 weeks of study treatment, both drugs were gradually tapered off over a 3-week period: daily sertraline dose was reduced to (or maintained at) 50 mg for 1 week, then reduced to 25 mg for 1 week, then discontinued; daily paroxetine dose was reduced to 20 mg for 1 week, then reduced to 10 mg for 1 week, then discontinued. Concomitant psychotropic drugs were not allowed during the study. If rescue medication became necessary for treating severe insomnia during the taper period, then chloral hydrate, zolpidem, or zopiclone could be given on a limited basis (≤ 3 times per week).

Clinical Assessments

Safety and efficacy assessments were obtained at baseline and at the end of study weeks 1, 2, 4, 6, 8, 12, and 15 (or at the final visit if patients discontinued prematurely).

The primary outcome measure was the clinician-rated PAS,[25,26] which provides a 5-point frequency/intensity rating of 13 items across 5 panic disorder dimensions: panic attacks (frequency, severity, duration); agoraphobia/avoidance behavior (frequency, number, and importance of feared situations); anticipatory anxiety (frequency, intensity); disability (family, social/leisure, work); and health worries (harm, somatic belief). The PAS was chosen as the primary efficacy measure because a comprehensive panic scale is a more reliable measure than panic attack frequency.[28] The PAS was associated with good interrater reliability ($r = 0.78$), internal consistency (Cronbach $\alpha = .85$), external validity (Spearman rank correlation with Clinical

Global Impression Scale (CGI), r = 0.91),[26] and sensitivity to change.[29,30]

Secondary outcome measures included (1) the 7-point clinician-rated Clinical Global Impression-Severity of Illness (CGI-S) and -Improvement (CGI-I) scales[31]; (2) the 14-item Hamilton Rating Scale for Anxiety[32]; (3) the 10-item MADRS[27]; (4) the Sertraline Quality of Life Battery[33]; (5) the Digit Symbol Substitution Task; (6) the Digit Span (forward and backward); and (7) the Patient Global Impression, a 7-point Likert scale measuring severity (ranging from 1 = normal, no impairment at all, to 7 = most severe impairment) and improvement (ranging from 1 = very much improved to 7 = very much worse). The Patient Global Impression is identical to the CGI except that it is a patient-rated scale. In addition, panic diaries were used to record the frequency and intensity of each panic attack and the associated anticipatory anxiety.

Adverse events, volunteered or observed, were recorded and classified in terms of onset, duration, severity, seriousness, cause (as judged by the investigator), action taken, and outcome. Vital signs were obtained at every visit, and body weight was measured at baseline and after 6 and 12 weeks. Routine laboratory tests were performed at the screen visit, including red and white blood cell and platelet count, hemoglobin, hematocrit, sodium, potassium, glucose, creatinine, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, γ-glutamyl transpeptidase, and thyroid-stimulating hormone.

Statistical Methods

The study was designed and powered as a noninferiority trial[34–36] with the PAS change score as the primary outcome. A noninferiority trial is performed to show that a new treatment is no less effective than an existing treatment. It may be more effective or it may have a similar effect. Usually, this analysis is performed with a 1-sided test using a probability score of $p < .025$. The power calculation was performed for a 1-sided t test with shifted null hypothesis, based on experience from previous trials with the PAS[30,37] that found a difference of 4 points on the PAS to be clinically relevant. This difference was used as the noninferiority margin. Based on an assumed attrition rate of approximately 25%, the power calculation indicated that a sample size of 160 patients would be required per treatment group to achieve a value of at least 90% for $1 - \beta$. The primary, a priori efficacy analysis was performed on the per protocol population (also known as the efficacy-evaluable population) as required by ICH, Topic E9, for noninferiority trials.[38] This sample of patients met the following criteria: (1) completed at least 8 weeks of study treatment; (2) had greater than 80% compliance in the final 4 weeks; and (3) had PAS assessments available at week 8 or later. A secondary analysis was performed on the intent-to-treat (ITT) population, which consisted of all patients who were randomly assigned to study drug and for whom at least 1 postbaseline PAS assessment was available. The completer population (used for the efficacy analysis during taper) consisted of all efficacy-evaluable patients who had an evaluable PAS assessment at week 15. Patients who took at least 1 dose of study medication during the taper period were included in the taper off safety population for the assessment of adverse events during taper.

The noninferiority margin was specified in the protocol as being a 4-point difference in the endpoint PAS change score; this was chosen as the minimum difference that would be considered clinically significant. The null (H_0) and alternate (H_a) hypotheses consisted of the following: $H_0 = E_{Parox} - E_{Sert} \geq 4$ and $H_a = E_{Parox} - E_{Sert} \leq 4$, respectively.

The null hypothesis is rejected if the upper bound of the 95% confidence interval (CI) for the difference between the 2 treatments is smaller than the specified margin of 4 points on the PAS, i.e., noninferiority can be concluded. The test of therapeutic equivalence (noninferiority) was based on a 1-sided t test using an analysis of covariance (ANCOVA) model with a shifted null hypothesis at the 2.5% level. Center effects and baseline values were included as covariates. The time course of improvement in primary and secondary outcome measures was evaluated using a repeated-measures analysis. Analysis of panic frequency was based on log-transformed data because of the nonnormality of baseline-to-endpoint change in panic attack frequency. For all continuous variables, 2-sided 95% CIs and least-squares means were calculated using ANCOVA models with baseline measure and center included as covariates. Binary data were analyzed with the chi-square test or Fisher exact test, with multiple imputation according to the propensity scoring methods.[39,40] A sensitivity analysis was conducted on the ITT population.

RESULTS

Patient Characteristics

Patient characteristics at baseline were similar in both treatment groups (Table 1).

Study Treatment and Patient Disposition

The mean ± SD daily dose used by patients at study endpoint was 84.5 ± 39.1 mg of sertraline and 48.1 ± 11.2 mg of paroxetine. Forty-four (39%) of the sertraline patients were titrated up to 100 mg at the end of week 4, and 13 (12%) were titrated up to 150 mg at the end of week 6. Thirty-two (28%) of the paroxetine patients were titrated up to 60 mg at the end of week 4.

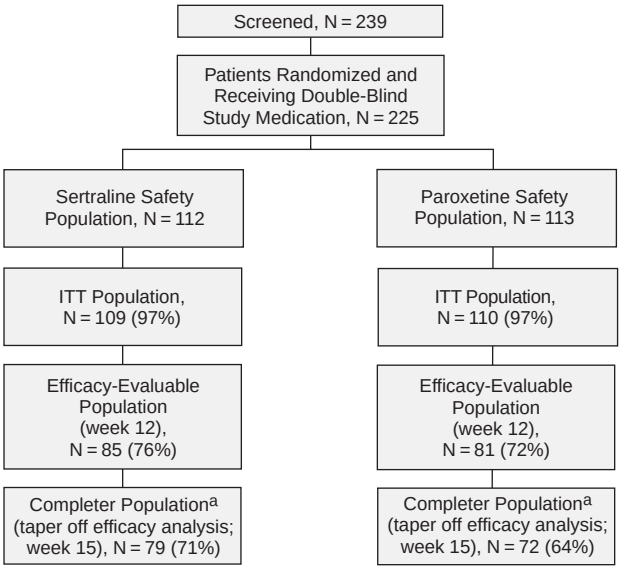
Eighty-five (76%) of the 112 patients assigned to sertraline and 81 (72%) of the 113 patients assigned to paroxetine fulfilled the criteria for the efficacy-evaluable

Table 1. Demographic and Clinical Characteristics of Patients (ITT sample)

Characteristic	Sertraline (N = 112)	Paroxetine (N = 113)
Age, mean ± SD, y	39.6 ± 11.7	38.1 ± 11.7
Female, %	60	66
Agoraphobia subtype		
Patients with subtype, %	68	63
Duration since first diagnosis, mean, y	3.9	3.8
Non-agoraphobia subtype		
Patients with subtype, %	32	37
Duration since first diagnosis, mean, y	3.4	3.2
Previous antidepressant treatment, %		
SSRIs and related drugs	21	28
Tricyclic antidepressants and related drugs	25	19
Baseline no. of panic attacks per week, mean ± SD	8.1 ± 8.8	6.2 ± 5.0
Baseline PAS total score, mean ± SD	29.4 ± 5.9	29.2 ± 6.1
Baseline HAM-A score, mean ± SD	22.8 ± 6.7	23.1 ± 6.1
Baseline MADRS score, mean ± SD	7.0 ± 3.5	7.6 ± 3.5

Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, ITT = intent to treat, MADRS = Montgomery-Asberg Depression Rating Scale, PAS = Panic and Agoraphobia Scale, SSRI = selective serotonin reuptake inhibitor.

Figure 1. Patient Disposition



[a]Defined according to study protocol.

population (Figure 1). Eighty-one (72%) of the sertraline patients and 76 (67%) of the paroxetine patients completed the study through week 15 (including the taper off period). Thirty-one (28%) of the sertraline patients discontinued (reasons: adverse event, N = 13; insufficient response, N = 1; protocol violation, N = 5; withdrew consent, N = 4; lost to follow-up, N = 5; other, N = 3), whereas 37 (33%) of the paroxetine patients discontinued (reasons: adverse event, N = 20; insufficient response, N = 3; protocol violation, N = 5; withdrew consent, N = 5; lost to follow-up, N = 4). Seventy-nine (71%) of the sertraline patients and 72 (64%) of the paroxetine patients were included in the completer population for the taper off efficacy analysis. Eighty-three (74%) of the 112 patients assigned to sertraline and 75 (66%) of the 113 patients assigned to paroxetine were included in the taper off safety analysis. Discontinuation due to adverse events occurred in 12% of the patients receiving sertraline and in 18% of the patients receiving paroxetine (Fisher exact test, p = .258, NS).

Treatment Response

Primary outcome measures. Treatment with sertraline and paroxetine resulted in equivalent levels of improvement on the a priori primary outcome measure, the PAS total score (Table 2). Noninferiority tests based on the primary efficacy-evaluable analysis and on the standard ITT analysis both yielded endpoint change score differences of less than 1 point between sertraline and paroxetine. The associated 95% CIs for each difference score (see Table 2) excluded a difference of more than 4 points. The associated test with shifted hypothesis ($p < .05$) showed noninferiority. Figure 2 shows very similar improvement over time in the PAS total score. For both treatment groups, > 35% reduction from baseline in the PAS total score had been achieved by week 6.

Secondary outcome measures. The 95% CIs show that we can exclude any meaningful (clinically significant) difference between the 2 drugs. Sertraline was found to be fully equivalent to paroxetine as a treatment for panic disorder across all secondary measures on the basis of both the protocol-specified efficacy-evaluable and ITT analyses (see Table 2). Mean improvement on individual PAS subscales was also similar at endpoint in both treatment groups (Figure 3). Furthermore, the efficacy of sertraline and paroxetine was equivalent (p = .487) with regard to the PAS across the agoraphobia and non-agoraphobia subtypes. The mean percent improvement at endpoint in the PAS total score was similar for sertraline versus paroxetine in the agoraphobia subtype (45% vs. 43%) and in the non-agoraphobia subtype (51% vs. 46%). An efficacy-evaluable analysis found that global illness severity at endpoint was reduced to the "mild-to-none" range in 72% of patients treated with sertraline and 64% of patients treated with paroxetine. Similarly, global response (CGI-I score ≤ 2) was achieved by 82% of the efficacy-evaluable population treated with sertraline compared with 78% of patients treated with paroxetine.

Treatment Tolerability

For the safety population (patients who took at least 1 dose of study medication), the following treatment-emergent adverse events were reported with an incidence of 10% or higher for sertraline versus paroxetine, re-

Table 2. Primary and Secondary Efficacy Variables at Baseline, Week 12, and Endpoint for Patients With Panic Disorder (efficacy-evaluable [EE] and ITT analyses; least-squares mean values, based on ANCOVA)[a]

	Sertraline			Paroxetine			Noninferiority		2-Sided
Efficacy Variable	N	Mean	95% CI	N	Mean	95% CI	Estimated Difference	95% CI	p Value for Superiority
PAS total score									
Baseline ITT	109	29.4		110	29.2				
Change at endpoint-EE	85	–15.9	–18.3 to –13.5	81	–15.4	–17.8 to –13.0	–0.46	–2.82 to 1.91	.749
Change at endpoint-ITT-LOCF	109	–13.5	–15.9 to –11.1	110	–12.7	–15.2 to –10.3	–0.76	–3.08 to 1.56[b]	.589
Panic attack frequency									
Baseline ITT	104	8.1		103	6.2				
Change at endpoint-EE	82	–2.86	–4.46 to –1.26	79	–2.61	–4.20 to –1.02	–0.25	–1.79 to 1.29	.786
Change at endpoint-ITT	104	–1.82	–4.15 to 0.52	103	–2.13	–4.49 to 0.24	0.31	–1.97 to 2.60	.821
HAM-A score									
Baseline ITT	103	22.8		101	23.1				
Change at endpoint-EE	80	–13.2	–14.9 to –11.9	80	–13.0	–14.7 to –11.4	–0.21	–1.82 to 1.40	.830
Change at endpoint-ITT	100	–12.5	–14.3 to –10.7	100	–12.1	–13.9 to –10.2	–0.43	–2.16 to 1.30	.684
MADRS score									
Screen ITT	99	10.1		94	10.8				
Change at endpoint-EE	81	–4.83	–5.82 to –3.84	79	–5.05	–6.06 to –4.05	0.23	–0.76 to 1.21	.702
Change at endpoint-ITT	96	–4.32	–5.51 to –3.13	93	–4.33	–5.58 to –3.07	0.01	–1.14 to 1.16	.989
CGI-S score									
Baseline ITT	109	4.7		110	4.7				
Change at endpoint-EE	85	–1.82	–2.13 to –1.52	81	–1.78	–2.09 to –1.47	–0.04	–0.34 to 0.26	.813
Change at endpoint-ITT	109	–1.65	–1.94 to –1.36	110	–1.55	–1.85 to –1.26	–0.10	–0.38 to 0.19	.575
CGI-I score									
Endpoint-EE	85	1.7		81	1.9		–0.16	–0.44 to 0.11	.320
Endpoint-ITT	109	2.2		110	2.4		–0.15	–0.46 to 0.16	.433
PGI-Severity score									
Baseline	108	5.1		110	4.9				
Endpoint-EE	84	–2.00	–2.36 to –1.64	81	–2.01	–2.37 to –1.65	0.01	–0.34 to 0.36	.971
Endpoint-ITT	108	–1.84	–2.18 to –1.50	110	–1.75	–2.09 to –1.41	–0.10	–0.43 to 0.23	.625
PGI-Improvement score									
Endpoint-EE	85	2.1		81	2.0		0.09	–0.20 to 0.38	.609
Endpoint-ITT	109	2.4		110	2.5		–0.09	–0.42 to 0.24	.659

[a]Patients in the EE analyses completed 8 weeks of treatment with assessment available.
[b]Change at endpoint based on multiple imputation: –0.76 (95% CI = –2.8 to 2.8); p = .978.
Abbreviations: ANCOVA = analysis of covariance, CGI-I = Clinical Global Impression-Improvement scale, CGI-S = Clinical Global Impression-Severity of Illness scale, HAM-A = Hamilton Rating Scale for Anxiety, ITT = intent to treat, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, PAS = Panic and Agoraphobia Scale, PGI = Patient Global Impression.

spectively: insomnia, 11% versus 11%; fatigue, 9% versus 13%; dizziness, 8% versus 14%; agitation, 14% versus 11%; headache, 21% versus 20%; and nausea, 21% versus 26% (all NS). Perhaps due to a gradual titration schedule, both sertraline and paroxetine were well tolerated, with many typical adverse events (sexual dysfunction, diarrhea, sedation) occurring at a rate less than 10%.

Clinically significant weight gain (≥ 7% increase in baseline body weight) occurred in < 1% of patients on sertraline treatment compared with 7% of patients on paroxetine treatment ($p < .05$).

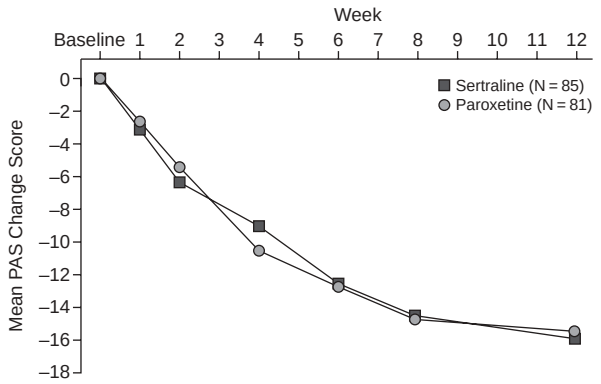
Outcome of Gradual Taper

The outcome (primary and secondary outcomes) of the 3-week taper was compared in patients in the per protocol population who completed the study through the week 15 visit (completer sample). The safety analysis (withdrawal symptoms) was performed on the taper off safety population (patients who took at least 1 dose of study medication in the taper period). CGI-I responder rates, and the proportion of patients reporting complete panic blockade, were similar for sertraline and paroxetine at week 12 (Figure 4). Paroxetine taper was associated with significantly greater illness exacerbation than sertraline taper. This clinical worsening was reflected in an increase in panic attack frequency, as well as overall panic symptomatology as measured by the PAS total score (Figure 5). A post hoc exploratory analysis, using items from a previously reported SSRI withdrawal checklist,[20] revealed a trend for a lower rate of taper-emergent withdrawal symptoms for sertraline as compared with paroxetine (10% and 20%, respectively; taper off safety population, Fisher exact test, df = 1, p = .07; Figure 6).

DISCUSSION

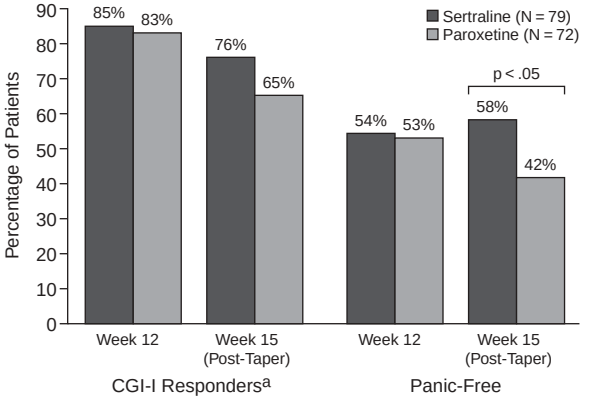
The current study is, to our knowledge, the first randomized, double-blind, head-to-head comparison of sertraline and paroxetine in the treatment of panic disorder. Unlike the majority of reported comparisons of 2 active treatments in affective and anxiety disorders, the current study was designed and powered as an equiva-

Figure 2. Effect of 12 Weeks of Treatment With Sertraline Versus Paroxetine on Panic and Agoraphobia Scale (PAS) Change Score (efficacy-evaluable analysis)[a]



[a]Least-squares mean values shown based on analysis of covariance performed on efficacy-evaluable population.

Figure 4. CGI-I Responder Status and Panic-Free Status at Endpoint and Post-Taper: Results of Completer Analysis for Sertraline Versus Paroxetine



[a]CGI-I score ≤ 2.
Abbreviation: CGI-I = Clinical Global Impression-Improvement scale.

Figure 3. Reduction in Panic and Agoraphobia Scale (PAS) Subscale Scores (efficacy-evaluable analysis)

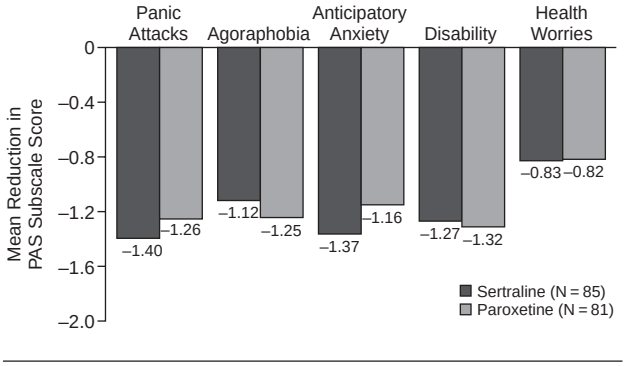
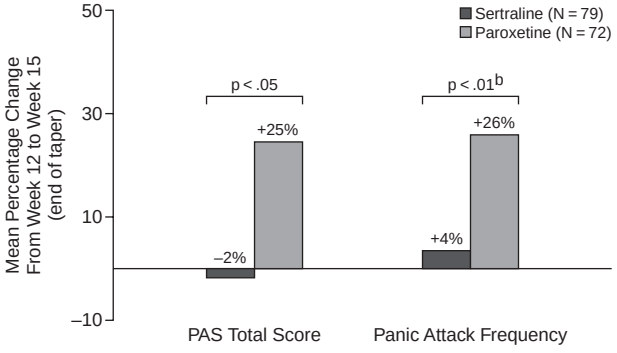


Figure 5. Change in Panic and Agoraphobia Scale (PAS) Total Score and Panic Attack Frequency During Taper: Completer Analysis[a]



[a]Positive values indicate worsening, negative values indicate improvement.
[b]Based on analysis of covariance of log-transformed panic attacks.

lence (noninferiority) trial with the objective of determining whether sertraline was therapeutically equivalent to paroxetine in panic disorder. To make this determination, a stringent equivalence margin was established that consisted of a difference score of 4 points on the PAS, judged to be the smallest difference in the PAS that could reliably be interpreted as clinically significant.

Using this equivalence margin, and the associated CIs, we found that sertraline was therapeutically equivalent to paroxetine on the primary outcome measure, the PAS total score. Furthermore, improvement was equivalent for sertraline and paroxetine across each of the PAS factor scores. At baseline, patients in the sertraline group were experiencing a nonsignificantly higher weekly frequency of panic attacks (8.1 vs. 6.2). Adjustment for this in an ANCOVA analysis yielded the same equivalence results.

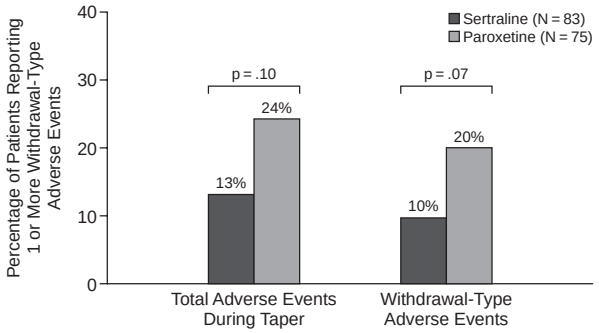
Consistent with endpoint results demonstrating therapeutic equivalence, the time course of improvement was also very similar for sertraline and paroxetine, with a mean reduction in PAS total score in the range of 40% to 45% by week 6 with both drugs.

Overall, the efficacy-evaluable population, consisting of patients that received an adequate course of acute treatment (at least 8 weeks), showed equivalently high CGI-I responder rates, 82% for sertraline and 78% for paroxetine. The presence of agoraphobia did not alter rates of treatment response to either drug.

Tolerability and Discontinuation Effects

While sertraline and paroxetine demonstrated equivalence in efficacy, there were notable differences in the tolerability of both acute treatment and of gradual taper from medication. Numerically more patients receiving paroxetine discontinued from the study due to intolerable ad-

Figure 6. Taper-Emergent Adverse Events (taper off safety analysis)[a]



[a]Events were agitation, anxiety, diarrhea, dizziness, headache, insomnia, myalgia, nausea, and paresthesia.

verse events (18% vs. 12%; NS). Clinically significant weight gain (> 7% above baseline) was reported in 7% of patients on paroxetine treatment compared with < 1% of patients on sertraline treatment ($p < .05$). This degree of weight gain is consistent with a long-term trial (26–32 weeks) that found ≥ 7% weight gain in 25% of patients on paroxetine treatment versus 4% on sertraline treatment.[41]

Gradual medication taper over 3 weeks resulted in a significantly greater clinical worsening with paroxetine compared with sertraline. Clinical worsening was reflected both in an increase in SSRI-like withdrawal symptoms and in an exacerbation of panic symptomatology. Taper-emergent SSRI-like withdrawal symptoms were reported in 10% of patients on sertraline treatment compared with 20% on paroxetine treatment ($p = .07$). Similarly, the proportion of patients remaining panic-free slightly increased from 54% to 58% with sertraline treatment, while the proportion decreased with paroxetine treatment, from 53% to 42% (difference between groups: $p < .05$). Withdrawal symptoms and reemergence of panic symptoms cannot be completely disentangled. However, it is likely that the increase in symptomatology is a function of serotonin withdrawal rather than a primary illness exacerbation, though discontinuation effects may well have had a "panicogenic" effect during the taper period. The discontinuation results obtained in this study are consistent with 3 previous double-blind studies comparing discontinuation of sertraline and paroxetine. In all 3 studies,[19–21] abrupt discontinuation of paroxetine after at least 4 months of treatment for MDD resulted in significantly more severe discontinuation symptoms than discontinuation of sertraline. The current results now suggest that a significant subgroup of panic patients treated with paroxetine is at risk for withdrawal-type symptoms after only 12 weeks of treatment and despite use of a gradual taper schedule. This finding suggests that patients with an anxiety disorder diagnosis are at greater risk for withdrawal effects than patients with depression. A previous benzodiazepine withdrawal study[42] found pre-taper anxiety severity to be a significant predictor of withdrawal symptom severity. Various mechanisms have been proposed to account for the significantly greater withdrawal observed with paroxetine, including its higher anticholinergic activity compared with that of sertraline,[43] as well as taper-related withdrawal of paroxetine's auto-inhibition of cytochrome P450 2D6 function.[44,45]

Further research is needed to evaluate the extent to which the tolerability and withdrawal differences identified in clinical trials such as this one generalize to clinical practice. A recent medical utilization study based on an analysis of a patient health care claims database found significantly greater reduction in health care services utilization with sertraline compared with paroxetine.[46] More research is needed to confirm these findings and to evaluate what efficacy and tolerability factors account for differences among treatments.

Equivalence Trial Designs: Use in Drugs With Proven Efficacy

Despite vigorous critiques[47] in the past decade of the use of placebo-controlled trials for the assessment of antidepressant efficacy, such trials continue to be the almost exclusively utilized gold standard. While equivalence trials represent an appealing alternative design, 2 issues have precluded their wider use: the lack of an internal metric (i.e., placebo) for determining assay sensitivity and the general need for larger sample size to ensure adequate power to test for noninferiority. Assay sensitivity is a crucial issue when attempting to establish the efficacy of an unproven treatment. For 2 treatments with established efficacy, though, such as sertraline and paroxetine in panic disorder, indexing response against placebo is less necessary. Three placebo-controlled trials of sertraline[10–13] and 3 placebo-controlled trials of paroxetine[7–9] in panic disorder have documented the efficacy of each drug for the treatment of this disorder. The effect size of each drug in reducing panic attack frequency has been reported[48] to be very similar for both sertraline (0.32, 0.27, 0.34) and paroxetine (0.31, 0.27; a third study[7] showed an effect size of 0.33, but is more difficult to interpret because of concomitant use of cognitive-behavioral therapy). The improvement in panic attacks, and other global indices, was in the same range in the current study compared with previously published studies of both sertraline[10–13] and paroxetine[7–9]; this provides an external index of assay sensitivity. The advantage of a 2-arm comparison of 2 established drugs is that more severely ill patients can be included than in a 3-arm study including a placebo group, although the patients in this study were not more severely ill (on average) than those in other studies with 3 arms.

In conclusion, the current study found sertraline and paroxetine to have equivalent efficacy, across all primary

and secondary measures, for the treatment of panic disorder with or without agoraphobia. Treatment with sertraline was modestly but significantly better tolerated, with a lower side effect burden, fewer discontinuations due to adverse events, and less weight gain. Improvement in panic anxiety was maintained during gradual sertraline taper, while gradual paroxetine taper was associated with significant clinical worsening. The results of this equivalence trial illustrate the importance of head-to-head comparator studies as the cornerstone of evidence-based medical decision-making.

Drug names: paroxetine (Paxil and others), sertraline (Zoloft), zolpidem (Ambien).

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