A Randomized, Double-Blind, Placebo-Controlled Study of the Effects of Adjunctive Paroxetine in Panic Disorder Patients Unsuccessfully Treated With Cognitive-Behavioral Therapy Alone

Mirjam Kampman, M.A.; Ger P. J. Keijsers, Ph.D.;
Cees A. L. Hoogduin, M.D., Ph.D; and Gert-Jan Hendriks, M.D.

Background: Both cognitive-behavioral therapy and treatment with selective serotonin reuptake inhibitors (SSRIs) have proved to be effective in the treatment of panic disorder. The present study examined the effects of paroxetine added to continued cognitive-behavioral therapy in patients who were unsuccessfully treated with initial cognitive-behavioral therapy alone.

Method: 161 patients with panic disorder with or without agoraphobia (DSM-IV criteria) underwent a manual-guided cognitive-behavioral therapy of 15 sessions. Forty-three unsuccessfully treated patients from this group were included in a double-blind, placebo-controlled, next-step treatment study consisting of continued cognitive-behavioral therapy plus adjunctive paroxetine at a dose of 40 mg/day or continued cognitive-behavioral therapy plus placebo.

Results: Overall, patients in the cognitive-behavioral therapy plus paroxetine condition improved significantly on agoraphobic behavior ($p < .05$) and anxiety discomfort ($p < .01$), whereas patients in the cognitive-behavioral therapy plus placebo condition did not. Effect sizes in the cognitive-behavioral therapy plus paroxetine condition ranged from 1.0 to 1.8 and in the cognitive-behavioral therapy plus placebo condition, from 0.4 to 1.0.

Conclusion: Patients with panic disorder who are unsuccessfully treated with initial cognitive-behavioral therapy may benefit from the addition of an SSRI as a second treatment modality. The importance of timely evaluation of treatment results is emphasized.

(J Clin Psychiatry 2002;63:772–777)

Received June 4, 2001; accepted Jan. 3, 2002. From the Department of Clinical Psychology and Personality, University of Nijmegen (Ms. Kampman and Drs. Keijsers and Hoogduin) and the Outpatient Clinic for Anxiety Disorders, Mental Health Care (Ms. Kampman and Dr. Hendriks), Nijmegen, the Netherlands.

The study was funded by the Department of Clinical Psychology and Personality, University of Nijmegen, Nijmegen, the Netherlands, as a dissertation project. No external funding was received.

Corresponding author and reprints: Mirjam Kampman, M.A., Angstpolikliniek, GGz-Nijmegen, P.O. Box 7049, 6503 GM Nijmegen, the Netherlands (e-mail: Kampman@psych.kun.nl).

At present, cognitive-behavioral therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs) have both proved to be effective for the treatment of panic disorder (PD) with or without agoraphobia. A meta-analysis by van Balkom and colleagues[1] showed that both treatments, administered individually as well as in combination, positively affect the various aspects of PD, such as panic attacks, agoraphobic behavior, and general anxiety. Both treatment modalities are equally effective in the treatment of panic disorder, and the choice between CBT and SSRIs depends largely on therapists' and patients' personal preferences and circumstances and on the availability of treatment modalities.[2]

Both treatment modalities have advantages and disadvantages. Compared with CBT, SSRI treatment is more available and requires relatively low effort on the part of the patient. Compared with SSRI treatment, CBT has fewer dropouts,[1] is more cost-effective,[3] and has fewer adverse side effects.[4] Both CBT and SSRI treatment have the disadvantage that a substantial number of patients (ranging from 20% to 52%) do not sufficiently improve with the use of either treatment.[2,5–7] To date, the important and relevant question of why a substantial proportion of patients fail to respond to CBT has not yet been answered. Research thus far has failed to identify consistent and replicable predictors of CBT nonresponse, and, in fact, it is questionable whether there are any common pretreatment characteristics of patients, symptoms, therapists, or treatment processes that could ever reliably predict CBT outcome (M.K., G.P.J.K., C.A.L.H., et al., manuscript submitted).

Surprisingly, despite the substantial number of patients that fail to improve in response to CBT or SSRI treatment, only a few studies have addressed the question of what the best next-step treatment modality or strategy for these nonresponding PD patients would be. A controlled study by Hoffart et al.[8] showed clomipramine to be effective as a next-step treatment after unsuccessful CBT. Another controlled study by Fava and colleagues[9] proved continued exposure to be just as effective as continued exposure combined with adjunctive treatment with either the tricyclic antidepressant imipramine or cognitive therapy after unsuccessful CBT. A naturalistic study by Brown and Barlow[10] did not reveal any adjunctive beneficial effects in patients who sought adjunctive pharmacotherapy after initial CBT.

Two open studies evaluated additional CBT as a next-step treatment modality for nonresponding pharmacotherapy (SSRI) patients.[11] Combining SSRI treatments with CBT was found to be effective in these studies. So far, a controlled study into the next-step treatment modality consisting of SSRI treatment for nonresponding CBT patients has not been conducted, which is surprising since both treatment modalities individually are the treatments of choice for PD. On the basis of the findings for tricyclic antidepressants, we expected that the use of an SSRI in combination with continued CBT would lead to symptom reduction in PD patients that failed to improve with CBT alone.[8] In the present study, nonresponding CBT patients, according to cutoff scores set in advance, were randomly assigned to either continued CBT plus the SSRI paroxetine or to continued CBT plus placebo as the next-step treatment modality.

METHOD

Patients

Participants were 43 patients who were classified as CBT nonresponders. The participating patients were recruited from a sample of 161 patients who were treated with a 15-session, manual-guided individual CBT. Patients were treated in 2 centers: an outpatient clinic for anxiety disorders and a university outpatient center. All 161 patients met DSM-IV criteria[12] for panic disorder with or without agoraphobia, as assessed by experienced psychiatrists using the Dutch adaptation of the Anxiety Disorders Interview Schedule-Revised (ADIS-IV) (reference 13 and T. K. Bouman, Ph.D.; C. de Ruiter, Ph.D.; C.A.L.H., unpublished, 1997). Inclusion criteria for initial CBT were a present diagnosis of PD, age between 18 and 65 years, and the patient's consent to the research procedures and measurements. Exclusion criteria were a present diagnosis of schizophrenia, organic mental syndrome, mental retardation, suicidal ideation, alcohol or psychoactive substance dependence, or ongoing treatment with other therapies. Patients who used antidepressant medication were asked to discontinue their medication under supervision prior to the start of CBT. They entered the study after a washout period of 2 weeks. Patients who used benzodiazepines were asked either to discontinue their medication under supervision or to adhere to a fixed daily dose throughout the duration of their treatment. Of the 161 patients, 129 patients completed the initial CBT; 32 patients (20%) dropped out.

CBT treatment was considered successful after the first phase when patients did not have considerable PD complaints during a 4-week period following the final treatment session. The cutoff scores for inclusion in the next-step treatment study were determined in advance and were based on a previous study with PD patients treated with manual-guided CBT.[14] In this previous study, 30% improvement equaled the following cutoff scores: (1) patients reported no panic attacks in the last 2 weeks (assessed with the panic attack frequency subscale of the Mobility Inventory for Agoraphobia),[15] (2) patients reported having had few agoraphobic catastrophic cognitions (cutoff score of 1.9 or lower on the Agoraphobic Cognitions Questionnaire [ACQ]),[16] and (3) patients reported no longer having marked anxious feelings in their idiosyncratic situations or circumstances (cutoff score of 5.9 or lower on the Anxiety Discomfort Scale [ADS]).[17] Applying these criteria to the patients in our study after the initial CBT, we identified 66 patients who were considered unsuccessfully treated. This group was therefore found suitable to be included in our next-step treatment study.

An additional inclusion criterion for the next-step phase was that patients had to agree to the double-blind randomization, and 3 additional exclusion criteria were planned pregnancy, pregnancy, and lactation.

Of the 66 patients for whom initial CBT had failed, 6 were excluded from the next-step phase because they wanted to become pregnant. Sixty patients remained eligible and were asked to participate in the next-step study. Seventeen patients refused to participate: 5 refused randomization because they did not want the risk of a placebo treatment and instead preferred medication; the remaining 12 patients refused to participate because they felt they had already improved to such a degree that they did not need to take additional medication. Finally, during the next-step treatment, 3 patients dropped out of the CBT plus paroxetine condition and 2 patients dropped out of the CBT plus placebo condition owing to adverse side effects. In total, 38 patients, equally divided across both conditions, completed the next-step treatment of the present study.

Treatment

There were 2 treatment phases. The initial treatment (CBT) consisted of 15 weekly sessions of fifty minutes each, in accordance with the Panic Control Treatment manual.[18,19] The treatment consisted of the following 5

components that provided patients with (1) information about panic and anxiety, (2) relaxation techniques, (3) cognitive therapy, (4) interoceptive exposure, and (5) exposure in vivo. Following the initial CBT, there was a 4-week interval prior to evaluation and eventually the next-step treatment. In the next-step treatment, unimproved patients received continued CBT for 4 sessions during 8 weeks, with emphasis on those treatment components that both patient and therapist had deemed the most effective during the previous 15 sessions. In addition to continued CBT, patients were randomly assigned to either paroxetine, 40 mg/day, or placebo. The dose was 20 mg for the first 2 weeks and 40 mg for weeks 3 through 8. Every 2 weeks patients visited the psychiatrist to receive their medication, to undergo medical checks, and to be monitored for side effects. The remaining medication was counted to check for compliance. Effects of paroxetine were expected within 8 weeks.[20,21]

Therapists

The therapists were experienced cognitive-behavioral therapists and graduate students in clinical psychology working as trainees at one of the clinics. All therapists had received intensive training in the manual-guided treatment. Throughout the duration of the study, the treatment was supervised by 4 experienced cognitive-behavioral therapists on a weekly basis. Deviations from the manual-guided treatment were discussed.

Instruments

Frequency of catastrophic agoraphobic cognitions was assessed with the Dutch adaptation of the ACQ.[16] Agoraphobic avoidance was measured with the Dutch adaptation of the Mobility Inventory (MI).[15] The MI contains 3 subscales: avoidance when alone (MI-AAL), avoidance when accompanied (MI-AAC), and frequency of panic attacks (MI-PF). MI-AAL and MI-AAC scores were added to yield 1 avoidance score (MI). The third subscale, MI-PF, contains a definition of panic attacks according to the DSM-IV followed by a question about the number of panic attacks that occurred during the past 14 days. The ACQ, the MI, and their Dutch adaptations were found to have good test-retest reliability, high internal consistencies, and reasonably concurrent validity.[15,16,22]

Fear and frequency of physical panic sensations were measured with the Dutch adaptation of the 2 subscales of the Body Sensations Questionnaire (BSQ),[16] the BSQ-fear and the BSQ-frequency. The original questionnaire and the Dutch version were found to be highly internally consistent and reliable.[17,23,24]

The global state of phobic symptoms and general discomfort was measured with the last item of the Fear Questionnaire (FQ-GA)[25]: "How would you rate the present state of your phobic symptoms on the scale below?" The ACQ, MI, BSQ, and FQ are frequently used in panic disorder treatment studies. In addition, the Dutch version of the ADS was used.[17] The ADS assesses 5 idiosyncratic situations or circumstances in which patients feel distressed or anxious.

Procedure

After patients were referred, 2 intake sessions took place. When patients were diagnosed with PD and after they had given their written informed consent to the treatment and research procedures, they entered the first phase of the study. One week after the intake sessions, patients completed Assessment 1. A diagnosis of PD had to be confirmed by an independent assessor using the Dutch version of ADIS-IV. When the diagnosis was not confirmed by the ADIS-IV, patients were excluded from the study. In addition to the ADIS-IV, patients completed the ACQ, the MI, the BSQ, the ADS, and the FQ.

Following Assessment 1, patients were assigned to a therapist and received 15 weekly sessions of standardized CBT. One week after the 15th session, Assessment 2 took place in which patients again completed the ACQ, the MI, the BSQ, the ADS, and the FQ. Assessment 2 was followed by a 4-week, therapy-free interval after which Assessment 3 was administered to obtain follow-up results. Assessment 3 consisted of the same measurements as those used in Assessment 2.

In the second phase of the study, paroxetine, 40 mg, or placebo (double-blind) was added to standardized CBT during the next 8 weeks. Assessment 3 served as a pretreatment measurement. After Assessment 3, randomization took place in blocks of 10, arranging an equal number of subjects in both conditions. After the 8 weeks of combination treatment, Assessment 4 was taken to obtain posttreatment measurements. Again, the measurements were the same as those taken in the previous assessments.

Statistical Analysis

The SPSS 10.0 statistical analysis package was used.[26] Outcome scores were analyzed with multivariate analyses of variance. Nonparametric data, such as number of panic-free patients, were analyzed with the Pearson chi-square test.

RESULTS

The outcome scores for the first phase of the treatment for the 129 patients were statistically significant for all outcome measures, and the effect sizes ranged from 1.1 to 2.2. These findings are presented in detail elsewhere (M.K., G.P.J.K., C.A.L.H., et al., manuscript submitted). At the time of Assessment 3, i.e., the start of the second phase of the treatment, the patients in the CBT plus paroxetine condition and the patients in the CBT plus placebo condition did not differ significantly with respect to age ($t = -0.36$, $df = 41$, $p = .86$) or gender ($\chi^2 = 2.22$, $df = 1$,

Table 1. Scores at Assessments 3 and 4 (pretest and posttest) and Effect Sizes for Panic Disorder Patients in the CBT Plus Paroxetine and CBT Plus Placebo Conditions[a]

	Assessment 3 (Pretest)[b]		Assessment 4 (Posttest)[c]		
Condition	Mean	SD	Mean	SD	Effect Size
CBT plus paroxetine (N = 19)					
ACQ	2.0	0.5	1.6	0.4	1.8
MI	2.4	0.7	1.8	0.5	1.5
FQ-GA	3.7	2.0	1.5	1.7	1.6
BSQ-fear	2.1	0.5	1.7	0.5	1.0
BSQ-frequency	2.6	0.5	2.2	0.6	1.2
ADS	4.0	1.8	2.6	1.8	1.5
CBT plus placebo (N = 19)					
ACQ	2.2	0.7	2.0	0.6	1.0
MI	2.2	0.6	2.0	0.6	0.5
FQ-GA	2.4	1.5	1.7	1.3	0.6
BSQ-fear	2.3	0.7	2.0	0.6	0.9
BSQ-frequency	2.5	0.8	2.3	0.7	0.5
ADS	3.7	1.5	3.4	1.5	0.4

[a]Abbreviations: ACQ = Agoraphobic Cognitions Questionnaire, ADS = Anxiety Discomfort Scale, BSQ-fear = Body Sensations Questionnaire-fear of sensations, BSQ-frequency = Body Sensations Questionnaire-frequency of sensations, CBT = cognitive-behavioral therapy, FQ-GA = Fear Questionnaire-General Anxiety, MI = Mobility Inventory.
[b]At the start of the pretest phase, 47% (N = 9) of the patients in the CBT plus paroxetine condition and 42% (N = 8) of the patients in the CBT plus placebo condition were panic free.
[c]At posttreatment, 74% (N = 14) of the patients in the CBT plus paroxetine condition and 47% (N = 9) of the patients in the CBT plus placebo condition were panic free.

p = .14). Neither group differed significantly on the outcome measures, except for the ADS (F = 5.42, df = 1,36; p < .05). Patients in the CBT plus paroxetine condition were worse on the ADS than patients in the CBT plus placebo condition. Of the patients in the CBT plus paroxetine condition, 10 patients had 1 or more comorbid disorders (4 mood disorders, 4 anxiety disorders, and 4 somatoform disorders) compared with 5 patients with 1 or more comorbid disorders (3 mood disorders and 3 anxiety disorders) in the CBT plus placebo condition. Fifteen patients in both groups were treated by graduate students, and 6 patients in the CBT plus placebo condition and 7 patients in the CBT plus paroxetine condition were treated by an experienced therapist.

Table 1 presents the mean scores of the outcome measures of Assessments 3 and 4 and the corresponding effect sizes. Effect sizes were calculated following Cohen's recommendations for repeated measurements.[27]

First, change scores, i.e., subtracting Assessment 4 scores from Assessment 3 scores, were obtained for each of the outcome measures. After the assumptions for normality and homogeneity of variances were checked, the change scores were analyzed with a multivariate analysis of variance for all outcome variables simultaneously, but separately for the 2 conditions. Wilks lambda (intercept) was significant for the CBT plus paroxetine condition (F = 5.35, df = 6,13; p < .05), but not for the CBT plus placebo condition (F = 2.09, df = 6,13; p = .13), indicating that, overall, patients in the CBT plus paroxetine condition showed a significant improvement for all outcome variables taken together, whereas patients in the CBT plus placebo condition did not.

Second, the change scores were analyzed with a multivariate analysis of variance for both conditions together, with treatment condition as the between-subjects factor. Wilks lambda (intercept) was significant (F = 6.39, df = 6,31; p < .0001), indicating that there was an overall main effect for symptom reduction on the outcome measures. In addition, there was a main effect for condition (F = 4.20, df = 6,31; p < .01), indicating an overall difference in symptom reduction for type of treatment. Subsequent univariate analyses of variance were used to test the symptom reduction for the outcome measures separately and to compare them between both conditions. Change scores for the MI (F = 5.35, df = 1,36; p < .05), the FQ-GA (F = 14.0, df = 1,36; p < .001), and the ADS (F = 10.59, df = 1,36; p < .01) were significantly larger for the CBT plus paroxetine condition than for the CBT plus placebo condition. Change scores did not significantly differ between the 2 conditions for the ACQ (F = 1.78, df = 1,36; p = .19), the BSQ-fear (F = 0.25, df = 1,36; p = .62), and the BSQ-frequency (F = 0.95, df = 1,36; p = .34).

At the start of the next-phase treatment, 47% (N = 9) of the patients in the CBT plus paroxetine condition and 42% (N = 8) of the patients in the CBT plus placebo condition were panic free. At posttreatment (Assessment 4), 74% (N = 14) of the patients in the CBT plus paroxetine condition and 47% (N = 9) of the patients in the CBT plus placebo condition were panic free. The number of panic-free patients at posttreatment between both conditions was not significantly different ($\chi^2 = 2.75$, df = 1, p < .10).

The same criteria for treatment failure that were used for the inclusion of patients in the second treatment phase were applied to patients in the next-step treatment, and 73% (N = 14) of the patients in the CBT plus placebo condition were considered as treatment failures compared with 37% (N = 7) of the patients in the CBT plus paroxetine condition.

DISCUSSION

On the basis of the findings of a previous controlled study in which tricyclic antidepressants were used in addition to continued CBT for patients failing to sufficiently improve from initial CBT alone,[8] we expected to find enhanced treatment results when paroxetine was added to CBT. Findings from the present study support this hypothesis. For 3 of 7 outcome measures, patients in the CBT plus paroxetine condition showed a significantly larger improvement than patients in the CBT plus placebo condition. There was a trend that showed more patients in

the CBT plus paroxetine group were panic free. Furthermore, for all outcome measures together in which there was a significant overall difference, there were marked differences in effect size between the 2 groups, and twice as many patients in the CBT plus paroxetine condition were considered treatment successes, again supporting better treatment results for patients who received continued CBT plus paroxetine.

In terms of symptom reduction, it can be concluded that patients who previously failed to respond to CBT did benefit significantly more from continued CBT with adjunctive paroxetine as a next-step treatment modality than those patients who received adjunctive treatment with continued CBT and placebo. Although patients in both conditions improved, the improvement was significant only for the patients who received adjunctive paroxetine. These findings are in line with the preliminary results of the studies conducted by Hoffart et al.,[8] Pollack et al.,[11] and Otto et al.,[7] all indicating that adding another treatment modality does enhance treatment outcome for panic disorder patients who fail to improve sufficiently from a single-treatment modality.

The findings of the present study, furthermore, stress the importance of timely evaluations of individual treatment programs. Continuation of treatment without modifications in patients who really failed to respond to CBT should be critically considered, because no further success can be expected. On the contrary, patients who adjunctively received another treatment modality did respond with advantageous results.

There are several critical remarks that need to be made with regard to the present study. First, the second-step treatment lasted 8 weeks. This may be a fairly short period compared with the 12-week treatment period commonly applied in medication trials.[21,28] On the other hand, other experiments demonstrated significant treatment effects after only 4 weeks of therapy.[20,21] It is possible that for both treatment conditions better outcome results would have emerged if treatments had lasted 12 instead of 8 weeks. It is worth investigating whether with a prolonged treatment the beneficial effects of CBT plus paroxetine would be even more pronounced than those found in the CBT plus placebo condition. In contrast to the majority of studies in which paroxetine was titrated from 10 mg upward, in the present study paroxetine was titrated from 20 mg upward. Of the 5 patients who dropped out because of adverse side effects, 3 were in the CBT plus paroxetine condition. Perhaps adverse effects could have been prevented by titrating from 10 mg upward.

A second critical remark concerns a selection bias more or less caused by the cutoff score. A number of patients (12%) considered as treatment failures chose not to take adjunctive SSRI treatment because they thought of themselves as improved and still improving. Perhaps the cutoff scores we used to determine treatment success were too strict. After all, some of the patients who we considered eligible to enter the study had improved significantly, but were nevertheless categorized as patients whose treatment had failed since they still had severe complaints.

Another remark concerns the comorbid conditions of both patient groups at the start of the second phase of the study. Although both groups at that point differed significantly on only 1 of the outcome measures (ADS), more patients in the CBT plus paroxetine condition had a comorbid disorder. In spite of this, patients in the CBT plus paroxetine condition were more improved than patients in the CBT plus placebo condition.

Furthermore, a limitation of the present study is that a clinician-rated outcome measurement was included in the outcome assessments. It is recommended that outcome assessments are multifaceted, involving different perspectives.[29] The results of the present study are based on sound and frequently used self-rating instruments. The results of the study would have been more conclusive had a clinician-rated assessment or behavior test been conducted as well.

Finally, although the present study made use of a double-blind design, 62% of the patients in the CBT plus placebo condition and 79% of the patients in the CBT plus paroxetine condition classified themselves correctly. This fact may have affected the outcome. Other researchers found more or less the same percentages.[30] Unless an active placebo is used, this problem will arise in this kind of study. Strikingly, all patients who dropped out thought they had been administered an SSRI.

In summary, the present study suggests that adjunctive use of an SSRI in patients not responding to CBT is useful. Further research in this area is desirable. In particular, controlled next-step strategy studies and studies into relapses after SSRI as single treatment modality may provide us with a deeper insight into the effectiveness of the various treatment modalities.

Drug name: 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. Ballenger JC. Current treatment in the anxiety disorders in adults. Biol Psychiatry 1999;46:1579–1594
3. Gould RA, Otto MW, Pollack MH. A meta-analysis of treatment outcome for panic disorder. Clin Psychol Rev 1995;15:819–844
4. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Panic Disorder. Am J Psychiatry 1998;155(suppl 5):1–34
5. Barlow DH. Cognitive-behavioral therapy for panic disorder: current status. J Clin Psychiatry 1997;58(suppl 2):32–37
6. Hunt C, Andrews G. Long-term outcome of panic disorder and social phobia. J Anxiety Disord 1998;12:395–406
7. Otto MW, Pollack MH, Penava SJ, et al. Group cognitive-behavior therapy for patients failing to respond to pharmacotherapy for panic disorder: a clinical case series. Behav Res Ther 1999;37:763–770

8. Hoffart A, Due-Madsen J, Lande B, et al. Clomipramine in the treatment of agoraphobic inpatients resistant to behavioral therapy. J Clin Psychiatry 1993;54:481–487
9. Fava GA, Savron G, Zielezny M, et al. Overcoming resistance to exposure in panic disorder with agoraphobia. Acta Psychiatr Scand 1997;95: 306–312
10. Brown TA, Barlow D. Long-term outcome in cognitive-behavioral treatment of panic disorder: clinical predictors and alternative strategies for assessment. J Consult Clin Psychol 1995;63:754–765
11. Pollack MH, Otto MW, Kaspi SP, et al. Cognitive-behavior therapy for treatment refractory panic disorder. J Clin Psychiatry 1994;55:200–205
12. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
13. DiNardo PA, Brown TA, Barlow DH. Anxiety Disorders Interview Schedule for DSM-IV: Lifetime Version. Albany, NY: Graywind Publications; 1994
14. Keijsers GPJ, Hoogduin CAL, Schaap CPDR. Prognostic factors in the behavioral treatment of panic disorder with and without agoraphobia. Behav Ther 1994;25:689–708
15. Chambless DL, Caputo GC, Jasin SE, et al. The Mobility Inventory for Agoraphobia. Behav Res Ther 1985;23:35–44
16. Chambless DL, Caputo GC, Bright P, et al. Assessment of fear of fear in agoraphobics: The Body Sensations Questionnaire and the Agoraphobic Cognitions Questionnaire. J Consult Clin Psychol 1984;52:1090–1097
17. Watson JP, Marks IM. Relevant and irrelevant fear in flooding: a crossover study of phobic patients. Behav Res Ther 1971;2:275–293
18. Craske MG, Barlow DH. Panic disorder and agoraphobia. In: Barlow D, ed. Clinical Handbook of Psychological Disorders. New York, NY: Guilford; 1993:1–47
19. Craske MG, Meadows E, Barlow DH. Therapist Guide for the Mastery of Your Anxiety and Panic II and Agoraphobia Supplement. Albany, NY: Graywind Publications; 1994
20. Ballenger JC, Wheadon DE, Steiner M, et al. Double-blind, fixed-dose, placebo-controlled study of paroxetine in the treatment of panic disorder. Am J Psychiatry 1998;155:36–42
21. Oehberg 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
22. de Beurs E. The Assessment and Treatment of Panic Disorder and Agoraphobia. Amsterdam, the Netherlands: Thesis Publishers; 1993
23. Bouman TK. Kort instrumenteel: De Agoraphobic Cognitions Questionnaire (ACQ). Gedragstherapie 1995;28:301–304
24. Bouman TK. Kort instrumenteel: De Body Sensations Questionnaire (BSQ). Gedragstherapie 1998;31:165–168
25. Marks IM, Mathews AM. Brief standard self-rating for phobic patients. Behav Res Ther 1979;17:263–267
26. SPSS. Base 10.0 User's Guide. Chicago, Ill: SPSS Inc; 1999
27. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988
28. Bakker A, van Dyck R, Spinhoven P, et al. Paroxetine, clomipramine, and cognitive therapy in the treatment of panic disorder. J Clin Psychiatry 1999;60:831–838
29. Kazdin AE. Comparative outcome studies of psychotherapy: methodological issues and strategies. J Consult Clin Psychol 1986;54:95–105
30. Bakker A, Spinhoven P, van Balkom AJLM, et al. Double-blindness procedure did not mask giving of medication in panic disorder. J Affect Disord 1999;54:189–192