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Paroxetine in the Treatment of Panic Disorder
A Randomised, Double-Blind, Placebo-Controlled Study

S. OEHRBERG, P. E. CHRISTIANSEN, K. BEHNKE, A. L. BORUP, B. SEVERIN, J. SOEGAARD, H. CALBERG, R. JUDGE, J. K. OHRSTROM and P. M. MANNICHE

Background. This study compared the efficacy and tolerability of paroxetine with placebo in the treatment of panic disorder.
Method. After three weeks of placebo, patients received 12 weeks of treatment with paroxetine (20, 40, or 60 mg) or placebo, and finally two weeks of placebo. Dosages were adjusted according to efficacy and tolerability. Standardised cognitive therapy was given to all patients. The primary measure of outcome was reduction in the number of panic attacks.
Results. Analysis of the results showed statistically significant differences in favour of paroxetine between the two treatment groups in two out of the three primary measures of outcome, i.e. 50% reduction in total number of panic attacks and number of panic attacks reduced to one or zero over the study period. For the third measure of outcome, the mean change in the total number of attacks from baseline, there was a positive trend in favour of paroxetine. The results of the primary measures of outcome were strongly supported by the results of the secondary efficacy measures of outcome. In addition, paroxetine, at all doses, was very well tolerated.
Conclusion. Paroxetine plus cognitive therapy was significantly more effective than placebo plus cognitive therapy in the treatment of panic disorder.

In 1980, panic disorder was recognised as a distinct diagnostic entity by the DSM–III (American Psychiatric Association, 1980). It is a common disorder, with a lifetime prevalence of about 2%. Being female, divorced, or separated is associated with higher prevalence of panic disorder. The hazard rates for panic disorder appear to be highest between the ages of 25 and 34 years for women and between the ages of 30 and 44 years for men (Wittchen & Essau, 1993).

Studies of pharmacological and psychological treatments have shown their efficacy in panic disorder. Of the psychological treatments, cognitive therapy is of particular note (Beck *et al*, 1992; Chambless & Gillis, 1993).

Studies of pharmacological treatments have centred mainly on benzodiazepines and antidepressants. The standard benzodiazepines, diazepam and clonazepam, have been shown to be effective at higher doses (Kahn & van Praag, 1992) and alprazolam has, in several studies, shown efficacy and rapid onset of action (Rosenberg *et al*, 1991). However, the use of benzodiazepines is associated with several disadvantages, including sedation, reduced coordination, impaired cognition, and, most importantly, development of dependence with associated withdrawal symptoms (Salzman, 1993).

Studies with antidepressants include those with clomipramine, imipramine, and desipramine and, more recently, with selective serotonin reuptake inhibitors such as fluvoxamine and fluoxetine (Schneier *et al*, 1990; Den Boer, 1988; Black *et al*, 1993), all of which show good efficacy in the treatment of panic disorder. However, the tricyclic agents are associated with significant anticholinergic side-effects which may be troublesome for some patients. No previous study has compared a serotonin reuptake inhibitor with placebo when both groups received standardised cognitive therapy.

The efficacy of paroxetine as an antidepressant is well established (Feighner & Boyer, 1989). The purpose of the present study was to evaluate the efficacy and tolerability of the highly selective serotonin reuptake inhibitor, paroxetine, in the treatment of patients with panic disorder.

Method

This study was a double-blind, placebo-controlled, parallel-group comparison. An initial three-week placebo period was followed by a 12-week treatment period with either paroxetine or placebo, after which patients underwent a two-week placebo period. Seven Danish centres participated in the study.

To be included in the study, patients of either sex had to be aged 18–70 years and have a diagnosis of panic disorder according to DSM-III-R (American Psychiatric Association, 1987), with or without agoraphobia, and have to have had at least three full panic attacks during the four weeks before entry in the study. A baseline score of 14 or less on the Hamilton Depression Scale (Hamilton, 1969), 17-item version, was also required.

Among the exclusion criteria were primary diagnosis of major depression (DSM-III-R) or generalised anxiety disorder (DSM-III-R), schizophrenia or dementia, organic brain disease, or alcohol or drug abuse, or concomitant treatment with psychotropics, monoamine oxidase inhibitors, anticoagulants, or benzodiazepines. In the case of benzodiazepines, patients were excluded if they were still receiving these drugs at entry to the three-week placebo period, or if there was an emergence of benzodiazepine-withdrawal symptoms in the placebo period.

All patients received placebo tablets in the first three weeks (placebo period), followed by random allocation to either paroxetine or placebo treatment. Regardless of the magnitude of improvement seen in the placebo period, patients could enter the active treatment period as long as they satisfied the inclusion criteria. In the first two weeks of study treatment, paroxetine doses were gradually increased from 10 to 20 mg/day ('low dose'). From week 3 onward, the dosage was flexible, either 20 mg/day ('low dose') or 40 mg/day ('medium dose'), and from week 4 onward dosage could be further increased to 60 mg daily ('high dose') according to efficacy and tolerability. In both treatment groups, all daily doses consisted of two visually identical tablets. Patient compliance was assessed at each visit by tablet counts. Urinalysis was done to determine whether patients had been taking concomitant benzodiazepines. In addition to pharmacological treatment, all patients received standardised psychotherapy according to the principles developed by Hawton *et al* (1989).

Patients were assessed at weekly intervals during the placebo period; at the end of weeks 1, 2, 3, 4, 6, 9, and 12, and at the end of the two-week placebo period. Throughout the study period, regular joint rating sessions with the participating psychiatrists were arranged to minimise interrater variability on the observer rating scales. Assessment of response was based on consecutive three-week intervals.

The principal measure of outcome was the reduction in the number of panic attacks, as recorded by the patient in a daily diary. A reduction equal to or more than 50% from baseline was considered to be beneficial. In addition, the percentage of patients who had their panic attacks reduced to zero, or one, in a three-week interval was determined, and the mean change in the number of panic attacks from baseline in each group was evaluated from the diary assessments. The daily diary card was used to document the severity of each panic attack, the duration of each attack, whether or not there were any precipitating factors, and the severity of agoraphobia, if present, for each attack.

Secondary measures of outcome included:

(a) a reduction in score equal to or greater than 50% on the Hamilton Anxiety Scale (HAM-A) (Hamilton, 1969)
(b) a response on the Clinical Global Impression (CGI) scale (Guy, 1976) where a response was defined as a score of 2 (borderline illness) or less at the assessments for patients whose baseline score was 3 (mildly ill) or more
(c) the mean reduction on the Zung Self-Rating Scale for Anxiety (Zung, 1971).

At each assessment, adverse events were noted. These were detected by observation or could be reported by the patient either spontaneously or in response to the open question, "Do you feel different in any way since starting the treatment or since the last visit?"

Safety assessments included vital signs, e.g., blood pressure, pulse and body weight and laboratory tests of haematology and clinical chemistry variables. Ethical considerations were all in accordance with the Helsinki Declaration.

The sample size was based upon the assumption that response rates in the paroxetine and the placebo groups would be 70% and 40%, respectively ($\alpha = 0.05$, $1 - \beta = 0.80$). To allow for a 30% attrition rate, we considered it necessary to recruit 120 patients in total. Data analysis of the efficacy variables was based on the Cochran–Mantel–Haenszel χ^2 test, adjusting for centre, categorical data, the Breslow–Day test for homogeneity over centres, and analysis of variance with the factors treatment, centre, and treatment/centre interaction for continuous variables. In all cases, a two-tailed significance level of 5% was used to determine presence of statistical significance.

Results

In the analysis of this study, two populations were considered – the intention to treat and the per protocol. Within these populations, the analyses used the observed cases data set, consisting of each patient's observations at each interval and the end-point, which was generated from the observed cases data

set by taking the last valid result between weeks 3 and 12. Results are presented for the intention to treat population (consisting of each patient's observations at each interval) only, as the other analyses yielded similar results.

Demographic data and patient history

A total of 129 patients were enrolled, nine patients dropped out during the placebo period, and the remaining 120 patients were equally allocated to receive either paroxetine or placebo. Thus, 60 patients in each group comprised the intention to treat analysis. The two treatment groups were comparable with respect to demographic variables. Eighty per cent of the paroxetine group and 72% of the placebo group were female, the mean ages being 37.7 years and 37.0 years for paroxetine and placebo, respectively; the age range was 21–69 years for the population. Familial disposition to panic disorder was seen in 33% of the paroxetine group and 25% of the placebo group. Almost all of the patients had panic attacks which were rated as moderate or severe at baseline. Only seven patients in the paroxetine group and nine patients in the placebo group did not report any agoraphobic avoidance at baseline. Of those that did report agoraphobic avoidance, 66% and 63% reported the severity as moderate or severe in the paroxetine and placebo groups respectively.

Patient withdrawals

Of the 120 patients entering the 12-week treatment period, 55 (92%) paroxetine patients and 52 (87%) placebo patients completed the 12-week treatment period. Five patients on paroxetine were withdrawn, as compared with eight on placebo: one paroxetine patient was withdrawn for lack of efficacy plus adverse events, three were withdrawn because of adverse events, and one was withdrawn for lack of compliance. The adverse events leading to withdrawal in this group were abdominal pain, confusion, decreased appetite, depression, dizziness, headache, incoordination, decreased libido, nausea, and unintended pregnancy. Three placebo patients were withdrawn for lack of efficacy/relapse, one for lack of compliance, three for protocol violations, and one for uncertain diagnosis.

Concomitant medication

No concomitant medication was taken at baseline by 49 paroxetine patients (82%) and 53 placebo patients (88%). During the study, 16 (27%) paroxetine patients and six (10%) placebo patients were prescribed analgesic, anti-allergic, or other non-psychotropic drugs. Concomitant psychotropic medication was not permitted during the study.

Efficacy

The primary efficacy evaluations were based on measures of changes in the frequency of panic attacks occurring in three-week intervals. Comparisons between the groups were based on consecutive three-week intervals. The first three-week interval after the placebo run-in period was referred to as week 3, the second as week 6, the third as week 9, and the fourth as week 12.

The number of patients with at least 50% reduction from baseline in number of panic attacks (Fig. 1) was significantly greater in the paroxetine group at six weeks, at nine weeks ($P=0.006$ and $P=0.001$, respectively), and at 12 weeks ($P=0.001$) when 82% ($n=42$) of the paroxetine patients, as compared with 50% ($n=25$) of the placebo patients, had responded. Both treatment groups showed early onset of action, improvement being evident in the first three-week period.

Evaluation of the reduction in number of panic attacks to one or zero (Fig. 2) showed similar differences in favour of paroxetine, although statistical significance was not seen until week 12 when 36% ($n=19$) of the paroxetine patients, as compared with 16% ($n=8$) of the placebo patients, had responded ($P=0.024$).

The third measure, the mean change from baseline in the number of panic attacks (Fig. 3), showed at week 12 a mean reduction of 16.0 from a baseline mean of 21.2 in the paroxetine group, as compared

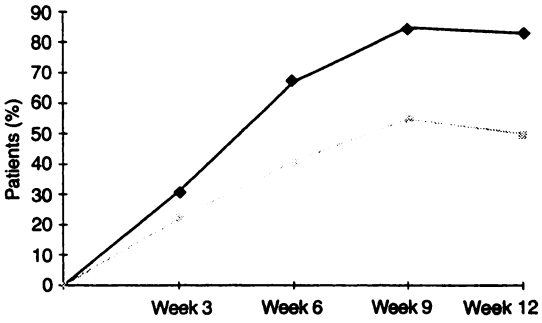

Fig. 1 Panic attack response rates. Percentage of patients with at least 50% reduction from baseline number of panic attacks per three-week period. Statistically significant differences in favour of paroxetine were seen at 6, 9, and 12 weeks ($P=0.006$, $P=0.001$, and $P=0.001$, respectively).◆–◆: paroxetine; ■ - ■ : placebo.

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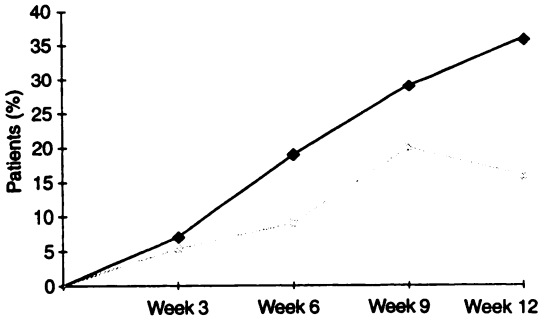

Fig. 2 Panic attack response rates–percentage of patients with number of panic attacks reduced to one or zero per three-week period. Statistically significant difference in favour of paroxetine was seen at 12 weeks ($P=0.024$). ◆-◆: paroxetine; ■-■: placebo.

with a mean reduction of 9.8, from a baseline mean of 26.4 in the placebo group (not statistically significant; $P=0.084$).

In the placebo group, all three measures reflected deterioration in the fourth three-week period, whereas such a pattern was not seen in the paroxetine group.

In the range of the secondary measures of outcome, the results all supported the response pattern seen on the primary measures of outcome. On the HAM–A and the CGI, the response rates were significantly higher in the paroxetine group at 6 and 12 weeks, as compared with the placebo group (Table 1).

On the patient self-rated assessment, the Zung self-rating scale, the effect of paroxetine, measured as the mean change from baseline score, was significantly superior to placebo at 6 and 12 weeks (Table 1).

As this study employed flexible dosing, it is not possible to determine a minimally effective dose. However, in the paroxetine group, most patients

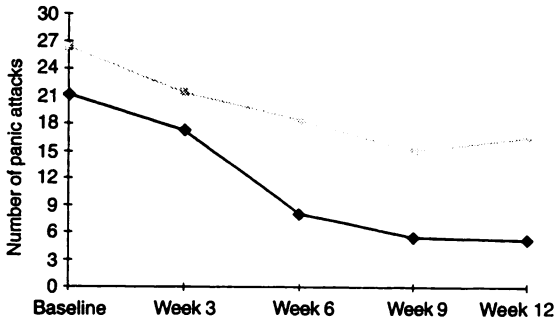

Fig. 3 Panic attack response rates–mean changes from baseline total number of panic attacks per three-week period. Differences were not statistically significant at any time point ($P>0.05$). ◆-◆: paroxetine; ■-■: placebo.

Table 1

Secondary efficacy meaures, Hamilton Anxiety Scale (HAM-A), Clinical Global Impression (CGI), and Zung Patient Self-Rating Scale for Anxiety (ZUNG): summary of statistically significant differences between treatment groups

HAM-A	Mean baseline score	Percentage of patients with at least 50% reduction from baseline score	
		Week 6	Week 12
Paroxetine	24. 3	59%	85%
Placebo	23.5	38%	51%
P value	–	0.021	<0.001
CGI		**Percentage of patients with severity of illness ≤2 (mildly ill)**	
	Baseline	Week 6	Week 12
Paroxetine	0%	42%	71%
Placebo	0%	22%	40%
P value	–	0.023	0.003
ZUNG	**Mean baseline score**	**Mean change from baseline score**	
		Week 6	Week 12
Paroxetine	42.1	-6.0	-6.5
Placebo	41.6	-3.4	-4.3
P value	–	0.013	0.042

P values for mean changes from baseline in ZUNG rating scale were obtained with F-tests in analysis of variance adjusting for centre. All other *P* values were obtained with CMH χ^2 tests.

(75%) were treated with a 40 or 60 mg dose and 47% of patients received the 60 mg dose at some point in the study.

Adverse events

The number of patients reporting at least one adverse event was 46 (77%) in the paroxetine group and 33 (55%) in the placebo group; this difference between groups was statistically significant ($P=0.012$).

Emergent adverse events (i.e., any adverse events which started on or after the first day of study medication) reported by 10% or more of the patients in either treatment group were as follows: for paroxetine: nausea (23%), sweating (23%), headache (22%), dizziness (17%), asthenia (15%), decreased libido (12%), and dry mouth (10%); for placebo: nausea (12%), sweating (5%), headache (23%), dizziness (7%), asthenia (3.3%), decreased libido (2%), and dry mouth (8%).

Anticholinergic events, particularly dry mouth, were observed with similar incidence in the two treatment groups. Overall, the side-effect profile for paroxetine was as expected of a drug of this class, and was not different from the side-effect profile seen in depressed patients treated with paroxetine.

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Two patients in both treatment groups had serious emergent adverse events during the study. These comprised 'joint disorder' and 'pulmonary oedema' in the paroxetine groups, and 'anxiety' and 'surgical procedure' in the placebo group. None of these events were considered by the investigators to be related to treatment.

Since most psychotropic medications seem to have some effects on discontinuation of medication, an attempt was made to ascertain the extent to which these occurred after discontinuation of paroxetine.

In this study, all patients who competed 12 weeks of active treatment then received two weeks of placebo, thus enabling adverse events occurring after discontinuation of paroxetine or placebo to be compared. In this placebo period, only 19 patients out of 55 (34.5%) who had received paroxetine reported any adverse event on discontinuation, as compared with seven out of 52 (13.5%) patients who had received placebo. Most patients reported just one adverse event, most being rated as of mild or moderate severity. The adverse event which was reported with greatest excess over placebo was 'dizziness'. This was reported by four patients (7.3%) who had received paroxetine and one who had received placebo.

Overall, paroxetine was well tolerated and most patients were able to discontinue abruptly without ill effect, even from the higher doses (40 and 60 mg).

Safety data

No clinically significant changes in haematologic variables, clinical chemistry variables, or vital signs that were considered to be related to treatment were observed.

Discussion

Significant improvement was seen in panic disorder (DSM–III–R) patients treated with paroxetine, as compared with placebo, for both the primary and secondary outcome measures. In the paroxetine group, clear improvement for the primary outcome measures was seen at three weeks, and statistical significance, as compared with placebo, was seen from week 6 onward. With regard to the primary outcome measures, the response in the paroxetine group increased and was maintained over the 12-week treatment period, while in the placebo group, deterioration, after initial improvement up until nine weeks, was seen during the last three-week period. Of particular clinical significance is the fact that from a baseline mean of 21.2 panic attacks in the paroxetine group, at week 12, 36% of these patients had become almost free of panic attacks in that their panic-attack frequency had been reduced to zero or one over at the last three weeks of the study.

Placebo response rates can be quite high for panic disorder patients – up to 40% being reported in some studies (Maier *et al*, 1991; Rosenberg *et al*, 1991). The placebo response seen in this study was higher, but that was to be expected since both treatment groups received standardised cognitive therapy.

Generally, unspecific treatment factors are probably responsible for high response rates on placebo; for example, patients receive more attention and explanation. These factors are also an inherent part of behaviour/cognitive therapies.

As expected, more adverse events were recorded among paroxetine patients. The predominant adverse events noted were class-specific effects of the SSRIs, and the same pattern of adverse events has been noted for depressed patients in trials with paroxetine (Dunbar, 1989).

However, the more frequent occurrence of adverse events in the paroxetine group did not lead to a higher withdrawal rate: 92% of the paroxetine patients, as compared with 87% of the placebo patients, completed with 12-week treatment period. Thus paroxetine appeared to be well tolerated, even at higher doses (40 and 60 mg).

Symptoms occurring after discontinuation of paroxetine were minor, occurring in only a few patients, despite the fact that 75% of patients were discontinued from doses of paroxetine of 40 mg or greater.

Previous studies of antidepressants in panic disorder, particularly fluoxetine (Schneier *et al*, 1990; Humble & Wistedt, 1992), have shown that an increase of some adverse events such as agitation, restlessness, jitteriness ('jitteriness syndrome') (Schneier *et al*, 1990), diarrhoea, and insomnia may occur, particularly if the dose is initiated at too high a level or increased too rapidly. In this study, such an increase of adverse events constituting the 'jitteriness syndrome' was not seen; therefore, it would appear that the slow titration of dose in the first week of this study was a well-tolerated regimen.

This study was not designed for dose finding, but 47% of the paroxetine patients received the highest dose of 60 mg daily. However, this may overestimate the required dose of paroxetine, since the trial method confounded dose and time.

No analysis was done to attempt to ascertain which patients are more likely to benefit from paroxetine or placebo.

Panic disorder appears to be a chronic condition in most patients. Although a minority of patients have a short episode, the rest have either recurrent

episodes of varying severity or chronic, persistent symptoms (Uhde *et al*, 1985). Thus, long-term treatment appears to be indicated for many patients, and therefore a safe and well tolerated treatment regimen is essential. Such long-term studies are under way with paroxetine.

This study is the first comparison of a SSRI with placebo in which both groups received standardised cognitive therapy. A clear advantage for combination therapy, i.e. paroxetine plus cognitive therapy, in the treatment of panic disorder, was demonstrated.

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S. Oehrberg, MD, Vor Frue Straede 4, DK-9000 Aalborg, Denmark; **P. E. Christiansen**, MD, Rosenkrantzgade 2, DK-8000 Aarhus, Denmark; **K. Behnke**, MD, Falkoner Alle 112, DK-2000 Frederiksberg, Denmark; **A. L. Borup**, MD, Radhusvej 12, DK-4180 Soroe, Denmark; **B. Severin**, MD, Noerrebrogade, DK-2200 Copenhagen N, Denmark; **J. Soegaard**, MD, Algade 63C, DK-4000 Roskilde, Denmark; **H. Calberg**, MD, Idraetsvej 101, DK-2650 Hvidovre, Denmark; **J. K. Ohrstrom**, MD, Novo Nordisk A/S, Krogshoejvej 41, DK-2880 Bagsvaerd, Denmark; **R. Judge**, MBChB, MRCPsych, SmithKline Beecham, New Frontier Science Park South, Harlow, Essex; **P. M. Manniche**, MSc, Novo Nordisk A/S, Krogshoejvej 41, DK-2880 Bagsvaerd, Denmark

Correspondence: Dr R. Judge, CNS Therapeutic Unit, SmithKline Beecham Pharmaceuticals, New Frontier Science Park South, Third Avenue, Harlow, Essex CM19 5AG

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