Regular Article

Psychotherapy and Psychosomatics

Psychother Psychosom 2015;84:100–109
DOI: 10.1159/000370162

Received: May 21, 2014
Accepted after revision: November 23, 2014
Published online: February 21, 2015

Treating Treatment-Resistant Patients with Panic Disorder and Agoraphobia Using Psychotherapy: A Randomized Controlled Switching Trial

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Key Words

Nonresponders · Treatment-resistant patients · Therapy switching · Acceptance and commitment therapy · Panic disorder · Agoraphobia

Abstract

Background: Nonresponsiveness to therapy is generally acknowledged, but only a few studies have tested switching to psychotherapy. This study is one of the first to examine the malleability of treatment-resistant patients using acceptance and commitment therapy (ACT). ***Methods:*** This was a randomized controlled trial that included 43 patients diagnosed with primary panic disorder and/or agoraphobia (PD/A) with prior unsuccessful state-of-the-art treatment (mean number of previous sessions = 42.2). Patients were treated with an ACT manual administered by novice therapists and followed up for 6 months. They were randomized to immediate treatment (n = 33) or a 4-week waiting list (n = 10) with delayed treatment (n = 8). Treatment consisted of eight sessions, implemented twice weekly over 4 weeks. Primary outcomes were measured with the Panic and Agoraphobia Scale (PAS), the Clinical Global Impression (CGI), and the Mobility Inventory (MI). ***Results:*** At post-treatment, patients who received ACT reported significantly more improvements on the PAS and CGI (d = 0.72 and 0.89, respectively) than those who were on the waiting list, while improvement on the MI (d = 0.50) was nearly significant. Secondary outcomes were consistent with ACT theory. Follow-up assessments indicated a stable and continued improvement after treatment. The dropout rate was low (9%). ***Conclusions:*** Despite a clinically challenging sample and brief treatment administered by novice therapists, patients who received ACT reported significantly greater changes in functioning and symptomatology than those on the waiting list, with medium-to-large effect sizes that were maintained for at least 6 months. These proof-of-principle data suggest that ACT is a viable treatment option for treatment-resistant PD/A patients. Further work on switching to psychotherapy for nonresponders is clearly needed.

Introduction

Nonresponsiveness to treatment is generally acknowledged as a considerable problem, with estimates ranging from 25 to 50% of patients who complete state-of-the-art treatments. Even in the case of anxiety disorders, which are generally considered to respond favorably to cognitive-behavioral treatment (CBT) [1], more than 20% of patients do not reach the criteria for high end-state functioning. These estimates do not include patients that drop

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out or remain impaired despite some measurable improvement [2].

Empirical studies on treatment-resistant patients are rare [3, 4], and empirically based guidelines to advise clinicians on how to help treatment nonresponders are lacking. Very few randomized controlled trials have examined the effects of switching from a psychotherapy that failed to adequately work to a different psychotherapy. Instead, most treatment-refractory studies are pharmacological in nature, both in terms of the original treatment and the alternative response [5]. Even when psychological treatments are examined, they are usually administered either directly following or in combination with pharmacology [6]. The problem of nonresponse is particularly challenging when state-of-the-art psychological interventions fail, such as CBT for patients with panic disorder and agoraphobia. Evidence exists that continued exposure can help in some cases [7]. A recent study [8] also addressed this issue in a multisite randomized controlled clinical trial of patients with primary panic disorder and/or agoraphobia (PD/A). These authors examined whether the addition of 9 monthly maintenance ('booster') sessions would increase the likelihood of sustained improvement and reduced relapse. Indeed, beyond maintenance of improvements, they also observed symptom reduction in previous nonresponders.

The systematic examination of treatment in nonresponders and the treatment development in general have been impeded by the disproportionate concentration on comparing the efficacy of various treatments [9]. Trials on groups of patients with specific characteristics, such as failed treatment [10] and close examinations of processes, are needed. Examining the mechanisms of action of treatment has only recently become the focus of randomized controlled trials (RCTs) [11–13]. Outside of this focus on positive effects remains the important challenge of what to do for the sizeable minority who do not respond to treatment, which is a pressing demand that has been acknowledged in efforts to formulate clinical approaches to sequential treatment [2, 10, 14, 15].

Acceptance and commitment therapy (ACT) is a cognitive-behavioral therapy that teaches psychological concepts, such as mindfulness, acceptance, cognitive defusion (flexible distancing from the literal meaning of cognitions), and other strategies to increase psychological flexibility and promote behavior change consistent with personal values. Within ACT, psychological flexibility is defined as the capacity to make contact with experience in the present moment, and – based on what is possible in that moment – to persist in or change behavior in the pursuit of goals and values [16, 26]. Clinical studies and RCTs provide evidence that ACT is effective for a wide array of disorders [17], including primary treatment for anxiety disorders, such as social anxiety disorder [18], panic disorder [19], and mixed anxiety disorders [20].

A unique aspect of ACT is its focus on helping patients learn to interact more flexibly with their symptoms (e.g., simply observe them as opposed to trying to eliminate them) and to continue pursuing their values and life goals even in the presence of symptoms [16]. ACT is therefore especially suitable to help treatment-resistant patients, precisely because the possibility that symptoms may persist has been elegantly integrated into its treatment rationale. Accordingly, this therapy helps patients abandon their longstanding, unsuccessful struggle with their symptoms. This stance allows for the possibility of meaningfully improving patients' lives, even when symptoms persist, and suggests that ACT could be a particularly efficacious and viable treatment option for patients who did not respond to state-of-the-art treatments.

In this study, we aimed to test the efficacy of an ACT intervention for patients with treatment-resistant primary PD/A. We hypothesized that (1) the ACT treatment group would report a significantly greater reduction in symptoms and an increase in functioning compared to the patients on the waiting list (WL; hypothesis 1), (2) treatment gains would be stronger in ACT-specific processes (i.e., acceptance, defusion, mindfulness) than in panic disorder-specific processes or more general symptom measures (hypothesis 2); and (3) treatment gains would be maintained over 6 months (hypothesis 3).

Methods

Please see the online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000370162) for details on Methods and Results.

Inclusion Criteria

Inclusion criteria were a reliable diagnosis of PD/A, age between 18 and 65 years, a Mobility Inventory (MI) score ≥1.5 [21], a Clinical Global Impression (CGI) scale score ≥4 ('moderately ill') [22], and informed consent. Additionally, all patients were required to have had one or more previous courses of psychological and/or pharmacological treatment consistent with state-of-the-art practice. For psychotherapy, this was defined as ≥20 sessions of empirically supported treatments in which all patients had received interventions inherent to these treatments, such as exposure in situ, interoceptive exposure, cognitive restructuring, etc.

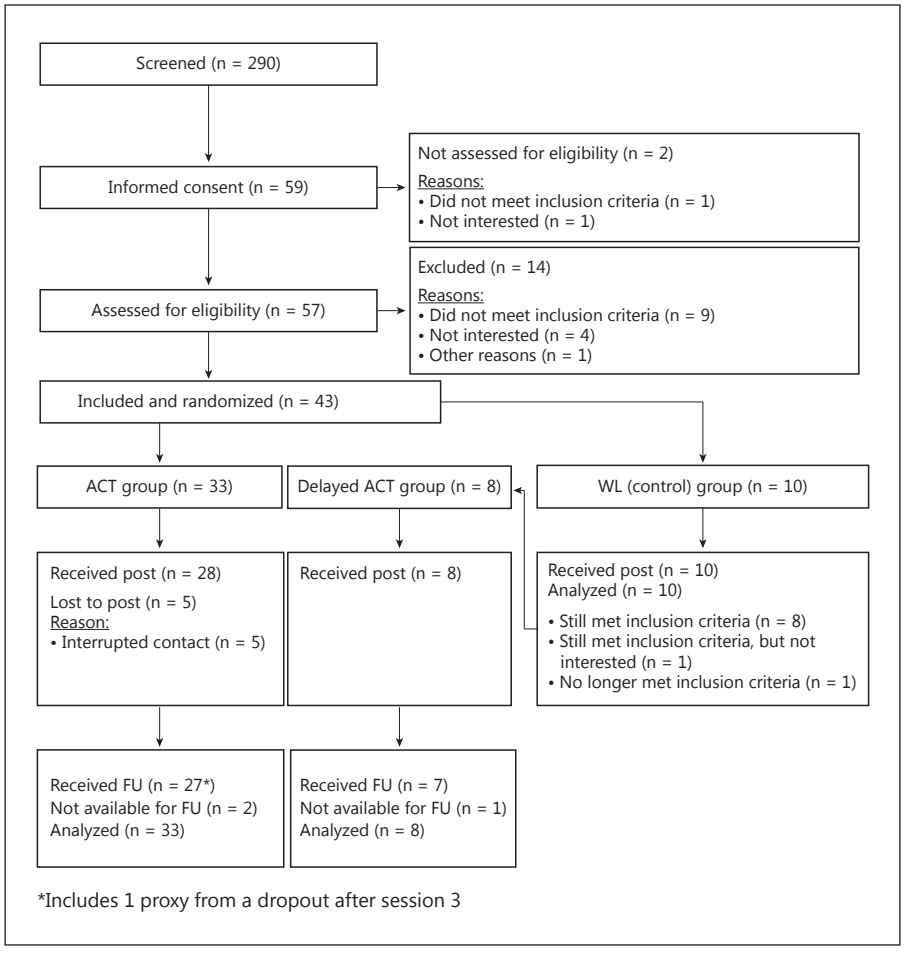

Fig. 1. Flowchart of patients included in the study.

(n = 38, 88.4%). For pharmacology, this was defined as intake of an approved drug at least at the minimum dosage and length as recommended by national and international therapy guidelines [23, 24] (n = 14, 32.6%).

Exclusion Criteria

Exclusion criteria were inadequate previous treatment, concurrent psychotherapy, and diagnoses of alcohol dependence, bipolar disorder, psychotic or eating disorders, benzodiazepine or other drug dependence. Patients who were actively suicidal were also excluded. If patients were taking psychopharmacological agents, they had to agree not to change the dose during the trial.

Design

This was a randomized, WL-controlled clinical trial conducted in Germany between June 2010 and June 2012, with the final follow-up assessment in December 2012. Patients and assessors were blinded to the hypotheses. Patients were randomized to either immediate treatment (n = 33) or a 4-week WL (n = 10). For ethical reasons, patients from the WL were offered treatment immediately after the 4-week waiting period (delayed treatment; n = 8). Patients did not receive any treatment during the follow-up period, and a total of 51 cases were included in the analysis (fig. 1).

Randomization

An independent statistician randomly allocated patients to immediate treatment or WL with a 3:1 ratio .

Intervention

A manual of ACT for anxiety disorders [25] was adapted for this trial. This manual was already successfully employed in a large randomized clinical trial comparing ACT and CBT [20]. The brief treatment consisted of eight sessions administered twice weekly over 4 weeks. The sessions lasted between 90 and 120 min. ACT is a behavioral treatment with the aim of promoting psychological flexibility and consists of six processes: acceptance, present moment awareness, defusion, self-as-context (observer perspective), value clarification, and committed action. Patients worked towards becoming more aware and accepting of anxiety and other uncomfortable emotions and experiences. This stance was adopted so that they could more willingly engage in important aspects of their life, irrespective of the presence of uncomfortable emotions and thoughts [27].

Therapists

Therapists were graduate students of a CBT university training center who were well trained and had experience in CBT but had no prior experience treating patients with ACT. Therapists were

trained via a 3-day intensive training, readings, self-study, and were required to pass a competency test.

Treatment Integrity

All treatment sessions were videotaped, and 19.7% (60/305) of all conducted sessions were analyzed for treatment adherence and therapist competency. The ratings were made by one of the manual developers (G.E.) who was not involved in the study management or clinical supervision. Ratings were made using the Drexel University ACT/CT Therapist Adherence and Competence Rating Scale [28]. On a scale from 1 (poor) to 5 (excellent), therapists demonstrated very good levels on items measuring (a) knowledge (mean ± SD, 3.9 ± 1.1), (b) skill (3.7 ± 1.4), (c) overall adherence to the manual (4.0 ± 1.3), and (4) overall performance (3.9 ± 1.4). Additionally, therapists were judged to have very good relationships with the patients (4.1 ± 0.9).

Assessors

Assessors were blinded to the treatment conditions. Before the study, assessors completed a 3-day training, testing, and subsequent certification of the assessment procedures. Regular supervision was conducted to maintain consistent strategies across assessors and questions.

Assessment

Patients completed measurements at baseline, post-treatment, and after 6 months of follow-up (FU-6). The primary outcome measures included overall panic and agoraphobia symptomatology (Panic Agoraphobia Scale, PAS [29, 30]), global clinical impression and functioning (CGI [31]), and agoraphobic avoidance (MI [32]).

Diagnoses were derived by the CIDI and validated by expert clinicians [33–38]. Additional measures targeting three areas were included: (1) panic-specific processes, (2) general symptomatology, and (3) ACT-specific processes. First, panic-specific processes were included that have been found to mediate other forms of CBT for PD/A and that are commonly used in the assessment and treatment of PD/A. These included: fear related to bodily sensations (Bodily Sensations Questionnaire, BSQ [39]), the Agoraphobic Cognitions Questionnaire (ACQ [39]), and the Anxiety Sensitivity Index (ASI [40]). Second, standard measures of more general anxiety and depression were assessed, including the Hamilton Anxiety Rating Scale (SIGH-A [22]), the Beck Depression Inventory (BDI-II [41]), and the Beck Anxiety Inventory (BAI [42]). Finally, measures for specific processes assumed to be active in ACT were difficulty with emotional regulation (Difficulty with Emotion Regulation Scale, DERS [43]), acceptance/thought suppression (White Bear Suppression Inventory, WBSI [44]), mindfulness (Kentucky Inventory of Mindfulness Skills, KIMS [45]), and defusion (Believability in Anxious Feelings and Thoughts Questionnaire, BAFT [46]).

Statistical Analysis

Hypothesis 1 (Efficacy)

For all primary and secondary outcomes, hypothesis 1 was tested using ANCOVA with baseline outcome values as covariates. For each comparison, the ACT treatment group was compared to the WL in terms of post-treatment. Analyses were run both for treatment completers and intent to treat following multiple imputations [47]. Only results based on completers are reported here because all outcomes were comparable (online suppl. material). Preliminary analyses found no differences in any of the outcome analyses between patients who received immediate treatment and those who first went through the WL, nor were there differences between patients with and those without previous pharmacological treatment.

Hypothesis 2 (Differential Response across Disorder-Specific Processes, General Symptoms, and ACT-Specific Processes)

We set up a multivariate random intercept model of the combined secondary outcomes to test whether treatment gains would be stronger in ACT-specific processes (i.e., DERS, WBSI, KIMS, and BAFT) than in panic disorder-specific process measures (i.e., BSQ, ACQ, and ASI) or in more general symptom measures (i.e., SIGH-A, BDI-II, and BAI).

Hypothesis 3 (Treatment Gain and Maintenance)

To test hypotheses 2 and 3, we used a linear mixed model [48] with a random intercept, assuming equal covariances among the three time points.

Response Rate

Consistent with previous research, response was defined as ≤18 ('mild' or less) on the PAS and 'mild' or less on the CGI [11, 12, 29, 30].

Results

Sample Characteristics and Randomization Check

The participants were 43 patients diagnosed with primary PD/A. They were largely female (69.8%), with an average age of 36.9 years. In addition to PD/A, patients endorsed 2.0 comorbid disorders on average. The average number of previous therapies was substantial: mean = 42.3, median = 25.0 psychotherapy sessions[1] and 2.1 valid psychopharmacological agents (table 1). No significant differences were observed between the ACT and the WL group at baseline on any outcome measure.

Attrition

Among the 51 cases, 46 (90.2%) completed post-assessment. Among the 41 patients who began treatment, 37 (90.2%) completed all eight sessions (fig. 1) and 1 (2.4%) dropped out after baseline, but prior to the first session. Three patients (7.3%) received a partial dose of therapy. Attrition was unrelated with any particular element of the treatment, as the dropouts during treatment occurred once following sessions 1, 3, and 5. One patient attended all eight sessions, but did not complete post-assessment.

[1] Regulations in Germany guarantee patients 25 sessions of short-term empirically supported CBT. Charted psychotherapists administered the therapies with quality controls administered by the regulated German social insurance system.

Table 1. Baseline characteristics by treatment condition

	ACT (n = 33)	WL (n = 10)
Age, years	36.7±8.9	37.5±8.9
Previous sessions	42.6±42.4	41.2±33.4
Comorbid diagnoses	1.9±3.2	2.3±2.7
Sex, n (%)		
Male	11 (33.3)	2 (20.0)
Female	22 (66.7)	8 (80.0)
Years of education		
8	1±3.0	1±10.0
10	14±42.4	4±40.0
12–13+	13±39.4	2±20.0
No formal degree	5±15.2	3±30.0
Living arrangement		
With parents	0	0
Alone	7±21.2	0
With partner	20±60.6	6±60.0
Other	6±18.2	4±40.0
Employment		
University student	1±3.0	0
Job training	1±3.0	1±10.0
Employed	20±60.6	6±60.0
Unemployed	6±18.2	0
Other	5±15.2	3±30.0
Social class		
Lowest	1±3.0	0
Lower middle	7±21.2	2±20.0
Middle	19±57.6	4±40.0
Upper middle	1±3.0	1±10.0
Upper	0	0
Marital status		
Married	6±18.2	4±40.0
Divorced/widowed/separated	5±15.2	0
Never been married	17±51.5	3±30.0
Comorbidity, 12-month diagnoses		
Alcohol abuse	1±3.0	0
Alcohol dependence	0	0
Generalized anxiety disorder	5±15.2	0
Social phobia	12±36.4	3±30.0
Any specific phobia	12±36.4	3±30.0
Obsessive-compulsive disorder	6±18.2	3±30.0
Posttraumatic stress disorder	1±3.0	1±10.0
Major depressive episodes	8±24.2	4±40.0
Dysthymia	5±15.2	2±20.0
Pain disorder	7±21.2	2±20.0
Comorbid diagnoses, number		
None	8±24.2	0
1–2	15±45.4	5±50.0
3–4	6±18.2	4±40.0
5+	4±12.1	1±10.0

Numbers vary across categories due to missing values.

Table 2. Primary outcome variables between group effects at post-treatment

	Difference between ACT and WL at post-treatment		Difference between group effects at post-treatment		
	Mean	SE	F	p	d
PAS	–6.8	3.0	4.99	0.02	0.72
CGI	–1.0	0.3	8.20	0.00	0.89
MI	–0.3	0.2	2.18	0.07	0.50

Adverse Events

The patients did not report any adverse events during the treatment or during the FU-6 period.

Treatment Efficacy (ACT vs. WL: Hypothesis 1)

Comparisons between the ACT and the WL group were made only at post-treatment due to the study design.

Primary Outcomes

As expected, the ACT group improved significantly more than the WL group in terms of panic/agoraphobic symptoms (PAS: d = 0.72) and general functioning (CGI: d = 0.89) (table 2). Despite a medium effect size, the comparison ACT/WL was nonsignificant on the MI (d = 0.50). Results based on multiple imputation resulted in comparable values (see online suppl. material).

Secondary Outcomes

The secondary outcome measures targeted three areas: PD/A-specific factors, general symptoms, and ACT-specific process measures. With the exception of two PD/A-specific measures (ACQ and ASI), the ACT group performed significantly better than the WL group on all secondary measures (fig. 2). Whereas the difference between the ACT and the WL group resulted in small-to-medium effects for the panic-specific factors of ACQ and ASI, comparisons between the groups resulted in medium-to-large effects for general symptoms, and large-to-very large effects for ACT-specific process measures.

Differential Response across Processes and Symptoms (Hypothesis 2)

The interaction between treatment group and differential category was highly significant (likelihood ratio = 14.6, $p < 0.001$). Thus treatment group results were highest for the category ACT-specific (–1.08, SE = 0.23), followed by panic-specific (–0.61, SE = 0.22), and general symptoms (–0.45, SE = 0.22). Differences for these effects

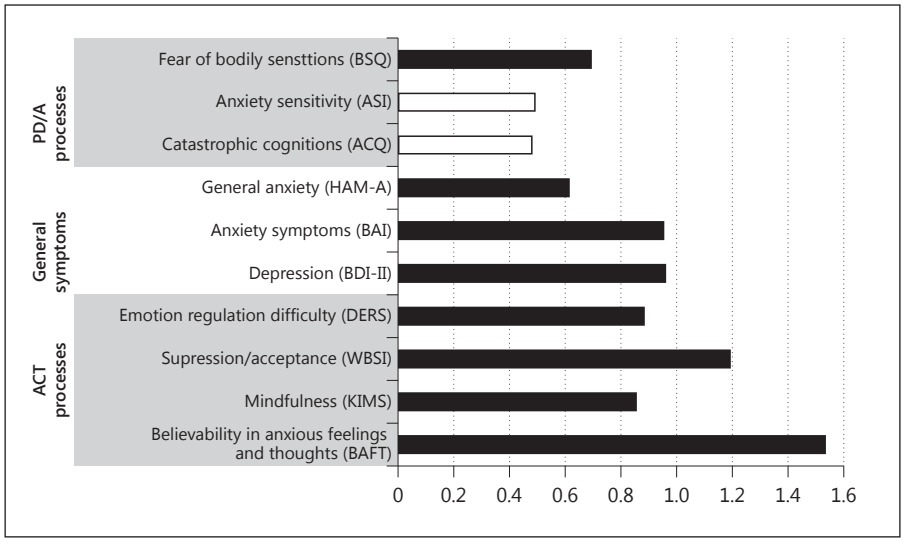

Fig. 2. Controlled effect size of secondary outcome measures at post-treatment (vs. WL group). All effects were significantly different ($p < 0.05$) from the WL group, except for the white bars.

were significant for ACT-specific versus panic-specific and ACT-specific versus general symptoms, but not for panic-specific versus general symptoms.

Within-Group Change and Maintenance of Gains following Treatment (Hypothesis 3).

Across all primary and secondary variables, values at FU-6 were statistically improved compared to baseline. They continued to significantly improve between post-treatment and FU-6 ($p < 0.05$) for panic symptoms and were nearly significant for MI ($p = 0.06$) and CGI ($p = 0.06$) (fig. 3). No variable demonstrated statistically significant worsening between post-treatment and FU-6. Taken together, these results clearly suggest that treatment gains are maintained for at least 6 months, do not recede, and to some degree continue to improve during this generalization period.

Response Rates

Categorical response rates were calculated at both post-treatment and FU-6. At post-treatment, response rates for PD/A symptomatology (PAS) and functioning (CGI) were 70 and 57%, respectively. At FU-6, response rates for PD/A symptomatology and functioning were 80 and 52% respectively.

Generalization (Change in Diagnoses)

The number of diagnoses was again calculated at FU-6 in order to test the breadth of the treatment effect. The mean number of diagnoses at FU-6 (1.2) was significantly reduced from that at baseline (1.8; $t_{40} = 2.72$, $p < 0.01$).

Discussion

This RCT demonstrated the efficacy of switching to a psychological treatment (ACT) for treatment-resistant patients with PD/A. Medium-to-large effects were observed on primary indices of PD/A symptoms and general functioning. These effects were significantly superior to those of the WL patients. Effects for agoraphobic avoidance were nearly statistically significant in comparison to the WL, with a medium-controlled effect size. These improvements were either maintained or improved in the 6 months following treatment. These results are promising and suggest a new option for the sizeable minority of treatment-resistant patients [49–51].

In the present study, the switch was made to ACT because this therapy specifically aims to alter the struggle with longstanding symptoms by undermining the unnecessary struggle with internal psychological barriers in order to engage with what is important in one's life. To test this, we assessed several interrelated clinical processes and compared these across numerous measures. Measures assessing ACT-specific constructs showed the largest effects. In particular, not suppressing uncomfortable thoughts and emotions (i.e., acceptance) and not taking anxious thoughts and feelings literally (i.e., defusion) showed the largest improvement in comparison to the WL group. Large effects were also seen on measures of mindfulness and general difficulty with unhelpful emotional regulation. Taken as a whole, these results are consistent with one of the central tenets of ACT, namely that directly targeting these core processes leads to beneficial

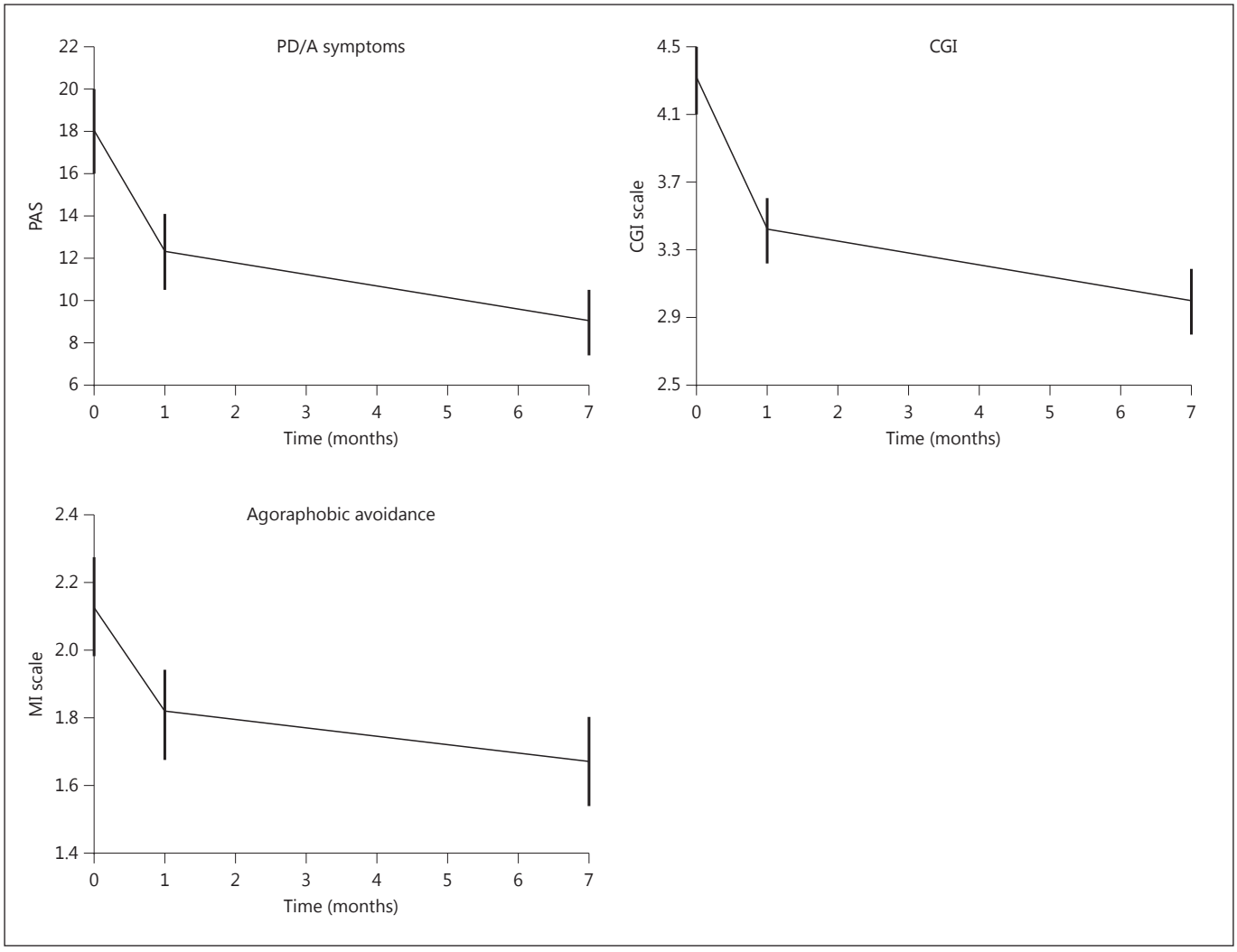

Fig. 3. Primary outcome response pattern across baseline, post-treatment, and FU-6.

changes in patients' lives. These data support this interpretation insofar as the patients reported increases in functioning despite some rest symptomatology.

The pattern across constructs was particularly revealing. For instance, although anxiety sensitivity (ASI) is one of the most consistently identified mediators of treatment in PD, the effect in comparison to the WL was small and nonsignificant. In contrast, when asked about the believability of the same type of items (BAFT), the change in comparison to the WL resulted in the largest effect size. Of clinical importance, this suggests that the content of the occurrence of evaluative anxiety statements is not as important as whether someone believes the thoughts. Consistent with this interpretation, the ACT process measures were consistently in the range of large effects, whereas traditional panic-related processes and general symptomatology were in the small-to-medium range, respectively. Taken as a whole, these results suggest that the psychological processes targeted by ACT processes have indeed been successfully changed.

As observed in this study, treatment gains were clearly maintained and continued to improve. Although the improvement was not always significant, all tested variables showed at least some improvement and none demonstrated deterioration. Furthermore, the number of comorbid diagnoses reduced significantly from baseline to follow-up, even though they were not targeted.

Results from this study are consistent with studies showing that acceptance- and mindfulness-based interventions achieved better outcomes for patients with comorbidity, whereas traditional CBT fared better for patients with only one disorder [52]. This is consistent with evidence observed in a noncontrolled group of depressed patients treated using mindfulness [53]. As the current sample was highly comorbid and treatment-resistant, mindfulness- and acceptance-based approaches may be especially effective in this population. The present results are also consistent with a small study of patients who did not adequately respond to exposure therapy, but showed improvement after focusing on well-being [54].

Of clinical importance, the dropout rate in this study (9%) was much lower than that in other treatment outcome studies. For example, two large studies of traditional CBT for panic disorder and agoraphobia reported dropout rates ranging between 19.6% [11] and 28% [1], with similar rates reported for CBT across anxiety disorders (23%) [55] and in pharmacological treatments for panic disorder (19.8%) [56]. We have no way of ascertaining the exact reason for the low attrition rate in this study. We suspect, however, that switching to the ACT content combined with the condensed format of our treatment program (i.e., two clearly structured sessions per week with regular homework assignments) had a favorable impact.

This study has several limitations. First, the sample size was small and may have led to increased type II error. This concern is mitigated by the medium-to-large effect sizes observed. Nevertheless, we concentrated our interpretation on effect sizes. Second, we cannot exclude the possibility that nonspecific factors were responsible for the observed changes as we were unable to include a clinical control group with a different treatment. Although the pattern of results, especially the stronger responses in ACT-specific measures, mitigates this concern somewhat future research will need to address the specificity of these findings. Third, including patients into the ACT treatment after they had been on the WL could have potentially led to a systematic bias. As suggested by our preliminary analyses, this did not appear to have an effect on the outcomes. Fourth, we were reliant on patients to provide some details about their treatment history. To assist them and to guard against imprecise reporting, we provided a list of interventions and techniques commonly used in empirically supported psychotherapy and other techniques and asked them to endorse what they had already experienced. For patients who had had prior pharmacotherapy, we compared their medication against national treatment guidelines. Further, we compared those patients for whom we had very detailed information from our previous controlled trial [49] against the others. No differences were found for any of these comparisons, suggesting that treatment history was not a confounder and that we only treated nonresponders whose previous treatment had been adequate. Fifth, this study only examined patients with primary PD/A. Although these patients were highly comorbid and the treatment addressed emotions in general, examination of other disorders is needed to determine the limits of generalizability. Sixth, we used therapists in training who may have a particularly high therapy alliance. Finally, although the 6-month assessment results are promising, even longer follow-ups are needed to determine if the skills learned during the treatment remain useful during additional challenges that are surely to arise in their lives.

Notwithstanding these limitations, we conclude that switching to psychotherapy can effectively treat treatment-resistant PD/A patients, particularly if the new treatment adopts a different approach than the original therapy and if it is administered in a structured manner that also requires the active involvement of patients [14, 15]. We agree that avoidance does indeed matter in treatment-resistant patients [57], and ACT appears to be a viable method to address both the numerous manifestations of subtle and overt experiential avoidance in cases that do not otherwise respond to first-line treatments. Further tests in other treatment-resistant populations are clearly needed and future research should continue to develop and refine interventions for this population.

Acknowledgements

The study was funded by the German Federal Ministry of Education and Research (BMBF; project No. 01GV0615) as part of the BMBF Psychotherapy Research Funding Initiative . This study was registered with the trial registration: ISRCTN 12042066. We wish to thank the therapists of this study for their dedication throughout the trial, the patients for their trust and the brave steps they took, and Marie-Noëlle Cottens for her assistance in the preparation of the manuscript.

Disclosure Statement

Dr. A.T. Gloster, Dr. R. Sonntag, Dr. A.H. Meyer, Dr. G. Eifert and Dipl. Psych. S. Heinze report no financial relationships with commercial interests. Dr. J. Hoyer received speaking honoraria by Astra Zeneca. Dr. A. Ströhle received research funding from the German Federal Ministry of Education and Research, the European Commission (FP6), and Lundbeck, as well as

speaker honoraria from Astra Zeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly and Co., Lundbeck, Pfizer, Wyeth, and UCB. He was a consultant for Actelion. Educational grants were given by the Stifterverband für die Deutsche Wissenschaft, the Berlin Brandenburgische Akademie der Wissenschaften, the Boehringer Ingelheim Fonds, the Eli Lilly International Foundation, Janssen-Cilag, Pfizer, and Eli Lilly and Co. Dr. H.-U. Wittchen is or has been on advisory boards of Servier, Pfizer, and Lundbeck. Via his university, he also has received grant support by Novartis, Lundbeck, and Pfizer. Travel compensation for scientific meetings were received from Servier, Pfizer, Lundbeck, and Novartis.

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