A Randomized Trial of Cognitive-Behavioral Therapy or Selective Serotonin Reuptake Inhibitor or Both Combined for Panic Disorder With or Without Agoraphobia: Treatment Results Through 1-Year Follow-Up

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Objective: To establish the long-term effectiveness of 3 treatments for *DSM-IV* panic disorder with or without agoraphobia: cognitive-behavioral therapy (CBT), pharmacotherapy using a selective serotonin reuptake inhibitor (SSRI), or the combination of both (CBT + SSRI). As a secondary objective, the relationship between treatment outcome and 7 predictor variables was investigated.

Method: Patients were enrolled between April 2001 and September 2003 and were randomly assigned to treatment. Academic and nonacademic clinical sites participated. Each treatment modality lasted 1 year. Pharmacotherapists were free to choose between 5 SSRIs currently marketed in The Netherlands. Outcome was assessed after 9 months of treatment (posttest 1), after discontinuation of treatment (posttest 2), and 6 and 12 months after treatment discontinuation (follow-up 1 and follow-up 2).

Results: In the sample (N = 150), 48% did not suffer from agoraphobia or suffered from only mild agoraphobia, while 52% suffered from moderate or severe agoraphobia. Patients in each treatment group improved significantly from pretest to posttest 1 on the primary outcome measures of level of anxiety ($P < .001$), degree of coping ($P < .001$), and remitter status ($P < .001$), as well as on the secondary outcome measures of depressive symptomatology ($P < .001$), and from pretest to posttest 2 for health-related quality of life ($P < .001$). Gains were preserved from posttest 2 throughout the follow-up period. Some superiority of CBT + SSRI and SSRI as compared with CBT was observed at posttest 1. However, at both follow-ups, differences between treatment modalities proved nonsignificant. Client satisfaction appeared to be high at treatment endpoint, while patients receiving CBT + SSRI appeared slightly ($P < .05$) more satisfied than those receiving CBT only.

Conclusions: No fall-off in gains was observed for either treatment modality after treatment discontinuation. SSRIs were associated with adverse events. Gains produced by CBT were slower to emerge than those produced by CBT + SSRI and SSRI, but CBT ended sooner.

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Panic disorder is associated with substantial reduction in quality of life[1] and carries considerable social and economic costs.[2,3] Additionally, panic disorder typically runs a chronic course, and relapse rates are high.[4] The question of maintenance of gains posttreatment is therefore of considerable clinical relevance.

Panic disorder can be treated with both psychological and psychopharmacologic interventions. Selective serotonin reuptake inhibitors (SSRIs) are recommended as first choice treatment within the pharmacotherapeutic armamentarium.[5,6] Cognitive-behavioral therapy (CBT) is considered to be the most effective psychological treatment for panic disorder.[7,8] In clinical practice, patients with panic disorder often receive a combination of these interventions, and these combination treatments have increasingly received attention within the field.

In a review[9] of 23 studies, it was concluded that combined treatments were superior to antidepressants in all phases monitored, that is, in the acute treatment phase, during continuation treatment, and also after termination of treatment. Combined treatments were also superior to psychotherapy in the acute treatment phase and during continuation treatment. In contrast, after termination of treatment (follow-ups ranging from 6 to 24 months), the combined treatments and psychotherapy proved to be equally effective. Not all studies included in this review allowed a direct comparison between CBT only, antidepressant only, and the combination of both.

In a study that did employ all 3 treatment modalities, Barlow et al[10] randomly assigned 312 patients to receive CBT, placebo, imipramine, CBT + imipramine, or CBT + placebo. Treatment lasted 9 months (12 weeks of acute treatment followed by a 6-month treatment continuation phase followed by the tapering of medication). Patients were reassessed

For Clinical Use

- One-year follow-up results show that cognitive-behavioral therapy, selective serotonin reuptake inhibitor, or both combined are generally equally effective in treating panic disorder with or without agoraphobia.
- Clinicians should balance treatment efficacy against factors such as time to onset, adverse effects, cost, and patient preference when selecting a mode of therapy for panic disorder with or without agoraphobia.
- When receiving adequate treatment, patients with panic disorder with or without agoraphobia generally do not need additional benzodiazepines. Patients using benzodiazepines on a daily basis reported lower physical health scores and less confidence in their ability to cope with future panic attacks as compared to patients not using benzodiazepines or using benzodiazepines infrequently.

6 months after treatment discontinuation. Results indicated that patients in the imipramine and CBT + imipramine groups had received the most additional treatment during the follow-up period. Also, CBT + imipramine treatment was associated with the highest relapse rate. At follow-up, the only groups found to be superior to placebo were CBT and CBT + placebo—not the medication groups, whether combined with CBT or not.

In sum, results of the Barlow et al[10] study suggested that results of the combined treatment were not fully maintained during follow-up. These findings have led Otto et al[11] to suggest that the combined treatment may "sap some of the stronger effects of CBT over time."[11(p78)] Such a falling-off in gains of the combined treatment is explained by Otto et al[11] and others from the following theoretical viewpoint. According to the cognitive-behavioral model, patients receiving CBT have tested and disconfirmed their feared catastrophes regarding feared bodily sensations (interoceptive exposure) and feared situations (exposure in vivo). In this way, a sense of safety is relearned.[7] However, animal[12] and human[13] studies suggest that this relearning of safety is context dependent.[14,15] Context refers not only to aspects of the external world but also to an internal state. This means that when safety is learned within a medicated state, as in a combined CBT and antidepressant treatment, safety might be abated once the medication is withdrawn. A combined treatment may thus result in relapse after discontinuation of the medication due to a shift in context.[11,16] We will refer to this as the "context-safety hypothesis."

In the present study, we compared the differential long-term effectiveness of CBT, SSRI, and the combination of both (CBT + SSRI). Several clinical trials have shown each of these treatment modalities to be superior to placebo. Our goal was to compare the differential effectiveness of these treatment modalities in a more naturalistic setting. Patients with panic disorder with or without agoraphobia were treated at both academic and nonacademic clinical sites in The Netherlands. Follow-up assessments were scheduled at 6 and 12 months after treatment discontinuation. Results after 9 months of treatment were previously reported.[17] The primary objective of the present study was to examine the differential long-term effectiveness of the 3 treatment modalities with the ultimate goal of determining the most effective treatment for panic disorder with or without agoraphobia. In light of the context-safety hypothesis, a fall-off in gains of the combined treatment after medication taper was expected and subsequently CBT was expected to have more durability during follow-up than either SSRI or CBT + SSRI. As a secondary objective, the relationship between treatment outcome and 7 predictor variables was investigated. These variables were chosen based on previous studies (for a review, see references 18 and 19) and include treatment site, baseline agoraphobia, duration of illness, Axis I and Axis II comorbidity, additional benzodiazepine use, and additional treatment during follow-up.

METHOD

Study Design

Patients were treated in 11 treatment facilities located throughout The Netherlands. Three kinds of sites participated: university training and research centers (2), university research clinics (2), and regular mental health clinics (7). The study was approved by the institutional review boards of all sites. Randomization was stratified by site. Patients were randomly allocated to treatment via a blind draw of a raffle ticket. Equal proportions of tickets for each treatment modality were present and the total number of tickets equaled the expected number of patients per site. Written informed consent was obtained prior to randomization and after a full explanation of procedures. Participating patients in each treatment modality received 1 year of treatment, including 3 months of tapering in case of SSRI use. Patients were seen twice during the subsequent follow-up year. Patients received CBT, SSRI, or CBT + SSRI and were assessed before starting treatment (pretest), after 9 months of treatment (posttest 1), immediately after discontinuation of treatment (posttest 2), and 6 and 12 months after

treatment discontinuation (follow-up 1 and follow-up 2). In between pretest and posttest 1, patients received 18 CBT and/or 9 SSRI sessions. In between posttest 1 and posttest 2, CBT patients received additional booster sessions resulting in up to 21 CBT sessions from pretest to posttest 2. Patients receiving SSRI tapered their medication during this period in which 3 additional sessions were scheduled, resulting in up to 12 SSRI sessions from pretest to posttest 2.

Study Participants

Regular patients seeking care at the participating treatment centers and meeting the study criteria were asked to participate in the study. Patients were also recruited through media advertisements and flyers that were distributed in general practitioner offices. Patients were enrolled between April 2001 and September 2003. Randomly assigned patients suffered from a primary diagnosis of panic disorder with or without agoraphobia. Patients who were pregnant, lactating, suicidal, psychotic, or severely depressed were ineligible to participate in the study. The inclusion and exclusion criteria are discussed in more detail elsewhere.[17]

Treatment Conditions

Each of the 3 treatments was delivered in every treatment center. Before the start of the study, coworkers of all participating treatment centers assembled to discuss the treatment modalities and to integrate existing views. Because the study was designed to follow common practice in the treatment of panic disorder, the treatment manuals were based on the outcomes of these gatherings to satisfy as closely as possible "care as usual" requirements. The manual-based treatments are summarized below.

Cognitive-Behavioral Therapy. The CBT protocol is based on the work of Clark[20] and Craske and Barlow.[21] Patients in the CBT group received up to 21 CBT sessions, each lasting approximately 50 minutes. Homework assignments were given throughout treatment, and these were discussed thoroughly at the beginning of each session. Sessions were scheduled from once per week to twice per week, and from session 16 onward, with 5-week intermissions. The CBT treatment consisted of interoceptive exposure, cognitive therapy, and exposure in vivo (see van Apeldoorn et al[17] for more details).

Selective Serotonin Reuptake Inhibitor. The SSRI treatment was described in a treatment manual and was based on the guidelines as formulated by the Dutch Psychiatry Association regarding pharmacotherapy for anxiety disorders.[22] Patients receiving an SSRI visited their therapist 12 times, with weekly sessions during the first month and the remaining sessions distributed evenly over the treatment period. Pharmacotherapists were free to choose between 5 SSRIs currently marketed in The Netherlands: fluoxetine, paroxetine, sertraline, citalopram, and fluvoxamine. Pharmacotherapists were instructed to withhold therapeutic interventions to avoid hidden exposure.

Cognitive-Behavioral Therapy + Selective Serotonin Reuptake Inhibitor. This treatment was administered according to the CBT and SSRI manuals. The 2 treatments started simultaneously and were delivered parallel. The CBT was delivered by the CBT therapist and the SSRI treatment was delivered by the pharmacotherapist.

Therapists

In the 2 university training and research centers, CBT was delivered by master's-level student-therapists who underwent extensive training and who were closely supervised. In the remaining treatment centers, CBT was performed by experienced clinical psychologists. All therapists received ongoing supervision on site. The SSRI treatment was delivered by experienced psychiatrists, psychiatrists in training, or trained physicians. Following each treatment session, all therapists completed a detailed form regarding the content of that session. These forms were evaluated by the research team in order to check treatment adherence.

Assessment

Primary outcome measures. The Hamilton Anxiety Rating Scale (HARS)[23] assesses general aspects of anxiety and was administered by trained research assistants. A higher score represents a higher degree of anxiety (range, 0–56). The coping scale of the Panic Appraisal Inventory (PAI)[24] assesses the degree of confidence in coping with future panic attacks. Reliability and validity of the PAI were established, and especially the coping scale proved sensitive to treatment effects.[24,25] PAI coping scores range from 0 to 100, a higher score representing better coping. Patients were defined as remitters according to the definition of high end-state functioning previously used by Roy-Byrne et al.[26] Patients had to meet all 3 of the following criteria: be free of panic attacks, have minimal anticipatory anxiety, and have minimal agoraphobia. In the present study, these criteria had to be met in the following way: To meet the first criterion, patients had to report no panic attacks in a panic log during the 2-week posttest 2 assessment. Anticipatory anxiety was measured by the PAI anticipated panic scale.[24] In order to meet the second criterion, there had to be a clinically significant change on the PAI anticipated panic scale according to guidelines as set forth by Jacobsen and Truax.[27] Finally, an agoraphobia subscale score of 10 or less on the Fear Questionnaire[28] was needed to meet the third criterion. The resulting primary outcome measure remitter status was dichotomous: remitter or no remitter.

Secondary outcome measures. Health-related quality of life was measured by the RAND-36 Health Status Inventory (RAND),[29] a commonly used multidimensional self-report questionnaire assessing 8 domains of health-related quality of life and yielding 2 summary scales: physical health (RAND-P) and mental health (RAND-M). Each summary scale (RAND-P, RAND-M) generates a transformed score ranging from 0 to 100, with a higher score representing

better health. The RAND-36 was completed at pretest, at posttest 2, and at follow-up 2. To control for comorbid depression, the Hamilton Depression Rating Scale (HDRS)[30] (range, 0–52) was administered together with the HARS. The extent to which patients were satisfied with the received treatment was assessed at posttest 2 with the Client Satisfaction Questionnaire (CSQ).[31] The mean CSQ score ranges from 1 to 4, with a higher score representing a higher degree of satisfaction.

Predictor variables. Screening of participating patients consisted of a structured interview, the Mini-International Neuropsychiatric Interview (MINI),[32] checking *DSM-IV* criteria for Axis I disorders. Axis I comorbidity was thus established on the basis of this interview. Axis II comorbidity was assessed by means of a self-report questionnaire that patients completed at pretest. This questionnaire, the Assessment of *DSM-IV* Personality Disorders (ADP-IV)[33] was designed to prevent overdiagnosis by additionally assessing distress or impairment characteristics of each *DSM-IV* criterion. Agoraphobia level was assessed, after inclusion, by the first author on the basis of chart review and the structured interview (the MINI). Patients were classified as not suffering from agoraphobia or as suffering from mild, moderate, or severe agoraphobia following guidelines set forth by the *DSM-III-R*.

Statistical Analyses

To obtain a proper comparison between treatments, we distinguished 3 types of patients: *completers*, *dropouts*, and *no-tapers*. Patients were defined as completers when treatment had ended with therapist consent. Also, completer patients received a minimum of 15 of 21 CBT sessions and/or 8 of 12 SSRI sessions. Dropouts were lost during the first treatment year because of various reasons (see Attrition section). No-tapers failed to taper medication and used an SSRI throughout the entire study period.

To investigate and compare the effects of the 3 treatments over time, multilevel modeling was used.[34,35] Three models were built, 1 each for the PAI coping scale, the Hamilton measures (HARS and HDRS), and the RAND measures (RAND-P and RAND-M). The latter 2 models involve a joint modeling of 2 outcome measures in a 3-level model to account for dependencies between those measures. In the multilevel models, the statistical significance of the fixed regression effects is tested using the approximate *t* test, and the statistical significance of the random effects is tested using the deviance test. The significance level was set at .05. For each of the 3 models, the modeling strategy was as follows: First, an adequate representation of the variance structure of the repeated assessments was found using dummy variables for posttest 1, posttest 2, follow-up 1, and follow-up 2. The dummy variables were coded such that each parameter expresses the change between the measurement concerned and its predecessor. Because it was expected that no important changes in scores would occur between posttest 2 and follow-up 1, the differential effect of follow-up 1 was retained only when significant. Second, initial and differential effects of treatment across time were examined using 2 dummy variables for treatment and in interaction with the 4 assessment dummies. Because of the randomization, no differences across treatments are expected at pretest, and the effect of pretest was preserved only when significant. To show possible differential effects across time, interactions between treatment and posttest 1 were always included in the model; the remaining interaction effects were preserved only when significant. Third, it was assessed whether those who completed the study differed from those who dropped out or those who failed to taper medication, using dummy variables. Possible differential effects across time and treatment were examined, but those effects were preserved only when significant. Fourth, possible effects of treatment site, baseline agoraphobia, duration of illness, Axis I and Axis II comorbidity, additional benzodiazepine use, and additional treatment during follow-up were examined, both as main effect and as interaction with received treatment. As random effects, the between-individual and within-individual variance were estimated. Random effects for the difference between pretest and posttest 1 were examined and were preserved when significant. All models were built using the program MlwinN.[36]

Univariate analyses of variance and post hoc Bonferroni pairwise comparisons were used to evaluate pretest differences between patient groups, posttest 2 differences between satisfaction scores, and differences regarding duration of received treatment. Chi-square analyses were used to investigate overall differences in dropout rate and remitter proportions. The differences between proportions were further evaluated by the Wilson 95% confidence interval around this difference.[37,38] Tests were 2-tailed, and α was set at .05.

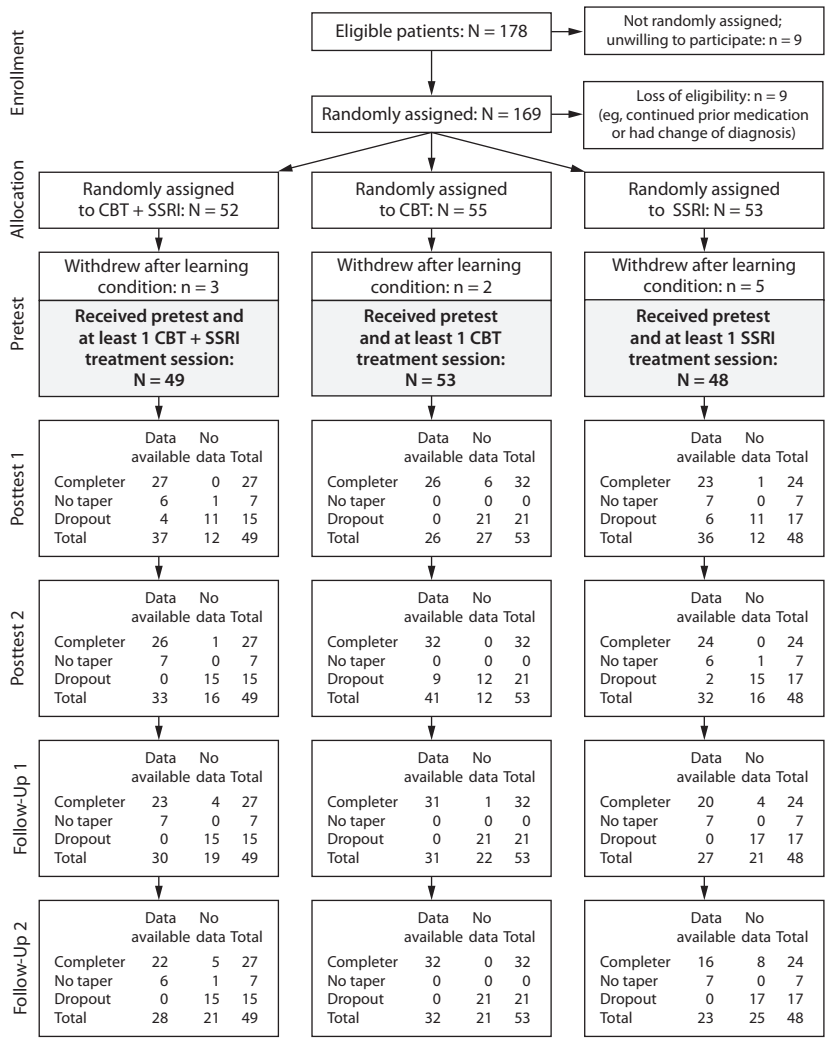
RESULTS

Patient Flow

After random assignment, 150 of 178 patients who were seen for screening (Figure 1) received a pretest and started treatment. Several pretest characteristics of the present sample are presented in Table 1. According to our definition of patient types, 83 of 150 patients are defined as completers. Further, 14 of 150 patients are defined as no-tapers. These patients started with an SSRI treatment (they were randomly assigned to SSRI or to CBT + SSRI) but never tapered their medication during the course of the trial. Three of these patients made an attempt to taper their medication but failed; the other 11 never tried (refused) to taper their medication. Finally, 53 of 150 patients did not complete treatment and dropped out during the first study year.

At follow-up 2, which was 12 months after treatment discontinuation, data were available for 83 patients, of whom

Figure 1. Flowchart of Study Recruitment, Treatment Allocation, and Follow-Up



Abbreviations: CBT = cognitive-behavioral therapy, SSRI = selective serotonin reuptake inhibitor.

28 received CBT + SSRI, 32 received CBT, and 23 received SSRI (Figure 1). Patients dropped out not only during treatment (see section on Attrition) but also during the second follow-up year: these patients did not attend follow-up(s) despite efforts from the research team to contact them. In the SSRI group, 8 patients were lost during the follow-up year, and, in the CBT + SSRI group, 6 patients were lost. All completer patients in the CBT group stayed in the study during the follow-up year.

Attrition

Fifty-three patients were lost during the first treatment year, resulting in an observed total dropout rate of 35%. Reasons for dropout and the rates per treatment are listed in Table 2. No pretest differences regarding patient characteristics and pretest scores for all outcome measures were found between patients who subsequently dropped out and patients who subsequently completed treatment (all $P \geq .27$).

Both the overall and pairwise differences between the 3 treatment groups regarding dropout rates proved nonsignificant (overall: $\chi^2_2 = 0.91$, $P = .64$).

Timing of Treatment Discontinuation

Posttest 2 (to be administered after 52 weeks) was rescheduled when treatment termination was delayed or advanced. The CBT completers (n = 32) showed a mean number of 50.4 weeks (SD = 10.8; range, 28.1–82.6 weeks) between pretest and posttest 2. The SSRI completers (n = 24) showed a mean of 61.4 weeks (SD = 14.5; range, 49.0–110.1 weeks), and the CBT + SSRI completers (n = 27), 60.0 weeks (SD = 9.8; range, 49.3–88.6 weeks). The overall difference between groups regarding number of weeks proved significant ($F_2 = 7.68$, $P = .001$). Pairwise comparisons revealed that CBT lasted significantly shorter than both the SSRI and CBT + SSRI treatments (95% CIs of difference in mean: 2.1–17.3 and 3.3–18.8 weeks, respectively). Patients receiving an SSRI (either with or without CBT) thus needed more time to discontinue treatment as compared to patients receiving CBT only.

Number of Received Sessions

The CBT completers received a mean of 19.0 sessions (SD = 4.0; range, 7–25 sessions).* The SSRI completers received a mean of 11.6 sessions (SD = 1.3; range, 9–15 sessions). The CBT + SSRI completers received a mean of 18.6 CBT sessions (SD = 3.01; range, 11–22 sessions) and a mean of 11.8 SSRI sessions (SD = 1.3; range, 9–14 sessions).

Selective Serotonin Reuptake Inhibitor Treatment and Adverse Effects

The 5 SSRIs in order of number of times prescribed are paroxetine (31 patients), sertraline (23), fluvoxamine (22), citalopram (22), and fluoxetine (4).† For paroxetine, the mean highest daily dosage throughout the treatment period was 30.0 mg (SD = 11.4; range, 10–50 mg); for

*In 4 CBT-only cases, therapist and patient both agreed that more treatment sessions were not needed because of early treatment success. These CBT completer patients received less than 15 CBT sessions (7, 11, 12, and 14 sessions, respectively).

†Numbers based on prescription data differ from number of SSRI users as can be obtained from the flowchart (Figure 1). This discrepancy is explained by both missing data and the fact that some patients switched from one SSRI to another and thus had more than one SSRI prescribed to them.

Table 1. Pretest Characteristics of Patients With Panic Disorder With or Without Agoraphobia Who Received Cognitive-Behavioral Therapy (CBT), Selective Serotonin Reuptake Inhibitor (SSRI), or Both Combined (CBT + SSRI)

Pretest Characteristic	CBT (n = 53), Mean (SD)	SSRI (n = 48), Mean (SD)	CBT + SSRI (n = 49), Mean (SD)	All Patients (N = 150), Mean (SD)
Duration of illness, y	8.1 (8.4)	10.2 (10.4)	7.2 (7.6)	8.5 (8.9)
Age, y	39.4 (10.2)	38.5 (10.5)	34.4 (10.6)	37.5 (10.6)
Number of panic attacks[a]	5.44 (9.57)	3.62 (4.50)	5.08 (5.75)	4.74 (6.99)
	n (%)	n (%)	n (%)	n (%)
Female sex	33 (62.3)	26 (54.2)	23 (46.9)	82 (54.7)
Currently married[b]	29 (54.7)	33 (68.8)	25 (51.0)	87 (58.0)
Currently employed	30 (56.6)	31 (64.6)	31 (63.3)	92 (61.3)
Level of completed education				
Low	10 (18.9)	11 (24.4)	11 (22.4)	32 (21.8)
Moderate	28 (52.8)	16 (35.6)	14 (28.6)	58 (39.5)
Above moderate	6 (11.3)	9 (20.0)	9 (18.4)	24 (16.3)
High	9 (17.0)	9 (20.0)	15 (30.6)	33 (22.4)
Level of agoraphobia				
None or mild	26 (49.1)	23 (47.9)	23 (46.9)	72 (48.0)
Moderate or severe	27 (50.9)	25 (52.1)	26 (53.1)	78 (52.0)
Received previous CBT treatment	2 (3.8)	3 (6.4)	7 (14.3)	12 (8.1)
Received previous SSRI treatment	17 (32.1)	12 (25.0)	14 (28.6)	43 (28.7)
Presence of comorbid Axis I disorder	28 (52.8)	20 (41.7)	20 (55.1)	75 (50.0)

[a]Mean number of panic attacks during 2-week pretest period.
[b]Includes cohabiting with steady partner.

Table 2. Reasons for Dropping Out of Study by Treatment Group (N = 53 for total dropouts)

Reason	CBT + SSRI (N = 49), n	CBT (N = 53), n	SSRI (N = 48), n
Side effects of medication	4	NA	7
Life event not related to treatment	0	3	1
Noncompliance	5	5	2
Other treatment needed	3	2	1
Losing motivation because of good results	0	1	0
Dissatisfaction with obtained results	1	4	2
Using medication outside protocol	0	3	0
Unspecified (unknown)	2	3	4
Total, n (%)	15 (31)	21 (40)	17 (35)

Abbreviations: CBT = cognitive-behavioral therapy, NA = not applicable, SSRI = selective serotonin reuptake inhibitor.

sertraline, 85.9 mg (SD = 37.6; range, 25–150 mg); for fluvoxamine, 144.3 mg (SD = 48.8; range, 50–200 mg); for citalopram, 29.0 mg (SD = 13.0; range, 10–60 mg); and for fluoxetine, 32.5 mg (SD = 18.9; range, 20–60 mg). Adverse effects related to medication were recorded on a symptom and side-effects checklist by the pharmacotherapist at each visit; we had adverse effects data for 91 patients. Taking the 5 SSRIs together, the most frequently reported adverse effects include nervousness (reported by 72 patients [79%]), weakness/fatigue (71 patients [78%]), headache (62 patients [68%]), sweating (57 patients [63%]), and insomnia (55 patients [60%]). There were some differences in adverse effects between the different SSRIs, based on the top 3 most reported side effects for each SSRI. Anxiety and weakness/fatigue were frequently reported for all 5 SSRIs. Headache was frequently reported as well but with the exception of citalopram. Drowsiness was reported only for fluoxetine, memory problems only for paroxetine, and nausea only for citalopram.

Outcome Measures

Estimated coefficients plus significance levels and standard errors of the multilevel models that were built for the measures HARS, PAI coping, RAND-M/P, and HDRS are depicted in Table 3. Figures 2, 3, 4, and 5 plot the model-based estimated scores for HARS, PAI coping, RAND-M/P, and HDRS, respectively, for a completer patient without agoraphobia or with only mild agoraphobia and without comorbid Axis I disorders, who does not use or only occasionally uses benzodiazepines and who has suffered from panic complaints for 8.22 years (which is the mean duration of complaints as observed in the sample). Observed proportions of remitters are depicted in Table 4. Possible differences between patient groups will be discussed in the section on dropouts and no-tapers compared to completers.

Primary outcome measures. Hamilton Anxiety Rating Scale. As can be derived from Table 3 and as depicted in Figure 2, on the HARS, CBT + SSRI treatment outperformed CBT (and to a lesser extent SSRI) up to posttest 1, hence, while treatment was continued. After treatment discontinuation, however, CBT caught up, and the monotherapies ran on parallel tracks from posttest 2 up to follow-up 2. All treatment groups improved significantly from pretest to posttest 1. The improvement for the CBT group from posttest 1 to posttest 2 was significant as well. The slight increase observed from posttest 1 to posttest 2 for the CBT + SSRI and SSRI groups proved nonsignificant. All treatment groups improved significantly from posttest 2 to follow-up 2. At posttest 1, pairwise comparisons revealed that both CBT + SSRI and SSRI were superior to CBT. This superiority was no longer observed at subsequent assessments when all pairwise differences between treatment modalities proved nonsignificant.

Panic Appraisal Inventory (PAI) coping. Regarding PAI coping (Figure 3), all treatment groups improved significantly from pretest to posttest 1, and no significant changes were observed after posttest 1 up to follow-up 2. This means that all treatment modalities were associated with an increased confidence in coping with future panic attacks, and this effect was maintained throughout treatment and follow-up. Although visual inspection of the plot in Figure 3 reveals higher coping scores for CBT + SSRI as compared to the monotreatments, no significant differences between treatment modalities were observed for PAI coping at any assessment.

Table 3. Estimated Coefficients and Standard Errors of the Hierarchical Models for the Measures HARS, PAI Coping, RAND-P, RAND-M, and HDRS[a]

Variable	HARS, Estimate (SE)	PAI Coping, Estimate (SE)	RAND-P, Estimate (SE)	RAND-M, Estimate (SE)	HDRS, Estimate (SE)
Fixed effects					
Intercept (mean score at pretest, CBT)	19.7 (1.2)***	44.0 (2.4)***	70.1 (2.1)***	53.5 (2.1)***	11.8 (0.9)***
Contrast posttest 1	−6.6 (1.4)***	32.2 (3.5)***	NA	NA	−3.5 (1.0)***
Contrast posttest 2	−2.5 (1.2)**	2.3 (1.5)[b]	3.5 (2.6)[b]	10.9 (2.7)***	−2.0 (0.9)*
Contrast follow-up 2	−2.4 (0.9)**	0.4 (1.6)[b]	4.4 (2.1)*	7.6 (2.3)***	−1.7 (0.7)*
SSRI at pretest	…	…	…	…	…
CBT + SSRI at pretest	…	…	…	…	…
Contrast posttest 1 × SSRI	−3.9 (1.5)*	−1.9 (3.8)[b]	NA	NA	−2.0 (1.0)*
Contrast posttest 1 × CBT + SSRI	−5.8 (1.5)***	4.4 (3.8)[b]	NA	NA	−3.8 (1.0)***
Contrast posttest 2 × SSRI	3.5 (1.6)**	…	7.4 (3.5)*	7.1 (3.6)*	2.0 (1.2)[b]
Contrast posttest 2 × CBT + SSRI	3.7 (1.6)**	…	7.8 (3.4)*	5.6 (3.5)[b]	2.6 (1.1)*
Contrast follow-up 2 × SSRI	…	…	…	…	…
Contrast follow-up 2 × CBT + SSRI	…	…	…	…	…
Dropout	−1.9 (1.8)[b]	2.2 (2.9)[b]	−4.9 (3.2)[b]	−6.4 (3.2)*	1.3 (1.1)[b]
No-taper	4.2 (2.1)[b]	−6.0 (4.7)[b]	−7.7 (4.5)[b]	−7.6 (4.4)[b]	3.6 (1.5)*
Contrast posttest 1 × dropout	5.5 (2.0)**	−16.3 (5.0)***	…	…	3.0 (1.4)*
Contrast posttest 1 × no-taper	…	−10.0 (5.4)[b]	…	…	…
Duration of complaints	…	0.2 (0.2)[b]	…	…	…
Contrast posttest 1 × duration of complaints	…	−0.5 (0.2)*	…	…	…
Level of agoraphobia	…	−9.6 (2.4)***	…	…	…
Comorbid Axis I disorder	5.7 (1.5)***	…	…	…	4.0 (1.0)***
Contrast posttest 1 × comorbid Axis I disorder	−3.7 (1.3)**	…	…	…	−2.9 (0.9)**
Comorbid Axis II disorder	…	…	…	…	…
Benzodiazepine use	…	−9.6 (3.3)**	−16.4 (4.0)***	−15.5 (4.1)***	…
Random effects					
Between-individual variance	43.1 (6.6)***	117.4 (24.8)***	168.7 (32.0)***	146.9 (31.2)***	20.9 (3.2)***
Covariance between dependent variables	28.1 (4.4)***	…	…	121.9 (26.9)***	…
Additional variance of contrast posttest 1	…	141.7 (34.6)***	…	…	…
Residual variance at measurement occasions	38.2 (2.8)***	125.8 (10.6)***	192.2 (20.1)***	220.3 (22.9)***	18.7 (1.4)***
Covariance between dependent variables at measurement occasions	20.6 (1.7)***	…	…	106.9 (17.1)***	…

[a]Contrast at a measurement occasion is the contrast between the measurement occasion and previous test occasion(s).
[b]Not significant ($P \geq .05$).
***$P < .001$; **$P < .01$; *$P < .05$.
Abbreviations: CBT = cognitive-behavioral therapy, HARS = Hamilton Anxiety Rating Scale, HDRS = Hamilton Depression Rating Scale, NA = not applicable, PAI = Panic Appraisal Inventory, RAND-M = summary scale mental health−related quality of life, RAND-P = summary scale physical health−related quality of life, SSRI = selective serotonin reuptake inhibitor.
Symbol: … = An effect is preserved in the model only when significant, and this effect appeared to be nonsignificant.

Table 4. Remitter Status for Completer Patients (N = 83) at Four Assessments by Treatment Group

	Completer Patients Meeting Remitter Criteria (yes or no)[a]					
	CBT + SSRI, n = 27		CBT, n = 32		SSRI, n = 24	
Assessment	Yes, n (%)	No, n (%)	Yes, n (%)	No, n (%)	Yes, n (%)	No, n (%)
Posttest 1	14 (52)	13 (48)	6 (19)	20 (63)	11 (46)	12 (50)
Posttest 2	14 (52)	11 (41)	14 (44)	18 (56)	8 (33)	15 (63)
Follow-up 1	10 (37)	12 (44)	14 (44)	16 (50)	6 (25)	14 (58)
Follow-up 2	13 (48)	9 (33)	10 (31)	20 (63)	6 (25)	10 (42)

[a]Completer patients for whom remitter status could not be established due to incomplete data were excluded from this table.
Abbreviations: CBT = cognitive-behavioral therapy, SSRI = selective serotonin reuptake inhibitor.

Remitter status. Table 4 shows the number of observed remitters in the completer group at 4 assessments. To assess possible differences between treatment modalities regarding remitter proportions, 4 χ^2 analyses (1 for each assessment) were performed. These analyses revealed no significant differences at any assessment (all $P \geq .07$).

Secondary outcome measures. Health-related quality of life. As can be seen from Figure 4, at pretest, physical health scores were higher as compared to mental health scores. This suggests that our sample of patients experienced problems regarding their mental health but not as much regarding their physical health. Estimated health scores were consistently lower for CBT patients as compared to SSRI and CBT + SSRI patients regarding both physical and mental health. For RAND-P, the improvement from pretest to posttest 2 was significant for the SSRI and CBT + SSRI groups but not for the CBT group. All treatment groups improved significantly from posttest 2 to follow-up 2.

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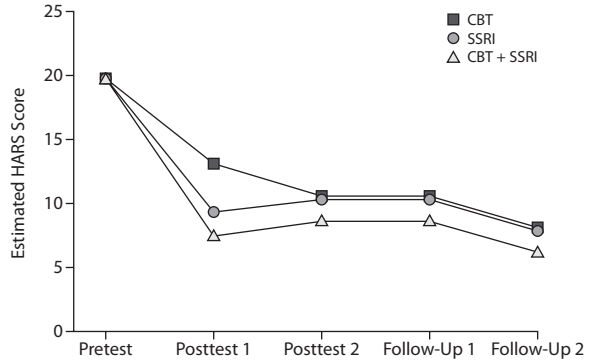
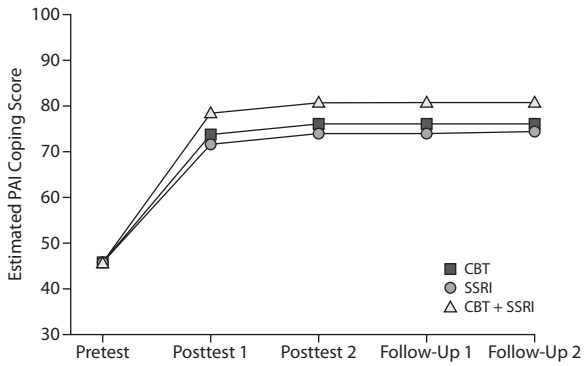
Figure 2. Model-Based Estimated Scores for the Hamilton Anxiety Rating Scale (HARS) by Treatment Group



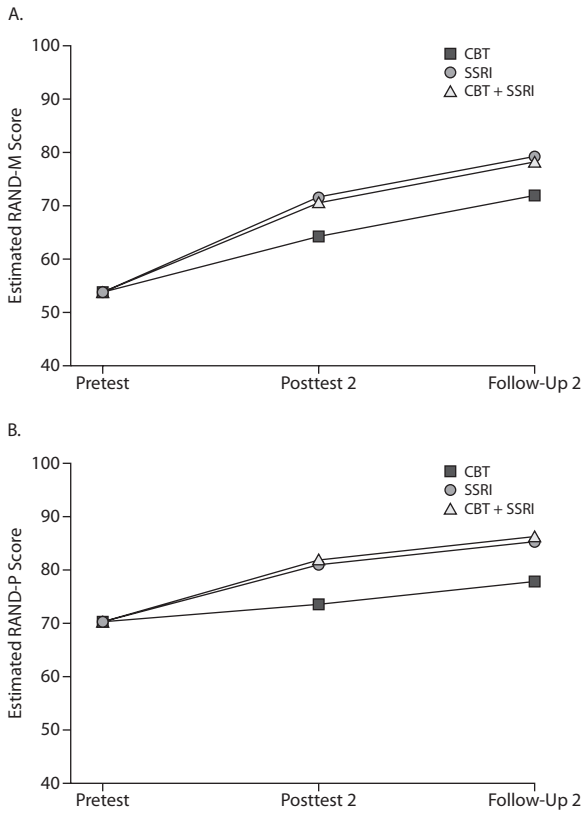
Abbreviations: CBT = cognitive-behavioral therapy, SSRI = selective serotonin reuptake inhibitor.

Figure 3. Model-Based Estimated Scores for Panic Appraisal Inventory (PAI) Coping by Treatment Group



Abbreviations: CBT = cognitive-behavioral therapy, SSRI = selective serotonin reuptake inhibitor.

Figure 4. Model-Based Estimated Scores for the RAND-M (A) and RAND-P (B) by Treatment Group



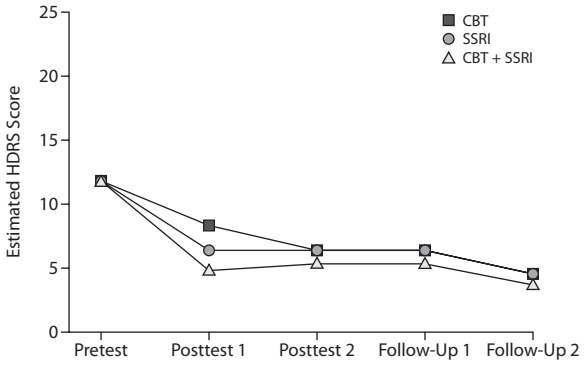
Abbreviations: CBT = cognitive-behavioral therapy, RAND-M = summary scale mental health–related quality of life, RAND-P = summary scale physical health–related quality of life, SSRI = selective serotonin reuptake inhibitor.

Pairwise comparisons revealed that both CBT + SSRI and SSRI were superior to CBT at posttest 2 and follow-up 2. For RAND-M, all treatment groups improved significantly from pretest to posttest 2 and from posttest 2 to follow-up 2. Pairwise comparisons revealed that SSRI (but not CBT + SSRI) was superior to CBT at posttest 2 and follow-up 2.

Hamilton Depression Rating Scale. As can be seen in Figure 5, the pattern of results for the HDRS generally matches the results as described for the HARS; however, HDRS scores were lower to begin with in our sample of patients. Also, differences between treatment modalities were even smaller as indicated by almost perfect parallel tracks. All treatment groups improved significantly on the HDRS from pretest to posttest 1. Subsequently, CBT improved significantly from posttest 1 to posttest 2, while posttest 1 to posttest 2 differences proved nonsignificant for the CBT + SSRI and SSRI groups. All treatment groups improved significantly from posttest 2 to follow-up 2. Pairwise comparisons revealed that at posttest 1, CBT + SSRI was superior to CBT. This superiority could not be confirmed at subsequent assessments when pairwise differences between treatment modalities proved nonsignificant.

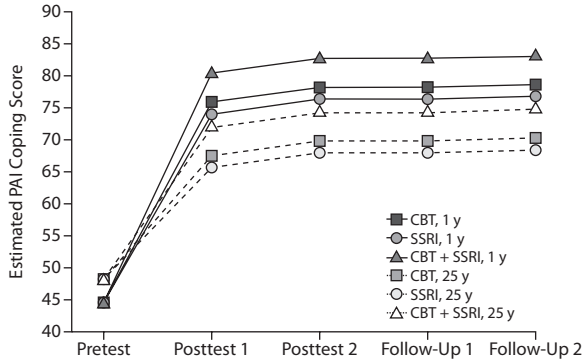
Client Satisfaction Questionnaire. At treatment endpoint, patients completed the CSQ, and the following means were established for the completer group: for CBT + SSRI, 3.62 (SD = 0.39); for CBT, 3.29 (SD = 0.48); and for SSRI, 3.40 (SD = 0.55). Given that the mean CSQ score ranges from 1 to 4, our sample of patients can be considered highly satisfied with the received treatment.[31,39] Overall differences proved significant between treatment groups ($F_{2,106} = 4.45$, $P = .014$). Subsequently, post hoc analyses revealed significant differences between CBT + SSRI and CBT (95% CI of difference: 0.06–0.60), implying that patients who received CBT + SSRI appeared slightly more satisfied with treatment as compared to patients who received CBT only. Finally, patients obtained equivalent high mean CSQ scores regardless of type of site at which they were treated and regardless of whether they were treated by student-therapists or professional therapists (all $P \geq .74$).

Figure 5. Model-Based Estimated Scores for the Hamilton Depression Rating Scale (HDRS) by Treatment Group



Abbreviations: CBT = cognitive-behavioral therapy, SSRI = selective serotonin reuptake inhibitor.

Figure 6. Model-Based Estimated Panic Appraisal Inventory (PAI) Coping Scores for 3 Treatment Modalities for Panic Disorder Durations of 1 Year and 25 Years



Abbreviations: CBT = cognitive-behavioral therapy, SSRI = selective serotonin reuptake inhibitor.

Dropouts and no-tapers compared to completers. The variable "type of patient" categorized patients into completers, dropouts, and no-tapers. A main effect of dropout was found for the measure RAND-M, which implies that dropout patients reported overall lower mental health scores as compared to completer patients. A main effect of no-taper was found for the measures HARS and HDRS, which implies that patients who failed to taper medication were associated with overall higher anxiety and depression levels as compared to completer patients. On no measure was an interaction effect observed between type of treatment and type of patient, which means that the effect of type of patient could not be shown to differ between treatments. At posttest 1, the difference between completers and dropouts was significant for PAI coping, HARS, and HDRS, suggesting that from pretest to posttest 1, dropout patients had experienced a smaller decrease in anxiety and depressive complaints and a smaller increase in coping, as compared to completer patients. Regarding treatment satisfaction, mean CSQ scores were compared. The mean for the completer group was 3.54 (SD = 0.41); for dropouts, 2.94 (SD = 0.59); and for no-tapers, 3.29 (SD = 0.54). Overall differences proved significant between patient groups ($F_2 = 10.37$, $P < .001$). Subsequently, post hoc analyses revealed significant differences between the completers and the dropouts (95% CI of difference: 0.27–0.93), implying that patients who had completed treatment were more satisfied with treatment as compared to patients who had dropped out of treatment.

Predictor Variables

Site effects. Sixty-three patients were treated at the 2 university training and research centers, 42 at the 2 university research clinics, and 45 at the 7 regular mental health clinics. Previous analyses[17] revealed no differences between the 3 kinds of participating sites regarding pretest scores, dropout rate, and treatment effect at posttest 1. In the present analyses, again no effect of site was found for any of the outcome measures at any assessment.

No/mild agoraphobia versus moderate/severe agoraphobia. About half of the patients in the present sample (48%) either did not suffer from agoraphobia or suffered from only mild agoraphobia while the other half (52%) suffered from moderate or severe agoraphobia. Only for the primary outcome measure, PAI coping, was a significant main effect of agoraphobia status found (no/mild vs moderate/severe), indicating that patients with moderate/severe agoraphobia reported less confidence in their ability to cope with future panic attacks as compared to patients without agoraphobia or with only mild agoraphobia.

Duration of illness. At pretest, the number of years that patients suffered from their complaints ranged from 6 months to 43 years (mean = 8.23, SD = 8.53 years). For PAI coping, a significant relationship was found between duration of illness, treatment effect over time, and the level of confidence in the ability to cope with future panic attacks. at pretest, patients who had suffered from their panic disorder complaints longer reported on average more confidence in their coping abilities as compared to patients who had suffered from their panic disorder complaints for a shorter period of time. However, the increase in confidence reported from pretest to posttest 1 appeared significantly lower for the longer-suffering patients, resulting in higher coping scores at subsequent assessments for the patients who suffered from their panic disorder complaints for a shorter period of time. To illustrate this phenomenon, Figure 6 shows the model-based estimated PAI coping scores for the 3 treatment modalities when panic complaints had been present for 1 year at the time of the intake and for 25 years.

Axis I comorbidity. Presence of comorbid Axis I disorders was checked at intake. At that time, 50% (n = 75) suffered from at least 1 additional Axis I disorder according to the standardized interview.

Table 5. Number of Benzodiazepine Users Among Completer Patients by Treatment Group

Pattern of Benzodiazepine Use[a]	CBT + SSRI Completers (n = 27), n (%)	CBT Completers (n = 32), n (%)	SSRI Completers (n = 24), n (%)	Total (N = 83), n (%)
No benzodiazepine use at any assessment	18 (67)	20 (63)	14 (58)	52 (63)
Benzodiazepine use at pretest, but no benzodiazepine use for at least 1 subsequent assessment	8 (30)	4 (13)	9 (38)	21 (25)
No benzodiazepine use at pretest, but benzodiazepine use for at least 1 subsequent assessment	1 (4)	3 (9)	1 (4)	5 (6)
Benzodiazepine use at each assessment	0	5 (16)	0	5 (6)

[a]Benzodiazepine use could vary between very infrequent use and daily use.
Abbreviations: CBT = cognitive-behavioral therapy, SSRI = selective serotonin reuptake inhibitor.

On both Hamilton scales, patients with at least 1 comorbid Axis I disorder reported significantly more anxious and depressive complaints at pretest as compared to patients with no comorbid Axis I disorder. At posttest 1, the difference between patients with and without comorbid Axis I disorders had become smaller but was still significant. The difference was maintained at subsequent assessments.

Axis II comorbidity. Axis II disorders were not formally diagnosed, but a screening self-report questionnaire[33] was completed at pretest. At that time, 20% of the patients met the criteria of at least 1 Axis II disorder. There were no differences between treatment groups ($\chi^2_2 = 0.03$, $P = .99$). No main effect (or interaction effect with time of assessment) of Axis II comorbidity was found on any outcome measure.

Additional benzodiazepine use. According to protocol, patients were not allowed to use psychotropic drugs except for small doses of benzodiazepines (maximum: the equivalent of 20 mg oxazepam per day). Benzodiazepine use was scored on a 4-point scale, with 1 = none; 2 = only infrequently; 3 = regularly, but not daily; and 4 = daily. The multilevel models for all measures revealed that patients scoring 1, 2, or 3 showed similar patterns of response, and, therefore, these were pooled in the so-called "no or occasional benzodiazepine use" group. This group of patients was compared to the group that used benzodiazepines on a daily basis, the "daily benzodiazepine use" group. The multilevel models revealed that using benzodiazepines on a daily basis proved to be a factor of importance as reflected on the measures PAI coping and RAND-M/P. On these measures, a significant main effect of additional benzodiazepine use was observed, indicating that, overall (in the same degree at each assessment), patients in the "daily benzodiazepine use" group reported lower health scores and less confidence in their ability to cope with future panic attacks as compared to patients in the "no or occasional benzodiazepine use" group.

To gain insight into the frequency of benzodiazepine use across treatment modalities and assessments, benzodiazepine use is summarized in Table 5. It seems that, once treatment was started, a few more CBT-only patients used additional benzodiazepines as compared to patients using an SSRI, either combined with CBT or not. The majority of patients (63% of completer sample), however, did not use any additional benzodiazepines at any assessment.

Additional treatment during follow-up. For the patients who completed treatment and were assigned to follow-up, it was recorded whether additional treatment was received during follow-up. Of the completer sample, 64% (n = 53) received no additional treatment during follow-up, 23% (n = 19) did receive additional treatment during follow-up, and information regarding additional treatment during follow-up was missing for 13% (n = 11). With respect to the different treatment modalities, 9 CBT + SSRI patients (33%) received additional treatment, 5 patients in the CBT group (16%) received additional treatment, and 5 patients in the SSRI group (21%) received additional treatment. The 9 CBT + SSRI patients with additional treatment received CBT (n = 2), an SSRI (n = 5), a combined CBT + SSRI treatment (n = 1), or a psychological treatment other than CBT (n = 1). The 5 CBT patients with additional treatment received an SSRI (n = 3) or a combined CBT + SSRI treatment (n = 2). The 5 SSRI patients with additional treatment received CBT (n = 2), SSRI (n = 2), or both CBT and SSRI but not simultaneously (n = 1). Treatment with CBT + SSRI thus yielded the highest, and CBT the smallest, proportion of patients receiving additional treatment during follow-up. The overall difference proved nonsignificant ($\chi^2_2 = 4.3$, $P = .12$). Subsequent pairwise comparisons of proportions revealed an almost significant difference between CBT + SSRI and CBT (95% CI of difference in proportion: −0.04 to 0.39), which might be indicative of a trend.

The variable "additional treatment" was included in the multilevel models to investigate the possible influence of receiving additional treatment during follow-up on long-term treatment outcome. No main effect (or interaction effect with time of assessment) of additional treatment was found on any outcome measure.

DISCUSSION

Based on the context-safety hypothesis, we expected CBT to have more durability during follow-up than CBT + SSRI and SSRI. However, no significant loss of gains after treatment discontinuation was observed for either treatment modality. One-year follow-up results suggested that the 3 treatment modalities were generally equally effective. Major changes occurred during the first 9 months of treatment, during which all 3 treatment modalities were associated

with statistically significant and clinically relevant improvement on all outcome measures. Subsequently, results were maintained during follow-up. On the measures HARS, HDRS, and RAND-M/P, even further improvement during follow-up was observed.

When evaluating treatment modalities pairwise, most differential effects were observed during the first treatment year. Significant differences on the primary outcome measures were observed at posttest 1 when SSRI and CBT + SSRI proved superior to CBT on the HARS. Subsequently, significant differences between treatment modalities were no longer observed at follow-up 2, which was 12 months after treatment discontinuation.

Results thus suggest that gains produced by CBT were slower to emerge than those produced by the other treatment modalities. The CBT treatment in the present study lasted 1 year, which is longer than the CBT in several other trials. In the Barlow et al study,[10] CBT lasted 9 months. In the present study, at 9 months CBT was not quite up to the level of the other treatments. Based on the comparison of effect sizes, however, the CBT in the present study seems as effective as the CBT delivered in other trials. Previously, we reported an effect size of 0.60 for the CBT group in the present study, while we established an effect size of 0.62[17] for the CBT group in the Barlow et al study.[10]

Consistent with previous reports, CBT was able to maintain its gains throughout follow-up. More surprisingly, however, SSRI alone was also not associated with a fall-off in gains, and this finding counters general consensus. It should be noted, however, that the general consensus is in part based on studies using benzodiazepines or antidepressant medication other than SSRIs (eg, imipramine). Studies presenting relapse rates after SSRI discontinuation are scarce. There is clearly a need for studies like the present one, investigating the long-term effects of SSRIs following cessation of pharmacotherapy.

Considering the present results, we must conclude that we have not succeeded in determining *the* most effective treatment for panic disorder with or without agoraphobia since no evidence was found for clear superiority of 1 treatment modality over another. Studies like the present one should eventually result in recommendations that can be passed on to practitioners.[40] At this point, however, we are not able to predict under what conditions and for which patients a stronger effect can be expected from a particular treatment modality. This leaves the practitioner with the task of making a thoughtful treatment selection for each individual patient. In this process, any previous patient experience with either treatment modality or a possible preference of the patient for either treatment modality can be taken into account. Also, taking into consideration some general drawbacks and plus points of each treatment modality might be helpful in selecting a treatment. In the present study, the delayed treatment effects associated with CBT might be considered a drawback of CBT-only treatment. Plus-points of CBT-only treatment include the fact that it was not associated with adverse effects or withdrawal effects and that treatment ended sooner (as in duration of treatment in weeks) than both the SSRI and CBT + SSRI treatments, which is important from a cost-effectiveness perspective. An advantage of the SSRIs is the observed more immediate effect as compared to CBT-only treatment. Also, the SSRI treatment consisted of half the number of treatment sessions of the CBT treatment while maintaining its gains equally through-out follow-up. On the other hand, SSRIs are associated with adverse events, which can be considered a drawback of medication treatment. Almost 80% of the patients using an SSRI in the present sample reported at least 1 adverse effect.

When comparing CBT + SSRI to SSRI only, it seems that CBT was a valuable and perhaps even indispensable addition to a pharmacotherapeutic treatment because CBT + SSRI was associated with lower HARS and HDRS scores, with higher PAI coping scores, and with more patients' achieving remitter status at each assessment as compared to SSRI only. From a cost-effectiveness perspective, however, CBT + SSRI might be less attractive as compared to a monotreatment.

Seven predictor variables for treatment effect were investigated in the present study, and some interesting findings emerged. Patients who suffered from their complaints for a longer period of time reported considerably less improvement regarding confidence in their coping abilities. Considering some preliminary evidence for the relationship between the related concept of self-efficacy scores and relapse,[41] it seems worthwhile to promote early treatment interventions.

Benzodiazepines are associated with the issues of dependence and withdrawal difficulties.[6] Present data suggest that using benzodiazepines on a daily basis is associated with lower health scores and lower coping scores as compared to no benzodiazepine use or infrequent benzodiazepine use. In the present sample, however, only a few patients used additional benzodiazepines on a daily basis. This fact might imply that, when receiving adequate treatment, patients generally do not need additional benzodiazepines.

Twenty-two percent of the completer patients were in need of additional treatment during the 1-year follow-up period. Data on this subject from other studies is limited. About one-half of the patients received treatment during follow-up in the study by Sharp et al,[42] who stated that patients receiving poststudy treatment should be excluded from follow-up analysis. In the present study, however, no relationship between receiving additional treatment and treatment outcome was found. According to the context-safety hypothesis, one would expect more CBT + SSRI than CBT-only patients to require additional treatment during follow-up. Although we found some indications for this in the present data, results were nonsignificant. At least as important is the finding that, just as in the CBT group, only 5 patients in the SSRI condition received additional treatment during follow-up. At the moment, we cannot explain

the difference between SSRI and CBT + SSRI regarding additional treatment during follow-up. Patients in the SSRI group experienced a shift of context when discontinuing medication, just as did patients in the CBT + SSRI group, but fewer patients apparently were subsequently in need of additional treatment. Because of the small numbers involved and the nonsignificance of the findings, future studies should again take this matter under scrutiny.

Strengths of the present study include the naturalistic character of the study, the fact that clinical sites as well as research sites participated, and the resulting high generalizability of findings. Also, our follow-up period was twice as long as in previously reported studies,[10,42] thereby yielding more insight into the long-term effectiveness of treatments. Further, patients with moderate or severe agoraphobia were not excluded, and results are thus generalizable to the whole agoraphobia continuum. Next, predictor variables were investigated in order to further clarify outcome. Finally, because we did not just look at differences between treatment modalities but also differentiated between different patient groups (completers, dropouts, and no-tapers), we were able to study specific treatment-patient interactions. Regarding this issue, please note the applied strict definitions of dropouts and completers. In the present study, a patient who received 14 CBT sessions and subsequently terminated treatment without therapist consent was considered a dropout, while in some other studies[42] such a patient would be categorized as a completer. We chose this definition in order to ensure a homogeneous completer group, but we recognize that this increased our number of dropouts.

Several limitations deserve mention. First, a binary variable such as remitter status naturally suffers from a loss of power. Furthermore, because remitter status is a composite measure, information on the effectiveness in terms of its separate constituents (agoraphobic avoidance, anticipation anxiety, and panic attacks) is lost. Second, the research assistants who administered the HARS and HDRS were thought to be independent and not partial to either treatment modality. However, they were not blind regarding allocation status, and this fact presents a possible source of bias. Third, treatment adherence was checked by evaluating detailed forms regarding session content as completed by all therapists following each treatment session. We refrained from more formal treatment integrity and fidelity checks because this type of checking was considered to be incompatible with our intention to simulate clinical practice. Although these evaluations revealed no deviations from the treatment manuals, we realize that checking treatment integrity in this way is not completely sound. Finally, the present sample size was limited as compared to, for example, the sample size in the study by Barlow et al,[10] meaning that we must take into consideration the possibility that some effects were nonsignificant due to a lack of power.

The present findings could not confirm the context-safety hypothesis. Previous work suggests that context may refer to an internal state implying that when safety is learned within a medicated state, safety is abated once the medication is withdrawn. However, an internal state might be defined not simply by the presence or absence of medication but rather by how the use of medication is explained by the individual patient. Context may thus refer to an internal state, which in turn is defined by the individual attribution of improvement. If improvement is attributed solely to the medication, then relapse following medication taper is to be expected. If, however, improvement is attributed to both CBT and SSRI, an internal state might not change so radically when tapering medication. This may explain observed differences between the combined treatment and the SSRI as a monotreatment. Some preliminary findings[43] to date warrant further investigation into this matter.

In conclusion, the present findings indicate that CBT only, SSRI only, and CBT + SSRI are effective treatments for panic disorder with or without agoraphobia. Future research should continue to strive for a better understanding of the role of predictor variables and specific working mechanisms associated with different treatment modalities to aid the practitioner in the process of treatment selection.

Drug names: citalopram (Celexa and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), imipramine (Tofranil and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, citalopram, fluvoxamine, and imipramine are not approved by the US Food and Drug Administration for the treatment of panic disorder.

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