Paroxetine, Clomipramine, and Cognitive Therapy in the Treatment of Panic Disorder

Abraham Bakker, M.D.; Richard van Dyck, M.D., Ph.D.;
Philip Spinhoven, Ph.D.; and Anton J. L. M. van Balkom, M.D., Ph.D.

Background: This 12-week, placebo-controlled study was carried out to compare the relative efficacy of paroxetine, clomipramine, and cognitive therapy in the treatment of DSM-III-R–defined panic disorder with or without agoraphobia.

Method: After a 3-week single-blind, placebo run-in period, 131 patients were randomly assigned to receive double-blind medication or 12 sessions of cognitive therapy based on the model of Clark. Efficacy assessments included the daily panic attack diary, the Clinical Global Impression scale, the Patient Global Evaluation, the Hamilton Rating Scale for Anxiety, the Marks-Sheehan Phobia Scale, the Montgomery-Asberg Depression Rating Scale, and the Sheehan Disability Scale.

Results: Comparisons with placebo revealed significant superiority of paroxetine (20–60 mg/day) and clomipramine (50–150 mg/day) on nearly all outcome measures. On most measures, paroxetine also showed higher efficacy than cognitive therapy. With few exceptions, cognitive therapy did not differ significantly from placebo. The number of subjects becoming panic-free (66%) was higher and the onset of action was faster in the paroxetine-treated group. Treatment with cognitive therapy yielded the highest drop-out rate (26%).

Conclusion: In this short-term study assessing treatment of panic disorder and agoraphobia, paroxetine and clomipramine were consistently superior to pill placebo, whereas cognitive therapy was superior on only a few measures.

(J Clin Psychiatry 1999;60:831–838)

Received March 12, 1998; accepted March 10, 1999. *From the Department of Psychiatry and the Institute for Research in Extramural Medicine, Vrije Universiteit, Amsterdam (Drs. Bakker, van Dyck, and van Balkom), and the Department of Clinical and Health Psychology and Department of Psychiatry, Leiden University, Leiden (Dr. Spinhoven), the Netherlands.*

Supported by a grant from SmithKline Beecham Pharmaceuticals.

The authors thank all the therapists and medical doctors involved in this study for their participation.

Reprint requests to: Abraham Bakker, M.D., Department of Psychiatry, Vrije Universiteit, Valeriusplein 9, 1075 BG Amsterdam, the Netherlands (e-mail: bramb@pca-znw.nl).

Many studies have demonstrated the efficacy of antidepressants in the treatment of panic disorder with or without agoraphobia.[1] Tricyclic antidepressants (TCAs) have been used since they were studied by Klein in the 1960s.[2] The serotonergic TCAs clomipramine and imipramine have been well studied.[3–6] More recently, the selective serotonin reuptake inhibitors (SSRIs) have shown antipanic efficacy as well.[7–10]

Psychological treatment of panic disorder has also been studied extensively.[11] Exposure in vivo has especially demonstrated its efficacy in the treatment of agoraphobic avoidance.[12,13] During the last 2 decades, cognitive-behavioral treatment methods for panic attacks have been developed, including techniques such as cognitive therapy, relaxation training, and exposure to interoceptive cues.[11]

A number of treatment outcome studies in panic disorder have been published that compare antidepressive treatment and cognitive-behavioral interventions.[9,14] Also, the combination of these treatments has been given attention in panic disorder, panic disorder with agoraphobia, and agoraphobia.[15–17] However, the results of comparisons of cognitive-behavioral methods and antidepressants do not yield consistent findings. Whereas, for example, the study by Black et al.[9] favored treatment with the SSRI fluvoxamine above cognitive therapy, the Clark et al.[14] study showed better outcome for cognitive therapy when compared with imipramine.

Until now, only placebo-controlled studies that compared one antidepressant with a cognitive-behavioral treatment have been reported for panic disorder with and without agoraphobia in a single design. The present study reports on the comparison of the SSRI paroxetine with both the TCA clomipramine and cognitive therapy as described by Clark.[18] This was done for the following reasons. First, clomipramine has never been compared in a study with a cognitive-behavioral intervention. Since it is suggested that clomipramine might have a better outcome than imipramine in the treatment of panic disorder,[5] such a comparison would be a useful extension of the Clark study.[14] Second, paroxetine has been compared with placebo in patients who had all been treated with standardized cognitive therapy.[15] In that 12-week study, paroxetine plus cognitive therapy was significantly more effective than placebo plus cognitive therapy in reducing the num-

ber of panic attacks. So far, no direct comparison of the efficacy of paroxetine and cognitive therapy as single treatments has been made. Third, a recent study reviewing the pros and cons of clomipramine in the treatment of panic disorder concluded that, in view of the alternatives now available, clomipramine should not be used as a first-line antipanic medication, because benefits are severely limited by a high dropout rate due to adverse reactions occurring mostly during the first weeks of treatment.[19] To increase acceptability and compliance, our trial used a low starting dose to avoid troublesome initial side effects.

METHOD

Design

In this 12-week study, patients with panic disorder with or without agoraphobia were randomly assigned to 1 of 4 treatments: paroxetine, clomipramine, and placebo, all administered double-blind, and cognitive therapy. During a single-blind run-in period of 3 weeks before the start of the study, patients received placebo treatment. Subjects in the 3 medication conditions received pill placebo (single-blind) during this run-in period, whereas subjects randomly assigned to cognitive therapy received an attention placebo treatment. The rationale provided for this attention placebo was that patients had to practice describing their panic attacks precisely prior to treatment, since secure registration was needed to benefit from cognitive therapy.

Patients were included in the study only if they had experienced at least 3 panic attacks during this placebo run-in period. Assessments took place at the end of the 3-week placebo run-in period (pretest) and after 12 weeks of active treatment (posttest). All patients who dropped out between pretest and posttest were included in the intent-to-treat sample.

Subjects

Outpatients between the ages of 18 and 70 years who met DSM-III-R criteria for panic disorder as a main diagnosis and had a minimum of 3 panic attacks in the 3-week run-in period were included. After 2 intake sessions with a psychiatrist with extensive experience in the field of anxiety disorders, the diagnosis of panic disorder was established. In a third session, patients were given a complete explanation of the present study. Those who wanted to participate gave written informed consent. Pregnant women and patients with severe somatic diseases were excluded. Patients who used antidepressants, neuroleptics, or benzodiazepines could enter the study only if they were willing and able to stop taking these drugs before the placebo run-in period.

Treatments

Patients were treated at the Outpatient Clinic for Anxiety Disorders at the Psychiatric Centre Amsterdam, Vrije Universiteit, Amsterdam, and the Jelgersma Outpatient Clinic of the Psychiatric Hospital Endegeest, Oegstgeest, the Netherlands.

Patients assigned to the medication group received double-blind paroxetine (20–60 mg/day), clomipramine (50–150 mg/day), or placebo. Medication was administered by residents in psychiatry. The residents had all been working at a specialized outpatient clinic for anxiety disorders for at least 1 year. They were supervised weekly by both an experienced psychiatrist and the main investigator. Treatment was started with a daily dose of paroxetine (10 mg/day), clomipramine (10 mg/day, increasing to 25 mg/day after 3 days), or matching pill placebo. Treatment was titrated upward to paroxetine, 20 mg/day, or clomipramine, 50 mg/day, at the end of the first week. Thereafter, at the end of weeks 2, 3, 4, and 6, the dosage could be adjusted, at the discretion of the medical doctor, on the basis of the efficacy index (clinical efficacy against side effects) of the Clinical Global Impression scale (CGI). At all times, the patient was unaware of any change in the dosing regimen. At every visit, compliance was checked by a capsule count. Patients failing to take study medication as prescribed for more than 4 consecutive days were defined as noncompliant and thus withdrawn from the study. In the second half of the study (weeks 7–12), medication was continued at a constant level, and patients came to the clinic for brief assessment sessions and new medication prescriptions every 2 weeks. The use of benzodiazepines was checked by urine samples at pretest, after 6 weeks, and at posttest.

Cognitive therapy was provided in 12 weekly 45-minute sessions by psychologists and psychiatrists with broad experience in cognitive-behavioral treatment of all anxiety disorders who had participated in previous trials as well. Cognitive therapy was based on the cognitive theory of Clark.[18] By means of a Socratic dialogue with the therapist, patients were challenged to replace their so-called causal catastrophic misinterpretations of benign bodily sensations by alternative, rational, and nondistressing thoughts. During the treatment, behavioral experiments were introduced to test the empirical basis for the causal catastrophic misinterpretations. Behavior such as staying away repeatedly without communication or failing to keep agreements that were part of the treatment was discussed with the therapist. If subjects failed to correct this behavior, they were withdrawn from the study because of noncompliance.

Both medication and cognitive therapy treatments were defined in detail to ensure that the active ingredients were actually delivered and to prevent the delivery of unwanted treatment ingredients. Standardization of treatments was ensured by the use of detailed treatment manuals, a therapist training program conducted by an expert in cognitive therapy, and regular supervision sessions. Only therapists trained in behavior therapy who had prior experience of

cognitive therapy participated in the cognitive therapy condition. All cognitive therapy sessions were audiotaped and discussed in weekly sessions by therapists and investigators to ensure that treatment was delivered properly.

No concurrent cognitive-behavioral therapy was given during treatment with medication; during cognitive therapy, no psychopharmacologic agents were provided. In all 4 conditions, the use of additional benzodiazepines was prohibited and was monitored by urine tests.

Measures

Each panic attack and the total number of symptoms experienced on each occasion were recorded by the patients in panic diaries on a daily basis. Panic attacks were defined as containing at least 4 DSM-III-R symptoms. A weekly panic frequency was derived from the panic diaries. The panic frequency was averaged over a 3-week period, yielding 5 consecutive intervals: the placebo run-in period and four 3-week periods between pretest and posttest. Patients were considered panic-free at posttest when they had been free of panic attacks during the last 3-week interval (weeks 10–12).

The following assessor rating scales were used to evaluate therapeutic effects: the Hamilton Rating Scale for Anxiety (HAM-A),[20] the Montgomery-Asberg Depression Rating Scale (MADRS),[21] and the CGI-Severity of Illness (CGI-S)[22] score. The assessors, all experienced residents in psychiatry, received central training using videotaped interviews with regard to reliable use of the scales.

Patients were asked to fill in the Marks-Sheehan Phobia Scale (MSPS),[23] the Patient Global Evaluation (PGE), and the Sheehan Disability Scale (SDS)[23] and to give an Overall Phobia Score and an Anticipatory Anxiety Score (both range 0–10).

Statistical Analysis

To check for pretest differences between the 4 conditions, a series of univariate analyses of variance or nonparametric equivalents were performed on sociodemographic and clinical severity variables. By means of t tests or chi-square tests, possible differences between completers and dropouts at pretest were analyzed. Differences in the number of patients panic-free at posttest across the 4 conditions were analyzed by means of chi-square tests. Moreover, a Cox regression analysis was used to assess differences between conditions in the rate of becoming and staying panic-free while controlling for differences in panic frequency at pretest. More specifically, being panic-free after 3, 6, 9, or 12 weeks was analyzed.

Since the panic frequency distribution was highly skewed, the weekly numbers of panic attacks (plus 1) were transformed using the natural log in order to provide more nearly normal distributions.[24] The results on the natural log-transformed panic frequency and on all other rating scales were statistically analyzed as follows. To diminish chance findings, we first used a 4 (group) by 2 (time) general linear model (GLM) repeated measures procedure to investigate whether the treatments yielded an overall time effect and/or an overall group-by-time interaction effect. In case of an overall significant time effect, the 4 conditions were analyzed separately with 2-tailed paired t tests to investigate whether the symptoms changed significantly between pretest and posttest. These t tests were considered significant at $p < .05$. In the case of an overall significant group-by-time interaction effect, a second GLM procedure was performed to identify differences in efficacy between the conditions. In this GLM procedure, pretest scores served as covariates. The 4 conditions were compared pairwise at posttest with respect to estimated marginal means adjusted for the covariate (2-tailed tests significant at $p < .05$). This second GLM procedure was also performed with the MSPS agoraphobia scores as a second covariate. This could possibly increase the power of the multivariate test. However, since the results were not influenced by adding agoraphobic avoidance scores as a covariate, the outcome of these tests will not be discussed separately in the results section.

In addition to completer analyses, intent-to-treat analyses were performed in which dropouts were also included. For the dropouts, the last observation was carried forward to serve as posttest.

Cohen's *d* effect sizes were calculated to rate the extent of possible time effects.[25] The effect sizes were calculated within each of the 4 treatment conditions by subtracting mean posttest from pretest and then dividing the difference by the pooled standard deviation of pretest and posttest scores of the treatment in question.[26]

RESULTS

Attrition

A total of 154 patients were enrolled at the 2 centers. Fifty-five subjects randomly assigned to 1 of the 3 medication conditions were also analyzed in the Lecrubier et al. study,[10] which reported psychopharmacologic treatment only. Of these 154 patients, 39 were scheduled to receive placebo, 39 clomipramine, 38 paroxetine, and 38 cognitive therapy. Twenty-three subjects entered the placebo run-in period, but were not included in the active treatment phase of the study because they did not meet inclusion criteria at pretest. Reasons for exclusion of these 23 patients at pretest were lack of compliance (N = 7), fewer than 3 panic attacks during the 3-week placebo run-in (N = 8), and not fulfilling other inclusion and/or exclusion criteria (N = 8). Of these 23 patients, 7 were scheduled to receive placebo, 7 clomipramine, 6 paroxetine, and 3 cognitive therapy. The number of dropouts during the run-in period did not differ significantly across the 4 conditions.

The remaining 131 patients were randomly assigned as follows: 32 paroxetine, 32 clomipramine, 32 placebo, and

Table 1. Demographic Characteristics of the Treatment Conditions (Intent-to-Treat Sample)

Variable	Cognitive Therapy (N = 35)	Paroxetine (N = 32)	Clomipramine (N = 32)	Placebo (N = 32)
Age, y, mean ± SD	33.7 ± 8.1	34.7 ± 8.9	35.3 ± 9.3	35.1 ± 7.6
Duration of panic disorder, y, mean ± SD	6.3 ± 6.3	6.7 ± 7.5	7.4 ± 6.1	7.3 ± 5.8
Severity of panic attacks (DSM-III-R), N (%)				
Moderate	13 (37)	10 (31)	11 (34)	15 (47)
Severe	22 (63)	22 (69)	21 (66)	17 (53)
Spontaneous panic attacks (%)	48.8	48.6	48.6	56.4
Severity of agoraphobia (DSM-III-R), N (%)				
None	3 (9)	0 (0)	1 (3)	2 (6)
Mild	14 (40)	16 (50)	14 (44)	11 (34)
Moderate	15 (42)	13 (41)	14 (44)	14 (44)
Severe	3 (9)	3 (9)	3 (9)	5 (16)
Men/women, N	12/23	13/19	14/18	8/24
Married or cohabiting, N (%)	21 (60)	25 (78)	24 (75)	20 (63)
Positive family history of anxiety disorders, N (%)	10 (29)	17 (53)	13 (41)	13 (41)
Previous drug treatment, N (%)				
Benzodiazepines	14 (40)	21 (66)	17 (53)	12 (38)
Antidepressants	2 (6)	0 (0)	1 (3)	0 (0)
Unknown drugs	2 (6)	0 (0)	0 (0)	0 (0)
Combination of antidepressants and benzodiazepines	1 (3)	0 (0)	4 (13)	7 (22)
None	16 (46)	11 (34)	10 (31)	13 (41)

35 cognitive therapy. The demographic data for the intent-to-treat sample are presented in Table 1. Of 131 patients, 6 (4%) met criteria for panic disorder without agoraphobia. The remaining 125 patients (95%) also suffered from agoraphobic avoidance. The agoraphobic avoidance was mild for 55 (42%) of 131 patients, moderate for 56 (43%) of 131 patients, and severe for 14 (11%) of 131 patients. There were no significant differences at pretest between the treatment groups on any of the demographic characteristics or efficacy measures.

Four patients (12.5%) in the paroxetine group, 3 (9.4%) in the clomipramine group, 9 (25.7%) in the cognitive therapy group, and 2 (6.3%) in the placebo group dropped out between pretest and posttest, i.e., during the active phase of the study. The reasons for dropout were lack of patient compliance (N = 11; cognitive therapy N = 8, paroxetine N = 1, clomipramine N = 1, placebo N = 1), lack of efficacy (N = 4; cognitive therapy N = 1, paroxetine N = 2, placebo N = 1), intolerable side effects (N = 2; nausea and constipation, both clomipramine), and patient improvement (N = 1; paroxetine). Noncompliance in the cognitive therapy condition consisted mainly of being repeatedly unable or unwilling to visit the outpatient clinic and, in the medication conditions, failure to take the medication correctly, as was concluded from the capsule count. The number of dropouts across the treatment conditions did not differ significantly ($p = .10$, Pearson χ^2 test). There were no significant differences between dropouts (N = 18) and completers (N = 113) on any of the demographic characteristics or outcome measures at pretest.

Outcome (Completers)

The mean ± SD daily dosage for paroxetine was 38.6 ± 16.3 mg and for clomipramine, 93.1 ± 37.1 mg.

At posttest, 11 patients (i.e., 37% of 30 completers) treated with pill placebo were free from panic attacks in the last 3-week interval of the study. For subjects treated with cognitive therapy or clomipramine this number was 14 (54%) of 26 completers and 17 (59%) of 29 completers, respectively. The highest response was found in the paroxetine-treated group: 21 (75%) of the 28 subjects completing the study were panic-free from weeks 10–12, or earlier. Pairwise comparisons with chi-square tests revealed a significant difference between paroxetine and placebo ($N = 58$; $\chi^2 = 7.03$, $df = 1$, $p = .008$).

A Cox regression analysis comparing the 3 active treatments with placebo while controlling for panic frequency at pretest (3 contrasts) showed a significant difference between paroxetine and placebo (odds ratio [OR] = 2.54; 95% confidence interval [CI] = 1.21 to 5.32, $p = .013$). These results indicate that in comparison to patients treated with pill placebo, patients treated with paroxetine were more likely to become and stay panic-free during an earlier phase of treatment.

The change in panic frequency was analyzed on the natural log-transformed weekly numbers of panic attacks (plus 1). GLM procedures were performed on the panic frequency of all separate 3-week intervals (week 3, 6, 9, and posttest). At week 3, neither significant time effects nor significant interaction effects were found. At week 6, week 9, and posttest, all 4 treatment conditions demonstrated significant time effects on the panic frequency (t tests significant at $p < .05$). From the second 3-week period (at week 6, 9, and posttest), there was a significant group-by-time interaction effect in the completer sample. Pairwise comparisons in the second GLM procedure revealed a superior effect from paroxetine in comparison with pill placebo at week 6, week 9, and posttest ($p = .006$, $p = .007$, and $p = .002$, respectively). At post-

test (week 12), both clomipramine and cognitive therapy showed differences with placebo as well (p = .027 and p = .018, respectively).

On all other rating scales (CGI-S, PGE, HAM-A, MSPS, Overall Phobia Score, Anticipatory Anxiety Score, SDS, and MADRS), there were significant time effects for the 4 treatments except for cognitive therapy on the MADRS and placebo on the Anticipatory Anxiety Score. This outcome indicates that in all conditions anxiety, agoraphobia, depression, and social disability ameliorated significantly.

On all these rating scales, a significant group-by-time interaction effect was demonstrable. This finding was further analyzed with a second GLM repeated measures procedure. Pairwise comparison of the 4 conditions revealed a superior effect of paroxetine over placebo on all these measures. Moreover, paroxetine was superior over cognitive therapy on all scales except panic frequency and PGE. Clomipramine showed superiority over placebo on all measures except MSPS agoraphobia and MADRS. The finding that cognitive therapy treatment yielded significant advantages over placebo only on panic frequency and PGE was striking. Differences between clomipramine and cognitive therapy were found only on the Overall Phobia Score and MADRS, both in favor of the antidepressant. The results are summarized in Table 2.

Outcome (Intent-to-Treat)

The mean ± SD dosage for paroxetine was 36.2 ± 16.4 mg/day and for clomipramine, 90.6 ± 36.9 mg/day.

For the intent-to-treat sample, the percentages of panic-free patients at posttest in the different conditions were as follows: placebo, 11 (34%) of 32 patients; cognitive therapy, 14 (40%) of 35 patients; clomipramine, 17 (53%) of 32 patients; and paroxetine, 21 (65%) of 32 patients. As in the completer analysis, pairwise comparisons between conditions (significant at p = .05) revealed a difference in the amount of panic-free patients between paroxetine and placebo (N = 64; $\chi^2 = 6.25$, df = 1, p = .012). Moreover, in this sample, significantly more patients treated with paroxetine were panic-free in comparison with cognitive therapy (N = 67; $\chi^2 = 4.40$, df = 1, p = .036).

In conformity with the completer sample, the Cox regression analysis showed a significant difference between paroxetine and pill placebo (OR = 2.49; 95% CI = 1.20 to 5.19, p = .015), indicating that patients treated with paroxetine have a higher chance of becoming panic-free during an earlier phase of treatment than those treated with placebo.

Globally, on all other outcome measures, the results of the intent-to-treat analyses were identical to those of the completer analyses. The following differences in outcome with the completer analyses were found: on the panic frequency, the superiority of clomipramine and cognitive therapy over placebo disappeared (p = .057 and p = .11, respectively, at posttest). However, this was not the case for paroxetine (p = .024, p = .023, and p = .011 at week 6, week 9, and posttest, respectively).

In the intent-to-treat sample, paroxetine differed from cognitive therapy on the PGE as well, indicating that paroxetine was superior over cognitive therapy on all measures except panic frequency. The superiority of clomipramine over placebo was not demonstrable in the intent-to-treat analysis on panic frequency and MADRS.

In the intent-to-treat sample, no significant differences were demonstrated between cognitive therapy and placebo. In addition to the differences found in the completer sample on Overall Phobia Score and MADRS, clomipramine also showed more improvement than cognitive therapy on the HAM-A, MSPS anxiety, Anticipatory Anxiety Score, and SDS in the intent-to-treat analyses. The intent-to-treat data are also presented in Table 2.

Effect Sizes

Since significant time effects were found in all treatment conditions, including placebo, Cohen's *d* effect sizes were calculated as well. The results are shown in Table 3.

Inspection shows that the effect sizes associated with placebo were between 0.27 (MSPS agoraphobia, intent-to-treat sample) and 0.79 (MSPS anxiety, completer sample), indicating a moderate effect.[25] If a *d* higher than 0.8 is considered to be a large effect size,[25] it follows that in the completer sample cognitive therapy, paroxetine, and clomipramine had large effect sizes for nearly all measures. In the intent-to-treat sample, the effect size lay between 0.31 and 0.80 for cognitive therapy, i.e., a moderate effect comparable with the effect sizes for placebo treatment. Both antidepressants yielded large effect sizes on the MADRS for completer as well as intent-to-treat data, whereas placebo and cognitive therapy had only small effect sizes (*d* between 0.31 and 0.53)[16] on this depression scale. In summary, the effect sizes of the active treatments were larger than those of placebo, in conformity with the differences found between the active treatments versus placebo.

DISCUSSION

We can conclude that paroxetine was more effective than pill placebo in reducing panic attacks, agoraphobic complaints, anxiety, depression, and social dysfunction in the present study. Outcome revealed superiority of paroxetine over placebo on all outcome measures in both intent-to-treat and completer samples. With the exception of some measures, the same holds true for clomipramine. Cognitive therapy did not differ significantly from pill placebo in alleviating panic and associated symptoms on the majority of measures. With the exception of scores on panic frequency, paroxetine also showed superiority over cognitive therapy on all rating scales.

Table 2. Mean ± SD Scores per Treatment Condition on Efficacy Measures[a]

Measure	Pretest (Intent-to-Treat) Mean	Pretest (Intent-to-Treat) SD	Posttest (Completers) Mean	Posttest (Completers) SD	p Values (Completers)	Posttest (Intent-to-Treat) Mean	Posttest (Intent-to-Treat) SD	p Values (Intent-to-Treat)
Panic frequency[b]								
Cognitive therapy	7.0	9.0	1.3	3.4	Cognitive therapy > placebo, p = .018	2.8	8.4	
Paroxetine	5.8	8.0	0.8	3.0	Paroxetine > placebo, p = .002	1.3	3.6	Paroxetine > placebo, p = .011
Clomipramine	6.0	4.9	1.4	3.0	Clomipramine > placebo, p = .027	2.0	4.2	
Placebo	4.4	6.1	1.9	4.5		2.2	4.7	
CGI-S (1–7)								
Cognitive therapy	4.7	1.0	3.3	1.3	Paroxetine > placebo, p < .001	3.6	1.4	Paroxetine > placebo, p < .001
Paroxetine	4.5	0.9	2.2	0.8	Paroxetine > cognitive therapy, p = .001	2.4	1.1	Paroxetine > cognitive therapy, p < .001
Clomipramine	4.5	0.9	3.0	1.2	Paroxetine > clomipramine, p = .010	3.1	1.2	Paroxetine > clomipramine, p = .042
Placebo	4.5	0.8	3.7	1.4	Clomipramine > placebo, p = .011	3.8	1.4	Clomipramine > placebo, p = .016
PGE (1–7)								
Cognitive therapy	4.1	1.3	2.3	1.3	Cognitive therapy > placebo, p = .014	2.9	1.7	
Paroxetine	4.3	1.4	1.9	0.9	Paroxetine > placebo, p < .001	2.2	1.2	Paroxetine > placebo, p = .001
Clomipramine	4.4	1.5	2.3	1.0		2.5	1.1	Paroxetine > cognitive therapy, p = .011
Placebo	3.8	1.4	3.0	1.3	Clomipramine > placebo, p = .007	3.1	1.4	Clomipramine > placebo, p = .014
HAM-A (0–56)								
Cognitive therapy	23.3	7.0	15.0	8.3	Paroxetine > placebo, p < .001	18.1	8.7	Paroxetine > placebo, p = .002
Paroxetine	24.0	8.5	10.6	5.5	Paroxetine > cognitive therapy, p = .011	12.4	7.5	Paroxetine > cognitive therapy, p = .001
Clomipramine	22.3	7.4	13.2	6.0	Clomipramine > placebo, p = .011	12.9	6.0	Clomipramine > placebo, p = .012
Placebo	21.0	7.7	16.2	8.0		16.9	8.2	Clomipramine > cognitive therapy, p = .007
MSPS anxiety (0–130)								
Cognitive therapy	52.8	22.9	33.4	19.9	Paroxetine > placebo, p = .002	37.8	25.6	Paroxetine > placebo, p = .002
Paroxetine	51.2	23.6	21.4	19.9	Paroxetine > cognitive therapy, p = .023	23.9	20.7	Paroxetine > cognitive therapy, p = .007
Clomipramine	56.5	25.8	30.2	29.9	Clomipramine > placebo, p = .029	30.4	28.9	Clomipramine > placebo, p = .011
Placebo	52.2	24.2	34.3	22.3		39.5	27.3	Clomipramine > cognitive therapy, p = .031
MSPS agoraphobia (0–52)								
Cognitive therapy	16.0	8.5	9.5	6.9	Paroxetine > placebo, p < .001	11.3	9.2	Paroxetine > placebo, p < .001
Paroxetine	17.0	8.3	7.3	6.0	Paroxetine > cognitive therapy, p = .047	8.1	6.5	Paroxetine > cognitive therapy, p = .010
Clomipramine	18.2	11.0	11.8	11.2	Paroxetine > clomipramine, p = .036	11.4	10.7	
Placebo	15.2	9.3	11.1	7.8		12.7	9.2	Clomipramine > placebo, p = .031
Overall phobia score (0–10)								
Cognitive therapy	7.1	1.8	4.8	2.6	Paroxetine > placebo, p < .001	5.4	2.8	Paroxetine > placebo, p = .001
Paroxetine	6.9	1.9	2.9	2.5	Paroxetine > cognitive therapy, p = .006	3.4	2.8	Paroxetine > cognitive therapy, p = .002
Clomipramine	7.2	2.1	3.4	2.5	Clomipramine > placebo, p = .001	3.8	2.7	Clomipramine > placebo, p = .003
Placebo	7.1	2.2	5.6	2.8	Clomipramine > cognitive therapy, p = .033	5.7	2.8	Clomipramine > cognitive therapy, p = .009
Anticipatory anxiety score (0–10)								
Cognitive therapy	6.1	1.9	3.8	2.4	Paroxetine > placebo, p < .001	4.6	2.8	Paroxetine > placebo, p < .001
Paroxetine	6.2	2.0	2.4	1.7	Paroxetine > cognitive therapy, p = .008	2.9	2.2	Paroxetine > cognitive therapy, p = .002
Clomipramine	6.3	2.1	3.3	2.0	Clomipramine > placebo, p = .002	3.6	2.1	Clomipramine > placebo, p = .004
Placebo	5.7	2.3	4.7	2.6		4.8	2.6	Clomipramine > cognitive therapy, p = .041
Sheehan Disability Scale (0–30)								
Cognitive therapy	19.8	5.9	13.6	10.1	Paroxetine > placebo, p < .001	15.6	9.6	Paroxetine > placebo, p < .001
Paroxetine	18.9	6.9	5.8	6.7	Paroxetine > cognitive therapy, p = .001	7.8	8.5	Paroxetine > cognitive therapy, p < .001
Clomipramine	19.0	7.3	9.5	7.9	Clomipramine > placebo, p = .011	10.0	7.7	Clomipramine > placebo, p = .011
Placebo	16.2	7.3	12.9	9.1		13.2	9.1	Clomipramine > cognitive therapy, p = .008
MADRS (0–60)								
Cognitive therapy	15.9	8.1	11.6	8.2	Paroxetine > placebo, p < .001	13.3	8.7	Paroxetine > placebo, p = .004
Paroxetine	16.9	8.3	4.9	4.3	Paroxetine > cognitive therapy, p < .001	6.8	7.3	Paroxetine > cognitive therapy, p < .001
Clomipramine	16.0	7.4	8.1	4.5	Paroxetine > clomipramine, p = .036	8.5	5.3	
Placebo	13.3	7.3	9.8	6.5	Clomipramine > cognitive therapy, p = .024	10.2	6.7	Clomipramine > cognitive therapy, p = .003

[a]Abbreviations: CGI-S = Clinical Global Impression-Severity of Illness, HAM-A = Hamilton Rating Scale for Anxiety, MADRS = Montgomery-Asberg Depression Rating Scale, MSPS = Marks-Sheehan Phobia Scale, PGE = Patient Global Evaluation.
[b]Panic frequency = mean number of panic attacks per week. Only p values < .05 are indicated.

This study could not replicate the findings of previous studies that conclude that cognitive therapy has significantly superior effects over control treatments in panic disorder.[14,27–30] An explanation for this finding may be the magnitude of the placebo response. Recent publications refer to a growing placebo response rate over the decades as an important explanation for difficulties in demonstrating therapeutic effects of promising compounds for anxiety and depression.[24] A reason for the large placebo effect might be a lower initial severity of complaints. Higher levels of baseline pathology are associated with increased sensitivity of a therapeutic trial to differences between an

Table 3. Cohen's *d* Effect Sizes at Posttest per Treatment Condition on Efficacy Measures

Measure and Condition	Posttest (Completer)	Posttest (Intent-to-Treat)
Panic frequency[a]		
Cognitive therapy	0.92	0.48
Paroxetine	0.91	0.78
Clomipramine	1.16	0.88
Placebo	0.47	0.41
CGI-S		
Cognitive therapy	1.22	0.75
Paroxetine	2.71	2.10
Clomipramine	1.43	1.33
Placebo	0.73	0.64
PGE		
Cognitive therapy	1.38	0.80
Paroxetine	2.09	1.62
Clomipramine	1.68	1.46
Placebo	0.59	0.50
HAM-A		
Cognitive therapy	1.08	0.66
Paroxetine	1.91	1.45
Clomipramine	1.33	1.40
Placebo	0.61	0.52
MSPS anxiety		
Cognitive therapy	0.91	0.62
Paroxetine	1.37	1.23
Clomipramine	0.94	0.95
Placebo	0.79	0.49
MSPS agoraphobia		
Cognitive therapy	0.84	0.53
Paroxetine	1.36	1.20
Clomipramine	0.58	0.63
Placebo	0.48	0.27
Overall Phobia Score		
Cognitive therapy	1.05	0.74
Paroxetine	1.82	1.49
Clomipramine	1.65	1.42
Placebo	0.60	0.56
Anticipatory Anxiety Score		
Cognitive therapy	1.07	0.64
Paroxetine	2.05	1.57
Clomipramine	1.46	1.29
Placebo	0.41	0.37
Sheehan Disability Scale		
Cognitive therapy	0.78	0.54
Paroxetine	1.93	1.44
Clomipramine	1.25	1.20
Placebo	0.40	0.37
MADRS		
Cognitive therapy	0.53	0.31
Paroxetine	1.90	1.29
Clomipramine	1.33	1.18
Placebo	0.51	0.44

[a]Panic frequency = mean number of panic attacks per week.

active compound and a placebo. Even though patients who are more severely ill never reach the same low endpoints as patients who are less ill, they do respond better to treatment than those with lower levels of pathology. This phenomenon has been described as the Law of Initial Value.[24] However, there are no indications that in this study the level of baseline pathology was relatively low. A second argument against the hypothesis that the placebo effect may have been too large is that both antidepressants demonstrated sound advantages over placebo and that paroxetine showed significant superiority over cognitive therapy.

Another criticism that may be raised to explain the negative results of cognitive therapy in this study is the possibility that cognitive therapy was not provided adequately. It is difficult, however, to support this criticism with solid arguments. Treatment was delivered by experienced therapists who had received extensive training from experts in the field and who were experienced in the use of treatment manuals. They had also participated in previous treatment studies in panic disorder and other anxiety disorders. There were supervision sessions on a regular basis, and in weekly meetings of therapists and investigators, the integrity of treatment was checked by discussing audiotaped visits of patients. Moreover, the results of cognitive therapy treatment in this study are not exceptionally unfavorable. The mean ± SD effect sizes in a recent meta-analysis of the treatment of panic disorder for the treatment condition psychological panic management that included cognitive therapy, were 1.25 ± 0.62 for panic and 0.91 ± 0.54 for agoraphobia.[1] These effect sizes were also calculated within treatment conditions for completer data only. As can be concluded from Table 3, the present study produced comparable effect sizes: 0.92 for panic frequency and 0.84–1.05 for agoraphobia (MSPS agoraphobia and Overall Phobia Score, respectively).

Nevertheless, the effects of cognitive therapy in our study fall behind those of most other controlled studies on the efficacy of cognitive therapy for panic: for completers, the reported percentages of panic-free patients range from 65% to 90%; for the intent-to-treat samples, from 50% to 78%.[14,27–31] The main difference from our study seems to be that other studies involved less complicated patient groups: severe agoraphobics were never included,[14,27–31] and the percentage of subjects with moderate agoraphobia was 33% at most.[14] In our cognitive therapy treatment group, 52% of included subjects suffered from moderate or severe agoraphobia. The duration of panic disorder was also longer in our sample when compared with the other most successful studies on the effects of cognitive therapy.[14,27]

Outcome in comparative treatment studies in panic disorder seems to be highly influenced by the selection of patient samples, especially the inclusion or exclusion of moderate-to-severe agoraphobic patients. Consequently, in comparison to previous studies on the efficacy of cognitive therapy, the present study concerns a more complicated group of patients with panic disorder. This might well explain the high dropout rate in the cognitive therapy sample: 26% in our study and in the aforementioned studies around 10%.[14,27–31] The percentage of panic-free patients treated with cognitive therapy in our completer sample (53.8%) did not differ from that of subjects treated with cognitive therapy in the study by Black et al.[9] (53%). That study also included more moderate and severe ago-

raphobic patients, and the Black et al. dropout rate in the cognitive therapy condition, 20%, was in the same range as ours.

A recent study discussed the place of clomipramine in the treatment of panic disorder.[19] In particular, the relatively high dropout rate due to adverse reactions led to the conclusion that clomipramine, given the alternatives, should not be used as a first-line antipanic medication.[19] In the present study, it was shown that a low starting dose and a relatively low maintenance dose of 150 mg/day maximum may reduce the number of dropouts due to adverse effects.

Compared with clomipramine, paroxetine seems to have better efficacy, especially in the comparison with cognitive therapy. Higher dosages of clomipramine might have been helpful to improve its efficacy, but would probably have led to more dropouts as well.

It is important to conclude that both antidepressants produced considerable alleviation of agoraphobic avoidance. In both completer and intent-to-treat samples, the agoraphobic measures (MSPS agoraphobia, Overall Phobia Score, and Anticipatory Anxiety Score) yielded effect sizes of at least 1.20.

In summary, in the present study paroxetine and clomipramine showed superior efficacy over placebo in the treatment of panic disorder, whereas cognitive therapy did not. The superiority of paroxetine over cognitive therapy on the majority of measures suggests that, in the short term, paroxetine may be the treatment of first choice in panic disorder. When indicated, psychological interventions can be added, for example, to overcome any remaining agoraphobic avoidance. In that case, exposure in vivo still seems to be the best modality, since it is known from meta-analyses that a combination of antidepressants with exposure is the most potent treatment for agoraphobia in the short term and perhaps in the long term as well.[1,32]

Drug names: clomipramine (Anafranil and others), fluvoxamine (Luvox), paroxetine (Paxil).

REFERENCES

1. van Balkom AJLM, Bakker A, Spinhoven P, et al. A meta-analysis of the treatment of panic disorder with or without agoraphobia: a comparison of psychopharmacological, cognitive-behavioral, and combination treatments. J Nerv Ment Dis 1997;185:510–516
2. Klein DF. Delineation of two-drug-responsive anxiety syndromes. Psychopharmacologia 1964;5:397–408
3. Cassano GB, Petracca A, Perugi G, et al. Clomipramine for panic disorder, I: the first 10 weeks of a long-term comparison with imipramine. J Affect Disord 1988;14:123–127
4. Johnston DG, Troyer IE, Whitsett SF. Clomipramine treatment of agoraphobic women. Arch Gen Psychiatry 1988;138:1215–1217
5. Modigh K, Westberg P, Eriksson E. Superiority of clomipramine over imipramine in the treatment of panic disorder: a placebo-controlled trial. J Clin Psychopharmacol 1992;12:251–261
6. Zitrin ZM, Klein DF, Woerner MG, et al. Treatment of phobias, I: comparison of imipramine hydrochloride and placebo. Arch Gen Psychiatry 1983;40:125–138
7. den Boer JA, Westenberg HGM, Kamerbeek WDJ. Effect of a serotonin uptake inhibitor in anxiety disorders: a double-blind comparison of clomipramine and fluvoxamine. Int Clin Psychopharmacol 1987;2:21–32
8. Evans L, Kenardy J, Schneider P, et al. Effect of a selective serotonin uptake inhibitor in agoraphobia with panic attacks. Acta Psychiatr Scand 1986;73:49–53
9. Black DW, Wesner R, Bowers W, et al. A comparison of fluvoxamine, cognitive therapy, and placebo in the treatment of panic disorder. Arch Gen Psychiatry 1993;50:44–50
10. Lecrubier Y, Bakker A, Dunbar G, et al. A comparison of paroxetine, clomipramine and placebo in the treatment of panic disorder. Acta Psychiatr Scand 1997;95:145–152
11. Barlow DH, Cerny JA. Psychological treatment of panic. New York, NY: Guilford; 1988
12. Trull TJ, Nietzel MT, Main A. The use of meta-analysis to assess the clinical significance of behavior therapy for agoraphobia. Behav Ther 1988;19: 527–538
13. Jacobson NS, Wilson L, Tupper C. The clinical significance of treatment gains resulting from exposure-based interventions for agoraphobia: a reanalysis of outcome data. Behav Ther 1988;19:539–554
14. Clark DM, Salkovskis PM, Hackmann A, et al. A comparison of cognitive therapy, applied relaxation and imipramine in the treatment of panic disorder. Br J Psychiatry 1994;164:759–769
15. Oehrberg S, Christiansen PE, Behnke K, et al. Paroxetine in the treatment of panic disorder: a randomised, double-blind, placebo-controlled study. Br J Psychiatry 1995;167:374–379
16. de Beurs E, van Balkom AJLM, Lange A, et al. Treatment of panic disorder with agoraphobia: comparison of fluvoxamine, placebo, and psychological panic management combined with exposure and of exposure in vivo alone. Am J Psychiatry 1995;152:683–691
17. Mavissakalian M, Michelson L. Agoraphobia: relative and combined effectiveness of therapist-assisted in vivo exposure and imipramine. J Clin Psychiatry 1986;47:117–122
18. Clark DM. A cognitive approach to panic. Behav Res Ther 1986;24: 461–470
19. Papp LA, Schneier FR, Fyer AJ, et al. Clomipramine treatment of panic disorder: pros and cons. J Clin Psychiatry 1997;58:423–425
20. Hamilton M. Diagnosis and rating of anxiety. Br J Psychiatry 1969;3: 76–79
21. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382–389
22. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
23. Sheehan DV. The Anxiety Disease. New York, NY: Charles Scribner's Sons; 1983:144–153
24. Uhlenhuth EH, Matuzas W, Warner TD, et al. Growing placebo response rate: the problem in recent therapeutic trials? Psychopharmacol Bull 1997;33:31–39
25. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd ed. Hillsdale, NJ: Erlbaum; 1988
26. Hunter JE, Schmidt FL. Methods of Meta-Analysis: Correcting Error and Bias in Research Findings. Beverly Hills, Calif: Sage; 1990
27. Arntz A, Van Den Hout M. Psychological treatments of panic disorder without agoraphobia: cognitive therapy versus applied relaxation. Behav Res Ther 1996;34:113–121
28. Beck AT, Sokol L, Clark DA, et al. A crossover study of focused cognitive therapy for panic disorder. Am J Psychiatry 1992;149:778–783
29. Beck JG, Stanley MA, Baldwin LE, et al. Comparison of cognitive therapy and relaxation training for panic disorder. J Consult Clin Psychol 1994;62: 818–826
30. Klosko JS, Barlow DH, Tassinari R, et al. A comparison of alprazolam and behavior therapy in treatment of panic disorder. J Consult Clin Psychol 1990;58:77–84
31. Ost L-G, Westling BE. Applied relaxation vs cognitive behavior therapy in the treatment of panic disorder. Behav Res Ther 1995;33:145–158
32. Bakker A, van Balkom AJLM, Spinhoven P, et al. Follow-up on the treatment of panic disorder with or without agoraphobia: a quantitative review. J Nerv Ment Dis 1998;186:414–419