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The Effectiveness of Therapy Components in Routine Care of Panic Disorder and Agoraphobia

Timo Klan Wolfgang Hiller

Psychological Institute, Johannes Gutenberg University of Mainz, Germany

Keywords
Panic disorder · Agoraphobia · Cognitive-behavioral therapy · Naturalistic therapy study · Exposure

Summary
Background: There is clear evidence of the efficacy of cognitive-behavioral therapy (CBT) in panic disorder/agoraphobia. Furthermore, existing literature shows that exposure in vivo may be the most effective component of CBT. **Methods:** 104 consecutive patients (intention-to-treat; ITT) with panic disorder/agoraphobia were examined at time of application for therapy, pre- and post-treatment, and at follow-up. The sample included 84 completers. The patients received individual CBT between 2004 and 2011 at a university outpatient clinic. The Brief Symptom Inventory, the Agoraphobic Cognitions Questionnaire, the Body Sensations Questionnaire, and the Mobility Inventory were used to assess treatment outcome. **Results:** Pre-post analyses showed significant symptom reduction and effect sizes between d = 0.53 and d = 0.78 (ITT); and d = 0.73 and d = 1.08 (completer); follow-up analyses indicated stable therapy effects. Response rates were 51.0% (ITT) and 60.7% (completer). A retrospective analysis of conducted therapy components yielded the following frequencies: cognitive therapy 73.0%, interoceptive exposure to internal cues 62.0%, exposure in vivo 59.8%, relaxation training 69.2%. Exposition in vivo was found to be highly effective; cognitive therapy and interoceptive exposure were moderately effective. **Conclusion:** Our results support the outstanding importance of exposure in vivo. Future research should focus on conditions which enhance the use of this treatment component.

Schlüsselwörter
Panikstörung · Agoraphobie · Kognitive Verhaltenstherapie · Naturalistische Therapiestudie · Exposition

Zusammenfassung
Hintergrund: Die Wirksamkeit der kognitiven Verhaltenstherapie bei der Panikstörung mit oder ohne Agoraphobie gilt als gesichert. Mehrere Studien weisen zudem darauf hin, dass die In-vivo-Exposition das möglicherweise wirkungsstärkste Behandlungselement darstellt. An der naturalistischen Stichprobe einer Hochschulambulanz wurden die Effektivität der durchgeführten Therapien sowie insbesondere die Frequenz und Wirksamkeit einzelner Behandlungselemente der kognitiven Verhaltenstherapie überprüft. **Methode:** Die Intention-to-Treat (ITT)-Stichprobe setzte sich aus N = 104 konsekutiven Patienten mit Panikstörung/Agoraphobie als Hauptdiagnose zusammen, von denen 84 die Therapie regulär beendeten. Als Outcome-Maße wurden das Brief Symptom Inventory (BSI) sowie die 4 Skalen des Fragebogens zu körperbezogenen Ängsten, Kognitionen und Vermeidung (AKV) eingesetzt. Mittels einer retrospektiven Aktenanalyse wurde geprüft, wie oft und wie konsequent einzelne Therapieelemente realisiert worden waren. **Ergebnisse:** Es ergaben sich Prä-Post-Effektstärken (Cohens d) zwischen d = 0,53 und d = 0,78 für die ITT-Stichprobe und zwischen d = 0,73 und d = 1,08 für die Completer. Katamnestisch erwiesen sich die Therapieeffekte auch nach 6 und 12 Monaten als stabil. Die Responseraten lagen bei 51% (ITT-Stichprobe) und 60,7% (Completer). Es zeigten sich folgende Häufigkeiten für die Durchführung der Therapieelemente: kognitive Therapie 73,0%, interozeptive Exposition 62,0%, In-vivo-Exposition 59,8%, Entspannungstraining 69,2%. Im Falle der Realisierung von In-vivo-Expositionen waren die Therapieergebnisse erheblich besser, während es bei der Realisierung von kognitiver Therapie und der interozeptiven Exposition nur mäßige Effektsteigerungen gab. Als nicht relevant für das Therapieergebnis erwies sich Entspannung. **Schlussfolgerung:** Die Ergebnisse bestätigen die herausragende Bedeutung der In-vivo-Exposition für den Behandlungserfolg. Zukünftige Forschung sollte sich mit der Frage beschäftigen, warum auf diese wichtige Therapiekomponente in naturalistischen Therapien in nicht wenigen Fällen verzichtet wird und durch welche Maßnahmen ein häufigerer Einsatz erreicht werden könnte.

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Dipl.-Psych. Timo Klan
Poliklinische Institutsambulanz für Psychotherapie
Johannes Gutenberg-Universität Mainz
Psychologisches Institut
Wallstraße 3, 55122 Mainz, Germany
klan@uni-mainz.de

Introduction

There is clear evidence of the effectiveness of cognitive-behavioral therapy (CBT) in panic disorder/agoraphobia. In the 'Evidenzbasierte Leitlinie zur Psychotherapie der Panikstörung und Agoraphobie' (Evidence-Based Guidelines for Psychotherapy of Panic Disorder and Agoraphobia) [Heinrichs et al., 2009], CBT is rated as Evidence Level I ('effective') for panic disorder without agoraphobia, panic disorder with agoraphobia, and agoraphobia without panic disorder. CBT is the method of choice in the treatment of these disorders. Many meta-analyses have described the excellent treatment effects of CBT [e.g., Bakker et al., 1998; Cox et al., 1992; Gould et al., 2012; Mitte, 2005; Norton and Price, 2007; Ruhmland and Margraf, 2001; Sánchez-Meca et al., 2010; Stewart and Chambless, 2009; van Balkom et al., 1997]. The effect sizes (ESs) identified in meta-analyses display a wide range and vary with the outcome measure used, the study design and the method of calculation, the population selected, and the treatment elements. Thus, the ESs identified in the various meta-analyses are only somewhat comparable. Overall, the ESs calculated for CBT are overwhelmingly in the high range. CBT interventions have tended to be superior to both pharmacotherapy and to other psychotherapeutic methods [Clum and Surls, 1993; Gould et al., 1995; Mitte, 2005; Ruhmland and Margraf, 2001]. In follow-up measurements, the effects achieved by CBT have proven stable in the long run [Bakker et al., 1998; Ruhmland and Margraf, 2001]. Ruhmland and Margraf [2001], in their meta-analysis, found an average pre-post ES of 1.19 for CBT in patients with panic disorder with agoraphobia. With the use of confrontation in vivo, the average ES increased to 1.64.

A large portion of the meta-analyses considered only the results of randomized controlled trials (RCTs), so-called efficacy studies [e.g., Clum and Surls, 1993; Gould et al., 1995; 2012; Mitte, 2005; Norton and Price, 2007; Sánchez-Meca et al., 2010; van Balkom et al., 1995; Westen and Morrison, 2001]. Gould et al. [1995] reported an average between-group ES (control group vs. treated group, each post-measurement) of 0.68 for CBT in patients with panic disorder with/without agoraphobia. Norton and Price [2007] report an average pre-post ES of 1.53 for CBT treatments in patients with panic disorder/agoraphobia. In recent years, meta-analyses have been published that consider studies in naturalistic settings (so-called effectiveness studies) [Hans et al., 2010; Steward and Chambless, 2009; van Ingen et al., 2009]. The results of these meta-analyses suggest that the treatment effects of CBT in routine care of patients with anxiety disorders are comparable to the effects in RCTs. According to Steward and Chambless [2009], the ESs for panic disorder range from 0.83 to 1.23 (depending on outcome measure). Hans et al. [2010], in their evaluation of outpatient CBT treatment of anxiety patients, obtained an average ES of 1.73 for the main symptoms, and according to van Ingen et al. [2009], the average pre-post ES was 1.53 (for all the anxiety disorders analyzed).

The designation CBT in the treatment of panic disorder/agoraphobia can be considered a generic term for various techniques, since in the literature several variants have been proposed, with different therapeutic components and combinations of those components. Lang et al. [2009], in their review of the determining factors of CBT, differentiate among psychoeducation, cognitive techniques, exposure methods (confrontation with internal and external stimuli) as well as relaxation techniques / breathing retraining. These authors recommend that cognitive therapy and in vivo exposure should be performed for panic disorder with agoraphobia. With agoraphobic avoidance behavior, in vivo exposure should be performed in any event. The use of relaxation/breathing techniques is considered crucial. In meta-analyses in which the ES is calculated and compared from studies with various treatment methods, the findings are sometimes contradictory. In the meta-analysis by Sánchez-Meca et al. [2010], the greatest effect was achieved with the combination of relaxation training / breathing retraining and exposure (ES = 1.84), followed by exposure alone (ES = 1.53). Norton and Price [2007] likewise report in their meta-analysis that the combination of relaxation with exposure is the most effective method (pre-post ES = 2.11). The least effective measure is the combination of relaxation with cognitive therapy (pre-post ES = 0.72). In the meta-analysis by Chambless and Gillis [1993], however, cognitive therapy (average pre-post ES from 0.98 to 1.75, depending on outcome measure) was at least equivalent to combinations of exposure and cognitive techniques (average pre-post ES from 0.63 to 1.14, depending on outcome measure). In the above-mentioned meta-analysis by Ruhmland and Margraf [2001], in vivo exposure was the most effective approach for panic disorder with agoraphobia (ES = 1.64). Hofmann et al. [2012] demonstrate that interoceptive exposure for panic disorder has moderate effects and is superior to relaxation training. The different and sometimes contradictory findings in the meta-analyses are probably also explicable by variations in the configuration of the therapy components used in the studies (e.g., duration/frequency). Peter et al. [2001] noted this in their critical review of meta-analyses of the combined treatment of panic disorder/agoraphobia with psychotropic drugs and behavioral therapy. Hand et al. [1986] and Peter et al. [2001] also note aspects of differential indication and call for increased consideration of subgroups (e.g., differentiation according to severity of the anxiety disorder. Thus, patients with a diagnosis of 'panic disorder with agoraphobia' may tend to be more strongly affected than patients with a diagnosis of 'panic disorder without agoraphobia').

In German-speaking countries, several studies of the effectiveness of CBT in university outpatient clinics were published back in the 1980s [Fiegenbaum, 1986; 1988; Fischer et al., 1988a;b; Hand et al., 1986]. The interventions were characterized by intensive exposure programs, lasting several hours and several days, which were conducted in individual or group therapy and extended over just a few weeks. Hand et al.

[1986] applied exposure training (exposure-panic management; in German, Exposition-Reaktions-Management, ERM, Hand [1993]), based on the 'flooding' concept developed by Hand et al. [1974] for group treatment of agoraphobia patients. In this international pilot study, the exposure treatment was performed for just 1 week (every 3 days with 4-hour exposure). Another alternative intervention evaluated by Hand et al. [1986] and Fischer et al. [1988a;b] was a manual-based, therapist-guided self-help training program (home-based treatment [Hand et al., 1986]). The self-help program, originally developed and evaluated by Mathews et al. [1977], is a graduated approach to confrontation with anxiety-provoking situations and is performed with a partner [Mathews et al., 2004]. The studies verified high effectiveness from exposure treatment, and the treatment effects were also found to be durable in the long term (follow-up period of up to 9 years [Fischer et al., 1988a]). The exposure training conducted by Hand et al. [1986] proved, both in an individual setting and a group, to be very effective in reducing symptoms of agoraphobic anxiety. The treatment effect also positively affected comorbid symptoms that some of the patients had (depression, social anxiety, obsessions/compulsions, psychosomatic complaints) [Hand et al., 1986; Fischer et al., 1988a;b]. The described self-help training proved to be just as effective as the group exposure overall, so that Hand et al. [1986] came to the conclusion that the self-help training is appropriate, including for patients with high psychological comorbidity. Fiegenbaum [1988] showed that ungraded massed exposure treatment leads to stronger long-term treatment effects than graded exposure (follow-up period of 5 years). More recent studies [Hahlweg et al., 2001; 2004] have demonstrated the effectiveness of a multi-day intensive exposure program in outpatient routine care. It has also been shown that an extensive exposure treatment (2-day vs. 1-day of exposure treatment) in an inpatient hospital setting also had a more durable and stable therapeutic outcome (at 1 year follow-up) [Wambach and Rief, 2012]. Lang et al. [2012a] showed that therapist guidance during the exposure led to 'more favorable treatment results in some cases'. Hand [1993; 2011] points out that therapist guidance during the exposure can be useful (e.g., to encourage motivation and to deal with cognitive avoidance), but not for more than 3 sessions of several hours each. Exposure should then be continued independently by the patient, without further therapist guidance.

In our view, both the findings in the meta-analyses mentioned above and the studies of exposure programs from German-speaking countries demonstrate clearly that in vivo exposure is crucial to the treatment of panic disorder/agoraphobia. However, it is not entirely clear what role in vivo exposure and other therapy components of CBT play, particularly in outpatient routine care of panic disorder/agoraphobia. While Lang et al. [2009] describe in their review several studies of the efficacy of individual treatment elements of CBT, the treatments cited do not occur in outpatient routine care. In meta-analyses of the effectiveness of naturalistic psychotherapies [Hans et al., 2010; Steward and Chambless, 2009; van Ingen et al., 2009], however, nothing is said about the effectiveness of the individual therapy components. Roth et al. [2004], in their study, do indeed deal with the prevalence of various methods of confrontation in health-care practice, but they do not look at the prevalence of other treatment elements of CBT or their effectiveness. The aim of this study is therefore to assess the effectiveness of CBT therapy components performed with patients who have panic disorder and/or agoraphobia, in the naturalistic setting of a university outpatient clinic. In a retrospective analysis of psychotherapies conducted in the university outpatient clinic, the goal was to determine, using patient records, how often and how consistently individual therapy components were implemented and how effectively the specific therapy components contributed to symptom reduction. Furthermore, to calculate the overall effectiveness of the therapy pre-post ES, the waiting phase is to be compared to the treatment phase, and the stability of the treatment effects (follow-up measurements) is to be studied.

Patients and Methods

Setting

The Outpatient Clinic for Psychotherapy of the Johannes Gutenberg University Mainz is a certified university outpatient clinic, authorized under the Psychotherapist Act for psychotherapy training as well as research and teaching. There are psychologists at the clinic who have completed a degree (Diploma or Master of Science) and are in advanced psychotherapy training, as well as licensed psychotherapists. The therapies used in the clinic are oriented toward the current scientifically accepted behavioral methods.

Study Design and Measures

A standardized evaluation system is used in the clinic, with measurement points before, during and after therapy. Upon the patient's registration, a measurement is taken at time point 1 (M1). Between registration and the intake interview there is a waiting period, usually of several months (due to a high demand for therapies). The pre-measurement is taken immediately before the start of therapy, and the post-measurement at the end of therapy. Starting with the probationary phase, measurements are taken approximately every 10 sessions (for both disorder-specific and non-disorder-specific parameters). The follow-up survey is conducted exclusively by mail after 6 or 12 months. The Brief Symptom Inventory (BSI) is used as a cross-disorder measure, starting with M1 [Franke, 2000]. The BSI includes 9 scales and 3 global parameters. Depending on the subscale, the instrument provides acceptable to satisfactory internal consistencies for healthy adults (Cronbach's α: 0.39–0.92) as well as outpatient psychiatric patients (Cronbach's α: 0.71–0.85). Test-retest reliability is in a medium to high range ($r = 0.68$ to 0.93) for outpatient psychiatric patients. The high correlation with the scale of the Symptom Checklist SCL-90-R for ambulatory psychiatric patients ($r = 0.92$–0.99) indicates very good convergent validity. The scales 'anxiety' and 'phobic anxiety' as well as the parameter for basic psychological stress of the Global Severity Index (GSI) were used as the outcome measures in this study. The questionnaire for body-related anxieties, cognitions, and avoidance (AKV) [Ehlers and Margraf, 2001] was also used as a disorder-specific measure, if indicated, at the beginning of therapy (during the probationary phase). The AKV is the German version of 3 English-language

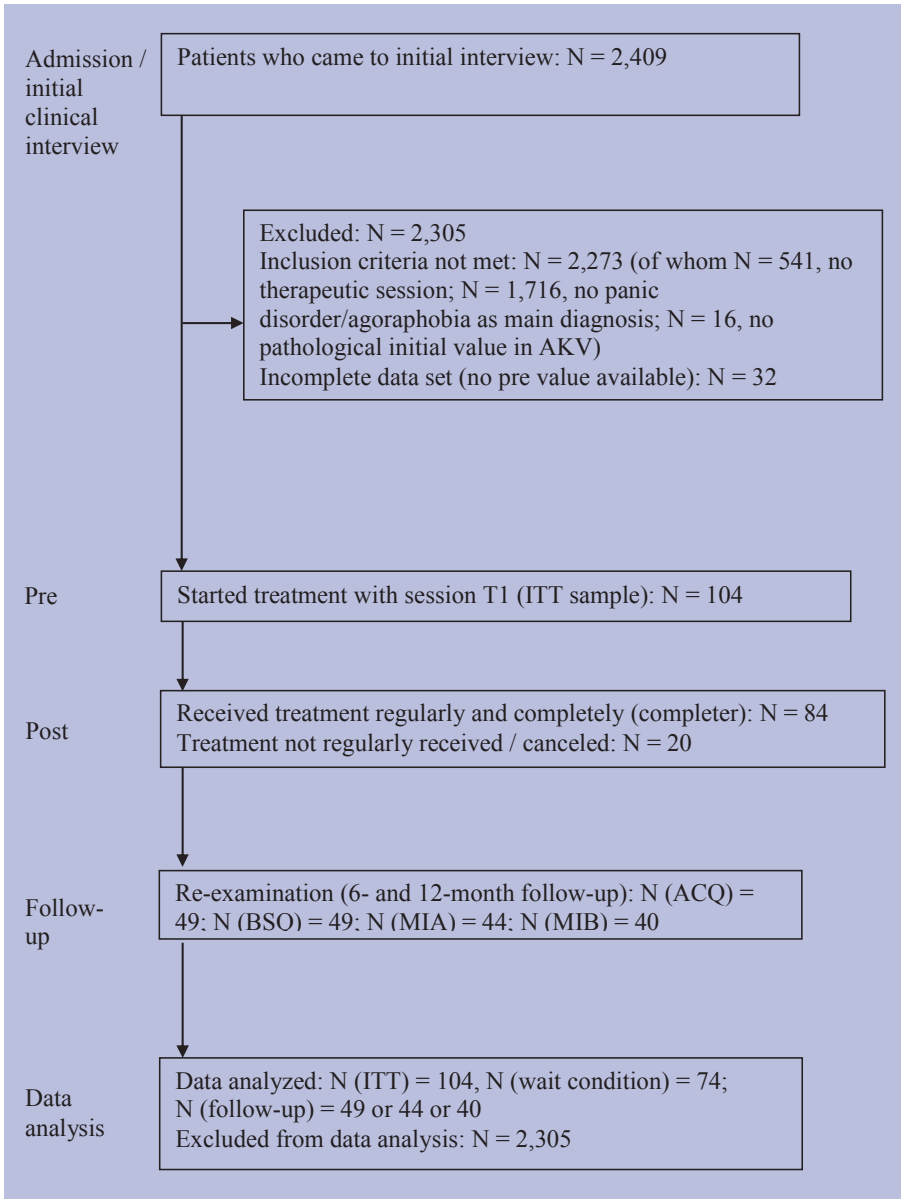

Fig. 1. Flow chart of study patients.

questionnaires [Chambless et al., 1984; 1985] and consists of the scales 'anxiety about physical symptoms' (Body Sensations Questionnaire, BSQ), 'anxiety-related cognitions' (Agoraphobic Cognitions Questionnaire, ACQ), and the Mobility Inventory (MI), with the subscales 'avoidance alone' (MIA) and 'avoidance when accompanied' (MIB). The individual scales of the AKV have satisfactory to very high internal consistency (Cronbach's α: BSQ = 0.87; ACQ = 0.79; MIA = 0.96; MIB = 0.96 for a sample of patients with panic syndrome/agoraphobia) and satisfactory to very high test-retest reliability (r: BSQ = 0.63; ACQ = 0.75; MIA = 0.92; MIB = 0.79 for a sample of patients with panic syndrome). In several studies validating the scales of the AKV, there were, as expected, high correlations with similar questionnaires/scales (e.g., the phobia scale of the SCL-90-R). In addition, the scales could discriminate between patients with anxiety disorders and those without any mental disorder.

Sample

The ITT (intention-to-treat) sample consists of N = 104 consecutive patients who were treated in 2004-2011 at the outpatient clinic and who, at the start of therapy, fulfilled the DSM-IV criteria for panic disorder with agoraphobia (n = 86), panic disorder without agoraphobia (n = 14), or agoraphobia without panic disorder (n = 4) as the main diagnosis (diagnosed using the Structured Clinical Interview, SCID, or the International Diagnosis Checklist, IDCL). Inclusion criteria were also at least 1 initial pathological value on 1 of the 4 scales of the AKV and at least 1 psychotherapy session (after the probationary phase). The response rate for the measurements during therapy (between start and end of therapy) averaged more than 90% in the last few years. The patient flow is depicted in figure 1. The ITT sample consists of 84 completers and 20 dropouts (19.2% dropout rate). Completers were those patients who completed at least 3 therapeutic sessions and for whom treatment ended regularly due to satisfactory results. If the therapy did not end regularly, the patients were classified as dropouts. The assessment of whether a therapy ended regularly was made by the treating therapist toward the end of therapy. In 14 of the 20 dropouts (70%), there were so-called quality-related reasons (usually low/nonexistent compliance). Completers mostly underwent long-term therapy (n = 57; 67.9%; average of 47 sessions; standard deviation (SD) = 11.2) and more rarely, short-term therapy (n = 27; 32.1%, average of 21 sessions; SD = 5.6). The prevalence of patients with comorbidity was significantly higher among those in long-term therapy than in those in short-term therapy (70% vs. 37%). The patients in the ITT sample were an average of

Table 1. Results of pre-post analysis

	Start of therapy (pre)	End of therapy (post)	Differences		
	M (SD)	M (SD)	t value	p	ES, d
ACQ					
ITT	2.16 (0.59)	1.84 (0.61)	5.18	<0.01	0.53
Dropouts	2.39 (0.60)	2.38 (0.62)	0.15	>0.05	0.02
Completers	2.11 (0.56)	1.71 (0.54)	5.51	<0.01	0.73
BSQ					
ITT	2.69 (0.67)	2.11 (0.81)	7.02	<0.01	0.78
Dropouts	2.84 (0.72)	2.94 (0.60)	–0.80	>0.05	–0.15
Completers	2.65 (0.65)	1.91 (0.72)	8.31	<0.01	1.08
MIA					
ITT	2.45 (0.95)	1.93 (0.87)	6.60	<0.01	0.57
Dropouts	2.89 (0.96)	2.85 (0.96)	0.49	>0.05	0.04
Completers	2.34 (0.92)	1.71 (0.68)	6.94	<0.01	0.78
MIB					
ITT	2.14 (0.84)	1.66 (0.72)	7.01	<0.01	0.61
Dropouts	2.58 (0.84)	2.43 (0.85)	1.46	>0.05	0.18
Completers	2.03 (0.81)	1.48 (0.55)	7,07	<0.01	0.79

M = mean; SD = standard deviation; ES = effect size; d = pre-post effect size according to Cohen [1988];
ACQ = Agoraphobic Cognitions Questionnaire; ITT = Intent-to-Treat; BSQ = Body Sensations Questionnaire;
MIA = subscale 'avoidance alone'; MIB = subscale 'avoidance when accompanied'.
Degree of freedom (df): 1.103 (ITT); df: 1.19 (dropouts); df: 1.83 (completers).

36.2 years old (SD = 12.3), 64% were female, 76% in committed relationships, 44.2% had higher education (baccalaureate or higher), and had an average of 34.7 (SD = 17.6) therapy sessions. 65 participants (62.5%) had a comorbid mental disorder. By far the most common comorbid disorder was a depressive disorder (n = 41; 39.4%), followed by a specific phobia (n = 13; 12.5%) and third, a somatoform disorder (n = 11; 10.6%). At the beginning of treatment, most patients (n = 67; 64.4%) were not taking psychopharmacological medication; 35 (33.7%) were taking such medication; and for 2 (1.9%) there was no information.

Statistical Evaluation Strategies

One-way analyses of variance were carried out to compare the completer and dropout samples with respect to the continuous variables (subscales of the AKV), and Chi^2 tests for dichotomous variables. Paired t-tests were calculated to determine the treatment effects, and Cohen's d was calculated for pre-post ESs (difference in means relative to the pooled standard deviation) [Cohen, 1988]. To analyze the wait condition (waiting time between registration for therapy and start of therapy; difference between M1 and pre-measurement) compared to the treatment condition (same patients; difference between pre- and post-measurements), a t-test was calculated for dependent samples (for each scale). Since measurement point M1 of the AKV had not yet been used on a disorder-specific questionnaire, the subscales anxiety and phobic anxiety, as well as the GSI of the BSI, were taken as outcome measures. Cohen's d was calculated as the ES for both the wait condition and the treatment condition. To analyze the follow-up data (for each subscale of the AKV), one-way analyses of variance with replication were calculated. The percentage symptom reduction method of Hiller and Schindler [2011] was used for analysis of response and remission. For response, we accordingly set a value reduction of at least 50% in the pathological range for each scale of the AKV (cutoff values: ACQ = 1.61; BSQ = 2.10; MIA = 1.93; MIB = 1.50; from Hiller and Schindler [2011]) and a value reduction of at least 25% in the total range of the relevant scale of the AKV. For example, a decrease of the scale value in the ACQ of 3.61 (i.e. 2 points above the cutoff) to 2.61 (1 point above the cutoff) is exactly a 50% reduction in the pathological range. Since with initial values near the cutoff range, even very small declines (not necessarily clinically relevant) lead to large percentage changes, Hiller and Schindler [2011] introduced a 25% criterion. Consequently, the above-mentioned initial value (3.61) has to be reduced by $0.25 \times 3.61 = 0.90$, in order to be classified as a response. Moreover, it is only sensible to determine response per patient (not per scale). We then defined a patient as a responder if he met the response criterion described on at least half of the scale on which he had a pathological score at the beginning of the treatment. If a patient scored pathological values on all 4 scales, he had to satisfy the percentage response criterion on at least 2 of the scales in order to be classified as a responder. With pathological initial values on 3 scales, the response criterion had to be met on at least 2 scales, and with pathological pre values on 1 or 2 scales, meeting the percentage response criterion on 1 scale was sufficient for the person to be classified as a responder. We defined remission as when a patient achieved responder status and, by the end of treatment, no longer scored a pathological value on any of the 4 subscales of the AKV.

For content analysis of the therapies performed, a coding scheme was developed based on Dietrich and Hiller [2011] and with reference to the treatment manuals for panic disorder/agoraphobia by Lang et al. [2012b] as well as by Schneider and Margraf [1998] and by Margraf and Schneider [1990] (the coding scheme can be obtained from the authors). Using the coding scheme, the therapies were subsequently assessed on the basis of the archived patient records. The assessment mainly dealt with the therapy components that had been used. The protocols of the therapy sessions, the application for therapy, and the epicrisis were mainly used for the evaluation. The concept of 'cognitive therapy' was thus applied very narrowly: The only measures classified as cognitive therapy were those in which misinterpretations of physical symptoms were revised according to the correction scheme of Schneider and Margraf [1998]. To evaluate the effectiveness of individual therapeutic measures, two-factor analyses of variance were conducted, with repeated measures on 1 factor. Here, the 2 categories 'rather marginal use' and 'used in an appropriate form' were combined into 1 category ('used'). The category 'no indications of use' was retained (corresponding to the designation 'not used'). The 4 subscales of the AKV and the subscales 'phobic anxiety' and 'anxiety' of the BSI were used as outcome measures.

Table 2. Analysis of the wait-control condition

BSI scale, n = 74	Beginning waiting time[a], M (SD)	Start of therapy[b], M (SD)	End of therapy[c], M (SD)	Wait condition, d[d]	Therapy condition, d[e]
GSI	1.14 (0.69)	1.15 (0.70)	0.70 (0.67)	–0.01	0.66
Phobic Anxiety Scale	1.51 (1.03)	1.48 (1.07)	0.87 (0.96)	0.03	0.60
Anxiety Scale	1.75 (0.89)	1.74 (0.94)	0.94 (0.86)	0.01	0.89

BSI = Brief Symptom Inventory; GSI = Global Severity Index; M = mean; SD = standard deviation; d = effect size according to Cohen [1988].
[a]Measurement point 1; [b]pre-measurement; [c]post-measurement; [d]measurement point 1 – pre-measurement; [e]pre-measurement – post-measurement.

Table 3. Analysis of follow-up data

Questionnaire	Post, M (SD)	FU6, M (SD)	FU12, M (SD)
ACQ (n = 49)	1.65 (0.52)	1.58 (0.58)	1.52 (0.49)
BSQ (n = 49)	1.92 (0.69)	2.02 (0.86)	2.01 (0.73)
MIA (n = 44)	1.74 (0.85)	1.82 (0.93)	1.91 (1.01)
MIB (n = 40)	1.47 (0.71)	1.49 (0.74)	1.57 (0.85)

M = mean; SD = standard deviation; FU6 = 6-month follow-up; FU12 = 12-month follow-up; ACQ = Agoraphobic Cognitions Questionnaire; BSQ = Body Sensations Questionnaire; MIA = subscale 'avoidance alone'; MIB = subscale 'avoidance when accompanied'.

Results

Comparison of Completers and Dropouts

By gender ($Chi^2 = 0.21$; df = 1; $p > 0.05$), age ($F = 1.41$; df = 1.102; $p > 0.05$), educational level ($Chi^2 = 0.33$; df = 1; $p > 0.05$), marital status ($Chi^2 = 0.48$; df = 1; $p > 0.05$), and current psychopharmacological medication ($Chi^2 = 1.31$; df = 2; $p > 0.05$) there were no significant differences between completers and dropouts. But there were significantly higher pathological initial values for the dropouts in the ACQ disorder-specific subscales ($F = 4.02$; df = 1.102; $p < 0.05$), MIA ($F = 5.68$; df = 1.102; $p < 0.05$), and MIB ($F = 7.13$; df = 1.102; $p < 0.05$). Only in the subscale BSQ ($F = 1.36$; df = 1.102; $p > 0.05$) was there no significant difference. The mean values and standard deviations are listed in table 1.

Pre-Post Analysis

In both the ITT and the completer sample, all scales of the AKV showed a significant reduction in anxiety symptoms (table 1). The effects of the completer sample were more pronounced in all cases than in the ITT sample. The strongest effect for the completers was on the BSQ scale (pre-post ES; d = 1.08), followed by the MIB scale (d = 0.79), MIA (d = 0.78), and ACQ (d = 0.73). There were no significant effects among the dropouts.

Analysis of the Wait-Control Condition Compared to the Treatment Condition

There was no distinction between the completer and dropout samples, because there were only a few dropouts (n = 15). In 27 cases, the waiting time was less than 6 weeks; these cases could not be included in the analysis (there were no separate values for M1 and the pre-measurement point, because the period between registration and start of therapy was too short). In the 3 outcome measures (GSI, phobic anxiety scale, anxiety scale), there were no significant differences between M1 and pre-measurement (waiting time condition) (GSI: $t = -0.08$; df = 73; $p > 0.05$; phobic anxiety scale: $t = 0.33$; df = 73; $p > 0.05$; anxiety scale: $t = 0.15$; df = 73; $p > 0.05$). The difference on these scales between pre- and post-measurement (treatment condition), however, was significant in each case (GSI: $t = 5.26$; df = 73; $p < 0.01$; phobic anxiety scale: $t = 4.68$; df = 73; $p < 0.01$; anxiety scale: $t = 6.56$; df = 73; $p < 0.01$). The mean values, SD, and ES are shown in table 2.

Analysis of Follow-Up Data

Due to the small sample size (ITT sample n = 49; sample of dropouts at 12-month follow-up only n = 2 (ACQ, BSQ) or n = 1 (MIA, MIB)), there was no distinction made between completers and dropouts. In none of the 4 subscales of the AKV was there a significant difference between the 3 measurement time points post, 6-month follow-up, and 12-month follow-up (ACQ: $F = 2.20$; df = 2.96; $p > 0.05$; BSQ: $F = 0.59$; df = 2.96; $p > 0.05$; MIA: $F = 2.12$; df = 2.86; $p > 0.05$; MIB: $F = 1.12$; df = 2.78; $p > 0.05$), indicating a stable treatment effect (table 3).

Response and Remission Analysis

Response and remission rates were calculated using the values in the AKV. The response rate for the ITT sample was 51% (n = 53), for the completer sample 60.7% (n = 51), and for the dropout sample 10% (n = 2). The remission rate for the ITT sample was 26% (n = 27), for the completer sample 32.1% (n = 27), and for the dropout sample 0% (n = 0). In the ITT sample, there was no significant difference in response

Table 4. Frequency of therapy components

Therapy component	No indications of use, % (n)	Rather marginal use, % (n)	Used in an appropriate form, % (n)	M (SD)
Psychoeducation[a]	6.7 (7)	9.6 (10)	83.7 (87)	
Panic treatment[b]				
Cognitive therapy (correction of misinterpretation of physical symptoms)	27 (27)	30 (30)	43 (43)	
Interoceptive exposure with therapist	38 (38)	26 (26)	36 (36)	
Interoceptive exposure as homework	82 (82)	6 (6)	12 (12)	
Agoraphobia treatment[c]				
Derivation of a treatment rationale for the in vivo exposure	19.6 (18)	15.2 (14)	65.2 (60)	
Performing the in vivo exposure with therapist	40.2 (37)	1.1 (1)	58.7 (54)	
In vivo exposure as homework	32.6 (30)	18.5 (17)	48.9 (45)	
Other elements[d]				
Relapse prevention	31.7 (33)	25.0 (26)	43.3 (45)	
Learning/practicing a relaxation method	30.8 (32)	24.0 (25)	45.2 (47)	
Motivation for regular physical activity	58.7 (61)	26.9 (28)	14.4 (15)	
Stress management strategies[e]	5 (4)	26.2 (21)	68.8 (55)	
Treating comorbid disorder(s)[f]				6.12 (2.96)

[a]Indicated in all patients in the sample, N = 104.
[b]Indicated only in patients with the diagnosis 'panic disorder' or 'panic disorder with agoraphobia', n = 100.
[c]Indicated only in patients with a diagnosis of 'panic disorder with agoraphobia' or 'agoraphobia without panic disorder', n = 92. The slight discrepancy with the above-mentioned (sample description) frequency distribution of diagnoses of n = 2 arises from the fact that 2 patients who were initially diagnosed with 'panic disorder without agoraphobia', were later diagnosed with 'panic disorder with agoraphobia', in the course of therapy.
[d]Indicated in all patients in the sample, N = 104.
[e]Individual development of strategies to cope with psychosocial stress/crucial life events. Indicated in 80 patients; evaluation according to the therapy application. The measures were related to workplace conflicts/ work-related stress (63.8%), experiences of loss (bereavement, separation; 22.5%), partner and/or family conflicts (61.3%), and other stresses (23.8%).
[f]Indicated only in patients with a comorbid mental disorder and/or a personality accentuation, n = 77. How well the other mental disorder/problem was co-treated (0 = no co-treatment; 10 = exemplary co-treatment).

rate between patients receiving short-term (≤25 sessions) and long-term therapy (>25 sessions) (Chi^2 = 0.92; df = 1; p > 0.05), between patients with and without comorbid mental disorders (Chi^2 = 1.60; df = 1; p > 0.05), or between patients with higher education (baccalaureate) and lower education (no baccalaureate) (Chi^2 = 0.38; df = 1; p > 0.05). The difference between the response rates of male patients (37.8%, n = 14) and female patients (58.2%, n = 39) was barely significant (Chi^2 = 3.96; df = 1; p < 0.05).

Content Analysis of the Therapies

The frequencies of use of the therapy components are presented in table 4. The results of the analyses of variance for assessing the effectiveness of individual therapy components (interaction between group factor (therapy components were used vs. therapy components were not used) as well as the measurement points (pre vs. post)) are shown in table 5. The therapy component 'in vivo exposure with therapist' had significant effects on all 6 outcome measures. For the therapy component 'cognitive therapy', there was a significant effect only on the subscale 'anxiety' (p < 0.05). For the therapy component 'interoceptive exposure with therapist', there was also a significant effect only on the subscale 'anxiety' (p < 0.05). There were no significant effects for the therapy component 'relaxation training'.

Discussion

The present study was able to confirm that CBT is effective in patients with panic disorder/agoraphobia in the outpatient routine care setting of a university outpatient clinic. The pre-post ESs achieved for the completer sample were in the high range (d = 0.73–1.08, depending on the scale of the AKV); the pre-post-ESs of the ITT sample were slightly lower (d = 0.53–0.78, depending on the scale of the AKV). The size of this ES is comparable to the values reported in the above-cited meta-analyses, although the ESs achieved here tend to be somewhat lower. The analysis of the wait condition compared to the treatment condition suggests that the effects achieved were caused by the CBT interventions and were not spontaneous improvements. The effects proved stable over the long term. Thus, there were no significant changes between post-measurement, 6-month follow-up, and 12-month follow-up.

The patients in the sample predominantly responded to the treatment (response rate of 60.7% in the completers and 51% in the ITT sample). These response rates are lower than the success rates of previous studies. Hand et al. [1986] reported a general success rate of 70%, and Hahlweg et al. [2001] a success rate of 80%. However, Hand et al. [1986], in their analysis of the subpopulation of severely impaired agoraphobic pa-

Table 5. Effectiveness of individual treatment components

Therapy component	Not performed				Performed				F[a]	df	p
	n	pre, M (SD)	post, M (SD)	d	n	pre, M (SD)	post, M (SD)	d			
Cognitive therapy											
ACQ	27	2.26 (0.57)	2.05 (0.66)	0.34	73	2.14 (0.59)	1.75 (0.59)	0.66	1.62	1.98	>0.05
BSQ	27	2.75 (0.77)	2.35 (0.83)	0.50	73	2.70 (0.63)	2.03 (0.81)	0.92	1.85	1.98	>0.05
MIA	27	2.56 (0.92)	2.24 (0.93)	0.35	73	2.41 (0.98)	1.79 (0.84)	0.68	2.65	1.98	>0.05
MIB	27	2.21 (0.80)	1.89 (0.79)	0.40	73	2.11 (0.87)	1.56 (0.69)	0.70	2.32	1.98	>0.05
BSI: phobic anxiety	26	1.65 (1.10)	1.00 (1.01)	0.62	71	1.35 (1.10)	0.69 (0.86)	0.67	<0.01	1.95	>0.05
BSI: anxiety	26	1.68 (0.82)	1.21 (0.90)	0.55	71	1.71 (1.01)	0.75 (0.81)	1.05	4.57	1.95	<0.05
Interoceptive exposure with therapist											
ACQ	38	2.21 (0.63)	1.99 (0.64)	0.35	62	2.15 (0.56)	1.73 (0.59)	0.73	2.31	1.98	>0.05
BSQ	38	2.74 (0.73)	2.26 (0.92)	0.58	62	2.70 (0.63)	2.03 (0.75)	0.97	1.10	1.98	>0.05
MIA	38	2.76 (0.94)	2.36 (1.04)	0.40	62	2.26 (0.93)	1.64 (0.64)	0.78	1.65	1.98	>0.05
MIB	38	2.36 (0.91)	2.02 (0.90)	0.38	62	2.00 (0.79)	1.42 (0.47)	0.89	3.00	1.98	>0.05
BSI: phobic anxiety	37	1.77 (1.17)	1.21 (1.13)	0.49	60	1.22 (1.01)	0.51 (0.60)	0.85	0.34	1.95	>0.05
BSI: anxiety	37	1.72 (1.02)	1.16 (1.04)	0.54	60	1.70 (0.93)	0.69 (0.66)	1.25	4.50	1.95	<0.05
In vivo exposure with therapist											
ACQ	37	2.10 (0.60)	2.06 (0.63)	0.07	55	2.18 (0.56)	1.74 (0.58)	0.77	10.75	1.90	<0.01
BSQ	37	2.64 (0.75)	2.38 (0.87)	0.32	55	2.69 (0.62)	2.02 (0.75)	0.97	6.36	1.90	<0.05
MIA	37	2.49 (0.91)	2.25 (1.02)	0.25	55	2.60 (0.96)	1.88 (0.74)	0.84	8.11	1.90	<0.01
MIB	37	2.16 (0.82)	1.94 (0.83)	0.27	55	2.30 (0.84)	1.60 (0.63)	0.94	11.31	1.90	<0.01
BSI: phobic anxiety	35	1.55 (0.97)	1.21 (1.16)	0.32	54	1.53 (1.17)	0.64 (0.63)	0.95	4.90	1.87	<0.05
BSI: anxiety	35	1.67 (0.92)	1.29 (1.01)	0.39	54	1.66 (0.94)	0.69 (0.66)	1.19	8.53	1.87	<0.01
Relaxation training											
ACQ	32	2.17 (0.64)	1.89 (0.60)	0.45	72	2.16 (0.55)	1.82 (0.62)	0.58	0.18	1.102	>0.05
BSQ	32	2.72 (0.80)	2.30 (0.82)	0.52	72	2.67 (0.60)	2.03 (0.80)	0.91	1.65	1.102	>0.05
MIA	32	2.81 (0.91)	2.26 (0.94)	0.59	72	2.28 (0.92)	1.78 (0.80)	0.58	0.08	1.102	>0.05
MIB	32	2.44 (0.89)	1.90 (0.77)	0.65	72	2.01 (0.79)	1.56 (0.68)	0.61	0.37	1.102	>0.05
BSI: phobic anxiety	30	1.90 (1.06)	1.13 (1.02)	0.74	71	1.23 (1.03)	0.63 (0.80)	0.65	0.49	1.99	>0.05
BSI: anxiety	30	1.62 (0.88)	1.09 (0.88)	0.60	71	1.71 (0.98)	0.77 (0.81)	1.05	3.60	1.99	>0.05

M = mean; SD = standard deviation; d = effect size according to Cohen [1988]; ACQ = Agoraphobic Cognitions Questionnaire; BSQ = Body Sensations Questionnaire; MIA = subscale 'avoidance alone'; MIB = subscale 'avoidance when accompanied'; BSI = Brief Symptom Inventory.
[a]Group interaction factor × repeated measures.

tients, achieved a success rate of only 63%. Since only patients with a certain severity of symptoms (a pathological initial value on at least 1 of the 4 scales of the AKV) were selected for our sample, the difference in success rate could be at least partially explained by the selection of the patient population. Furthermore, different types of evaluation strategies/operationalization of treatment outcome play a role, which was also discussed by Hand et al. [2000] as well as by Geissner et al. [2013]. However, in subpopulations of our sample (short-term vs. long-term therapy, with vs. without a comorbid mental disorder, higher vs. lower level of education), there were no significant differences in the response and remission rates. In female patients, however, the response rate was 20.4% higher than in male patients ($p < 0.05$). But it is notable from the content analysis of the treatments, using a specially developed coding scheme, that only in 59.8% of cases was in vivo exposure treatment performed. This figure corresponds roughly to the frequency of use of exposure treatments in outpatient care. Thus, according to a study by Roth et al. [2004] on health care practice by established medical and psychological psychotherapists (behavioral therapy), about 26.8% always use and 37.0% mostly use confrontation with response prevention for treatment of anxiety disorders; in vivo exposure is always used by 17.4% and mostly used by 37.0%. Among therapists in an educational institution, however, a more consistent use of this measure was to be expected. Interoceptive exposure was performed in 62.0% of cases, to significantly different extents: Only in 36.0% of cases was interoceptive exposure used for a sufficient duration. The surprisingly low frequencies of use of in vivo and interoceptive exposure might be a reason for the low success rate of treatment in our patients.

Although relaxation techniques had no additional effect [Lang et al., 2009], there was a relatively high rate of relaxation training (45%). This might be seen in the context of the comorbidity rate in our sample: 39% (n = 41) of patients also suffer from a depressive disorder, and improvement of the

ability to relax is certainly indicated for this symptom. Another possible explanation for the relatively frequent use of relaxation techniques, despite insufficient evidence of their efficiency, is the widespread dissemination of manuals for the treatment of panic disorder by renowned authors and educational institutions [e.g., Schmidt-Traub, 2008].

In the assessment by variance analysis of the effectiveness of individual therapy components, our sample also showed that in vivo exposure is a highly effective treatment component. Thus, the effects of this treatment were significant on all 6 outcome measures (4 subscales of the AKV as well as the subscales 'phobic anxiety' and 'anxiety' of the BSI). This finding is consistent with the review by Lang et al. [2009] as well as the meta-analyses of Ruhmland and Margraf [2001] and Sánchez-Meca et al. [2010]. No significant effect was found in our sample for the therapy component 'relaxation training'. The findings here are contradictory; the importance of relaxation training, and in particular the use of breathing techniques, is being discussed critically [Lang et al., 2009; Meuret et al., 2012], especially because the use of breathing techniques contradicts, to a certain extent, the therapeutic rationale of exposure (symptom control vs. symptom provocation). At least a slight effect was found for the therapy components 'cognitive therapy' and 'interoceptive exposure'. To assess the therapy component 'cognitive therapy', it should be noted that other therapeutic components are of course also 'cognitive' (e.g., psychoeducation, exposure). In some cases it is difficult to distinguish therapy components from one another. Thus, behavioral experiments such as the 'hyperventilation test' are classified as cognitive therapy (disputation of dysfunctional assumptions), whereas in therapeutic practice, the dividing line between that and interoceptive exposure can be difficult to draw.

Unfortunately there is not enough data available to assess to what extent the implementation of coping strategies (individual strategies to cope with psychosocial stress) affects anxiety symptoms. Although such measures were performed with almost all patients (95.0%), no meaningful analysis of variance could be calculated (only 4 patients, with whom no such measures were performed, despite indications). In the study by Fischer et al. [1988b], 15 out of 56 patients (27%) reported that they had 'wanted to address other problem areas even more strongly'. In the study by Fiegenbaum [1986], however, no greater treatment outcome was achieved with additional training in problem-solving, in a group therapy setting. Peter et al. [1993] found evidence, in their study of 25 agoraphobics and their partners, of the importance of relationship variables in the development and maintenance of agoraphobia, suggesting that partnership factors should be considered in therapy. Hand and Lamontagne [1976], in their pilot study, deal with the deterioration of couple relationships after successful exposure treatment, which likewise suggests that partnership dynamics should be included in the therapy. In our sample, for at least 61.3% of patients with a psychosocial stress factor, partnership or family problems were identified.

Finally, it should be noted critically that the rating of the patient records by the coding scheme described previously was done by only 1 person, so that nothing can be said about the reliability of the evaluations. It is also the case that the retrospective analysis was based on subjective notations by the therapists. It cannot be said precisely in what form or with what quality the therapeutic content documented by the therapists was actually performed in the treatment. A further criticism of the study is that self-evaluation questionnaires were used exclusively for assessment of therapeutic outcome. Other factors (e.g., changes in the psychopharmacological medication) were not considered. Another weakness of the study is the relatively small sample, which, especially in the case of follow-up data, allows only limited assertions about the stability of the effects that were achieved.

The conclusion to be drawn is that it would be important in the future for in vivo exposure to be performed more consistently in psychotherapeutic routine care and in training institutions, as a highly effective treatment element for panic disorder/agoraphobia. We cannot account for why no in vivo exposure was carried out with at least 40% of the patients and no interoceptive exposure with 38% of the patients. Finally, the conduct of several successive therapy sessions (certainly for intensive exposure treatment) would be very attractive for therapists in training, also working for their advantage toward a rapid completion of the treatment hours required for their psychotherapy training. Marks [1993] notes that approximately a quarter of patients refuse stimulus confrontation or end it prematurely. Hand [2011] finds that the refusal rate is 10–20% 'with adequate preparation'. It is unclear to what extent, in our sample, the reasons should also be seen in the context of the therapy training and the supervision of the therapist's training, or whether factors having to do with the patient are more relevant. Fischer et al. [1988b] found that 30% of agoraphobia patients did not benefit from an exposure treatment. Gloster et al. [2013] showed that refractory patients significantly benefited from manualized Acceptance and Commitment Therapy. There may be a subpopulation of patients who cannot be reached with exposure treatment or do not benefit from such a treatment. Future investigations should ask what conditions are required for in vivo / interoceptive exposure treatment. Also, the question of the effectiveness of other treatment components (exposure as homework, psychoeducation, physical activity / sports, relapse prevention, etc.) merits further investigation. In this context, an operationalization as precise as possible of the therapy components used would be desirable.

Disclosure Statement

The authors declare that they have no conflicts of interest regarding this work.

Translated by Susan Welsh,
welsh_business@verizon.ne

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