Original Article

Panic Disorder in Primary Care

The Effects of a Team-Based Intervention—a Cluster-Randomized Trial

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Summary

Background: We evaluated a team-based program of exercises for patients with panic disorder with or without agoraphobia (PDA) in primary care.

Methods: 419 patients with PDA (mean age 46.2 years, standard deviation 14.4 years; 74% female) were included in this cluster-randomized, controlled intervention trial. The patients were blinded with respect to their group assignment at baseline. Patients in the intervention group (36 primary-care practices, 230 patients) underwent a 23-week exercise program combined with case management, while patients in the control group (37 practices, 189 patients) received standard care. Symptoms of anxiety (according to the Beck Anxiety Inventory, BAI) at six months were the primary endpoint. Patients were followed up at six months (n = 338, 81%) and at twelve months (n = 318, 76%). The analysis was by intention to treat.

Results: Symptoms of anxiety improved to a significantly greater extent in the intervention group (p = 0.008). The intergroup difference in the reduction of the BAI score (range: 0–63) was 3.0 points (95% confidence interval [–5.8; –0.2]) at six months and 4.0 points [–6.9; –1.2] at twelve months. In the intervention group, there was a significantly greater reduction in the frequency of panic attacks (p = 0.019), in avoidant behavior (p = 0.016), and in depressiveness (p < 0.001), as well as a greater improvement of the quality of treatment (p < 0.001).

Conclusion: In primary-care patients who have panic disorder with or without agoraphobia, a team-based exercise program combined with case management can improve symptoms to a greater extent than standard primary-care treatment.

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Panic disorder with/without agoraphobia (PDA) is associated with decreased quality of life of those affected (1) and increased health care costs (2). In Germany, the prevalence of panic disorder in primary care is approximately 5% (3, 4). Even though it is a comparatively common condition, panic disorder is frequently overlooked and not treated (5). For most patients with panic disorder, the general practitioner is the first, and often the only, contact (6). Cognitive behavioral therapy and antidepressants are effective first-line therapies (7, 8).

Previous studies used collaborative care models (adaptions of Wagner's chronic care model [9, 10]) to improve treatment in the primary care setting. These models typically comprise systematic monitoring, collaboration between the primary care provider and the specialist/therapist as well as psychiatric counseling (9, 11). A systematic review with meta-analysis on the effect of collaborative care for patients with anxiety disorders in the primary care setting showed

The clinical perspective

General practitioners can treat patients with panic disorder with/without agoraphobia using an easily accessible and effective treatment program, comprising elements of cognitive behavioral therapy: psychoeducation, interoceptive and situational anxiety exposure exercises, and relapse prophylaxis. In the Jena-PARADIES study, interoceptive exposure exercises (body exercises) were exceptionally well accepted. These can be introduced by the general practitioner in a controlled fashion and are in general easily performed by patients. Situational exposure exercises are typically indicated in patients with concomitant agoraphobia; however, this strategy was less consistently implemented during our study. The treatment program was carried out using an outpatient case management strategy: Practice nurses (MFA) in the GP practices regularly contact patients by phone to record the symptom and treatment progress using a checklist (structured clinical monitoring). The MFA basically acts as the “extended arm” of the general practitioners. In this role, they support the continuity of the treatment and thus are instrumental to the success of the treatment strategy presented here. Neither the general practitioner nor the MFA offer comprehensive psychotherapy services. However, severe or complex clinical conditions and lack of success of the program can be easily identified by the general practitioner. These patients should then be referred to a specialist.

that collaborative care was superior to treatment as usual (TAU) (effect size for all anxiety disorders: standardized mean difference [SMD]: 0.35; 95% confidence interval: [0.14; 0.56]; effect size for panic disorder: SMD: 0.59; [0.41; 0.78]) (12). Apparently, anxiety patients prefer psychotherapeutic interventions, such as cognitive-behavioral therapy (CBT), to pharmacotherapy (13). CBT contributes to long-term clinical improvements too (14).

In Germany, waiting times for psychotherapeutic treatment to become available can be up to several months (15). Thus, a low-threshold treatment offering adapted to the general practitioner (GP) practice setting seems to be a suitable option to bridge the waiting time (16). The aim of this study was to evaluate the effects of a team-based intervention with case management in patients with panic disorder in a primary care setting. It was hypothesized that this intervention results in a significantly greater improvement of symptoms of anxiety after six months compared to treatment as usual.

Methods

Study design and subjects

See the *eMethods* section for a detailed description of the methodology used.

“Jena-PARADIES” (Patient Activation for Anxiety Disorders) was a cluster-randomized intervention study with a two-arm parallel group design (intervention group versus TAU control group) (17). To prevent contamination of control group patients, GP practices were the randomization units (clusters).

Patients were screened by the teams of the participating GP practices, using the Overall Anxiety Severity and Impairment Scale (OASIS) (18) and the panic modules of the Patient Health Questionnaire (PHQ)

(19). The general practitioner invited patients with suspicious scores for a diagnostic interview during which the patient’s eligibility for participating in the study was verified using validated ICD-10 check lists (ICD, International Classification of Diseases) (20).

Only adult patients diagnosed with PDA (ICD-10: F41.0 or F40.01) were included in the study. The exclusion criteria were as follows: suicidality, psychotic or substance-related disorders, severe physical impairments, pregnancy or ongoing anxiety-specific psychotherapy. The general practitioners were responsible for including eligible patients and obtaining their informed consents to study participation.

Randomization

After a three-month recruitment period for each practice, cluster randomization of the GP practices was performed (allocation ratio 1:1).

Interventions

The practice team–supported exposure training comprised evidence-based elements of CBT (psychoeducation, interoceptive and situational anxiety exposure exercises) (21) as well as intervention elements from the chronic care model (22).

Intervention group patients received a therapy companion book, providing information about psychoeducation and how to perform the exercises, as well as exposure log sheets. Four structured GP visits were scheduled in a 23-week period; during the first 3 visits, an introduction into the CBT elements was given. Starting from the second GP visit, patients were encouraged to independently perform anxiety exposure exercises at least twice a week. To ensure current symptoms of anxiety are monitored at regular intervals and to enhance treatment adherence, checklist-based telephone monitoring was carried out by a nurse of the GP practice (23). In case of suboptimal monitoring results, the general practitioners could arrange for additional patient contacts and/or adaptations to be made to the exercise plan. Patients in the control group received standard therapy, i.e. guideline-based psychosocial or psychopharmacological treatment (6, 24).

The general practitioners were free to administer whatever treatment they deemed necessary and make referrals at their own discretion.

Endpoints

The primary endpoint was the clinical severity of the anxiety symptoms measured using the Beck Anxiety Inventory (BAI) (25). The patients used this instrument to rate how severely affected they had been by 21 typical symptoms of anxiety (range 0–63) during the last week.

Secondary endpoints included

- number and severity of panic attacks, measured using 2 items (A1, A2) of the panic and agoraphobia scale (PAS) (26)

FIGURE

CONSORT flowchart (CONSORT, consolidated standards of reporting trials) of the Jena-PARADIES study

TABLE 1a

GP practice sample description

	Control group	Intervention - group
Number of GP practices	37	36 (39 GPs)
Age of the GPs: years (mean [SD])	51.1 (8.2)	52.4 (8.5)
Number of female GPs (%)	19 (51.4)	21 (58.3)
Primary specialist training, n (%)		
General medicine	35 (94.6)	31 (79.4)
Internal medicine	1 (2.7)	6 (15.4)
Other/none	1 (2.7)	2 (5.2)
Age of MFA: years (SD)	36.1 (11.4)	40.1 (10.9)
Female MFA, n (%)	37 (100.0)	36 (100.0)
Work experience of MFA >5 years, n (%)	27 (73.0)	29 (80.6)
Practice locations, n (%)		
Rural	23 (62.2)	25 (69.4)
Urban	14 (37.8)	11 (30.6)
Single-GP practices	22 (59.5)	23 (63.9)
Number of practice patients per quarter, n (%)		
<1001	12 (32.5)	8 (22.2)
1001–1500	13 (35.1)	18 (50.0)
> 1500	12 (32.4)	10 (27.8)

MFA, practice nurse ("medizinische Fachangestellte"); SD, standard deviation

- agoraphobic avoidance behavior, measured using the mobility inventory (MI), "alone" subscale (27)
- depression measured using the Patient Health Questionnaire (PHQ-9) (19)
- patient evaluation of the medical care received, measured using the Patient Assessment of Chronic Illness Care (PACIC) (28)..

Measurements were performed at baseline (T0), at 6-month follow-up (T1) and at 12-month follow-up (T2). Patient-side baseline variables were reported by the patients or by their general practitioners.

Sample size calculation

With a standard deviation of the BAI of 11 (2), a standardized effect size of 0.35 (i.e. a BAI mean difference of 3.85 points) could be demonstrated with a power of 80% in a patient-randomized study with 130 patients per treatment group, using the t test. Assuming an intraclass correlation of 0.07 (2) and a cluster size of 6, a design effect of 1.35 (correction factor for sample size adaption with cluster randomization) was calculated. When in addition a dropout rate of 20% was assumed, 222 patients from 37 practices per treatment group were required.

Statistical analysis

Intention-to-treat (ITT) analyses were performed using the SAS 9.4 software package. For the analysis of

intervention effects, linear mixed models (LMMs) and generalized LMMs, taking the hierarchical data structure into account (maximum likelihood method), were adapted (29). Fixed-effects estimators are reported with 95% confidence intervals. The statistical test for clinical improvements referred to the interaction between the factors treatment group and time (two-sided $\alpha = 0.05$).

Using the "clinical significance" approach (30), dichotomous measures for response to treatment and for remission were calculated. "Response" was defined as a statistically reliable BAI score decrease. "Remission" was defined as a BAI score decrease below the weighted midpoint between the empirical BAI score distribution in our sample (T0) and a comparable patient sample without anxiety disorders (30, 31).

The data on remission after 12 months were used to calculate the number needed to treat (NNT).

Results

Course of the study

The *Figure* shows the CONSORT flowchart. The median cluster size was 6 (interquartile range [IQR] 4–7). Altogether, 219 patients (53.2%) were included prior to practice randomization. The 6-month follow-up was responded to by 175/230 (76%) patients of the intervention group and by 163/189 (86%) patients of the control group; the 12-month follow-up by 168/230 (73%) and 150/189 (79%), respectively (dropout analysis in the *eTables 1* and 2).

Study participants

The two treatment groups were similar with regard to practice and patient characteristics (*Tables 1a* and *b*). Prior to the intervention, 341 patients (82%) experienced up to 3 panic attacks weekly (*eTable 3*), 73 (18%) experienced 4 or more attacks weekly. The severity of these panic attacks (*eTable 4*) was rated by 96 patients (24%) as mild or moderate and by 226 (55%) as severe or extremely severe. Comorbid depression was observed in 143 patients (35%).

Conduct of the intervention

Data on the conduct of the scheduled GP visits were obtained from 199/230 patients (87%). These data showed that 129 (65%) patients received all 4 GP visits, 152 (76%) at least the first 3 GP visits (which informed about the CBT elements), 168 (84%) at least the first 2 GP visits, and 17 (9%) no visit at all (information about dropouts provided in *eTable 5*).

A median of 10 practice nurse monitoring activities (IQR: 6–10) was performed. The mean consultation time was 27.4 minutes (standard deviation [SD]: 5.8; range: 15–45) and practice nurse monitoring time 8.2 minutes (SD: 3.5; range: 2–30). The mean duration of the total intervention (up to GP visit 4) was 157 days (IQR: 140–196).

In the control group, the patients had a median of 4 GP visits during the intervention period (IQR: 3–6). The general practitioners of the control group patients

usually provided the following interventions:

- exploration of psychosocial problems
- recommendation not to avoid anxiety-triggering stimuli (72%), and
- prescription of selective serotonin reuptake inhibitors (SSRIs) (62%), benzodiazepines, as required, (40%) and/or tricyclic antidepressants (18%) (24).

Analysis of the primary endpoints

The ITT analysis (Table 2) showed at 6-month follow-up in each of the two groups a significant decline in mean anxiety severity (BAI, range: 0–63) (intervention group: –8.5 [–10.3; –6.6], control group: –5.4 [–7.3; –3.4]; raw data listed in eTable 6). Between the 6-month follow-up and the 12-month follow-up, this trend continued in a weakened form. A significant interaction of the factors group and time ($p = 0.008$) confirmed that the intervention group had seen stronger improvements compared to the control group. The group differences in mean BAI scores were as follows: after 6 months –3.0 [–5.8; –0.2] and after 12 months –4.0 [–6.9; –1.2]. The location of the GP practice (urban versus rural [stratification variable]) had no significant effect ($p = 0.93$). A sensitivity analysis based on multiple imputation (see eMethods) confirmed these results.

As shown by explorative analyses of individual BAI score changes, patient response to treatment was more frequently observed in the intervention group (i.e. decrease of the BAI score by at least 10.3 points). After 6 months, this occurred in the intervention group in 59 patients (37%) and in the control group in 46 patients (31%); after 12 months in 66 (42%) and 45 (32%) patients, respectively. Likewise, remission of symptoms (i.e. decrease of the BAI score to less than 11.1 points) was significantly more often observed in the intervention group. After 6 months, this was noted in the intervention group in 44 patients (27%) and in the control group in 19 patients (13%); after 12 months in 54 patients (34%) and 23 patients (16%), respectively. The NNT was 6.

Analysis of secondary endpoints

In both groups, the number of panic attacks was found reduced (eTable 7); the decrease was significantly greater in the intervention group compared to the control group ($p = 0.019$). Likewise, the intervention group showed greater improvements with regards to agoraphobic avoidance behavior (MI), depression (PHQ-9) and perceived quality of care (PACIC) compared to the control group (Table 2). The severity of panic attacks was reduced in both groups (eTable 8, $p = 0.13$). Intake of psychotropic medications was reported by 55% of patients (eTable 9); there was no difference in this respect at the 12-month follow-up between the two groups.

Discussion

In patients with panic disorder with/without agoraphobia, practice team-supported exposure training led

TABLE 1b

Sample description of GP patients with panic disorder

	Control group	Intervention group
Patients, n ^{*1}	189	230
Age: years (mean [SD])	46.2 (14.8)	46.1 (14.1)
Female, n (%)	145 (76.7)	166 (72.2)
Education: Years (median [IQR])	10 (10–12)	10 (9–11)
Working, n (%)	114 (61.0)	148 (65.5)
Retired, n (%)	48 (25.7)	34 (14.9)
Living in relationship, n (%)	114 (60.3)	144 (62.6)
Number of chronic illnesses (IQR)	3 (1–4)	3 (1–5)
Comorbid agoraphobia, n (%)	135 (71.4)	180 (78.3)
OASIS (SD) ^{*2}	12.5 (2.8)	12.5 (2.7)
BAI (SD) ^{*3}	28.2 (12.4)	28.3 (12.3)
MI (SD) ^{*4}	2.30 (0.81)	2.24 (0.83)
PHQ-9 (SD) ^{*5}	11.2 (5.9)	11.2 (5.6)
PACIC (SD) ^{*6}	6.41 (2.71)	5.99 (2.51)

BAI, Beck Anxiety Inventory; IQR, interquartile range; MI, mobility inventory;

OASIS, Overall Anxiety and Impairment Scale;

PACIC, Patient Assessment of Care for Chronic Conditions questionnaire on patient satisfaction with outpatient treatment;

PHQ-9, Patient Health Questionnaire, depression scale; SD, standard deviation

^{*1} Missing data on

Education: in 1 patient from the intervention group;

Occupation: in 2 patients of the control group and 4 patients of the intervention group;

Retired: in 2 patients of the control group and 2 patients of the intervention group;

OASIS: in 3 patients of the control group and 4 patients of the intervention group;

Raw data availability regarding BAI, MI, PHQ-9, and PACIC is detailed in eTable 6.

^{*2} Range: 0–20. Higher scores indicate higher anxiety levels and increased clinical impairment. .

^{*3} Range: 0–63. Higher scores indicate greater severity of clinical anxiety.

^{*4} Range: 1–5. Higher scores indicate increased agoraphobic avoidance behavior.

^{*5} Range: 0–27. Higher scores indicate more severe depressive symptoms.

^{*6} Range: 1–10. Higher scores indicate better outpatient chronic illness care

to a more pronounced reduction in anxiety symptoms compared to treatment as usual. The mean anxiety levels improved in both groups during the intervention period from severe to moderate. Differences in anxiety reduction between the groups were minor to moderate, largely comparable with effect sizes of measures of anxiety observed in collaborative care studies with specialist involvement (12, 32, 33). The effects remained stable over a period of 12 months. This could indicate that patients in the intervention group learnt health-related behavior and self-management strategies which stabilized the progress made (34).

Based on the 12-month remission data, an NNT of 6 was calculated. This indicates a rather good effect of the intervention (35) and is comparable to results of similar studies (13). The improvements with regard to avoidance behavior and depression achieved in the intervention group were statistically significant. This may have facilitated the interaction between general practitioner and patient and improved treatment adherence by the patient (36).

TABLE 2

Intention to treat analysis of the endpoints ^{*1}

Endpoint and times of measurement	Control group (n = 189)	Intervention group (n = 230)	Difference between means	p-value
Primary endpoint				
BAI [95% CI] ^{*2}				0.008 ^{*3}
Baseline	28.2 [26.3; 30.1]	28.3 [26.4; 30.1]	0.1 [-2.5; 2.7]	0.965
6 months	22.9 [20.8; 24.9]	19.8 [17.8; 21.8]	-3.0 [-5.8; -0.2]	0.033
12 months	22.1 [20.0; 24.2]	18.1 [16.1; 20.1]	-4.0 [-6.9; -1.2]	0.006
Secondary endpoints				
MI [95%- CI] ^{*4}				0.016 ^{*5}
Baseline	2.26 [2.13; 2.39]	2.25 [2.13; 2.36]	-0.01 [-0.18; 0.16]	
6 months	2.17 [2.03; 2.30]	1.96 [1.84; 2.08]	-0.21 [-0.39; -0.03]	
12 months	2.06 [1.92; 2.19]	1.84 [1.72; 1.97]	-0.21 [-0.40; -0.03]	
PHQ-9, [95% CI] ^{*6}				<0.001 ^{*5}
Baseline	11.2 [10.4; 12.0]	11.2 [10.4; 11.9]	-0.0 [-1.1; 1.0]	
6 months	9.4 [8.6; 10.2]	7.4 [6.7; 8.2]	-2.0 [-3.1; -0.9]	
12 months	8.9 [8.1; 9.8]	6.5 [5.7; 7.3]	-2.4 [-3.6; -1.3]	
PACIC, [95% CI] ^{*7}				<0.001 ^{*5}
Baseline	6.30 [5.80; 6.80]	6.02 [5.55; 6.48]	-0.28 [-0.96; 0.41]	
6 months	6.31 [5.81; 6.82]	7.16 [6.67; 7.65]	0.84 [0.14; 1.55]	
12 months	5.94 [5.42; 6.46]	6.96 [6.46; 7.46]	1.02 [0.30; 1.74]	

BAI, Beck Anxiety Inventory; CI, confidence interval; MI, mobility inventory; PACIC, Patient Assessment of Care for Chronic Conditions questionnaire on patient satisfaction with outpatient treatment; PHQ-9, Patient Health Questionnaire, Depression scale

^{*1} Shown are mean estimates with 95% confidence intervals, calculated based on linear mixed models using the least-squares method (eTable 6 shows data on raw data availability). The reported p-values refer to the interaction between the factors "treatment group" and "time".

^{*2} Range: 0–63. Higher scores indicate greater intensity of clinical anxiety.

^{*3} Analysis of the primary endpoint using a mixed linear model which included: the treatment group, the point in time, the interaction between treatment group and time as well as practice location as fixed factors; the patients nested in the GP practices as random factors.

^{*4} Range: 1–5. Higher scores indicate increased agoraphobic avoidance behavior.

^{*5} Analysis of secondary endpoints using mixed linear models which included: the treatment group, the point in time, the interaction between treatment group and time as fixed factors; the patients nested in the GP practices as random factors.

^{*6} Range: 0–27. Higher scores indicate more severe depressive symptoms.

^{*7} Range: 1–10. Higher scores indicate better outpatient chronic illness care.

In an earlier study where general practitioners had been trained in anxiety treatment, no effects on the clinical endpoints was noted (2). The treatment effects observed in our study are comparable with those in studies on stepped care or collaborative care models for anxiety disorders in a primary care setting, all of which involved a psychologist/psychotherapist and/or other healthcare professionals to perform or monitor the intervention (13, 32, 33, 37). Our study shows the practice team-supported interventions are feasible. Offering low-threshold interventions in primary care may help to optimize patient safety, quality of care and access to evidence-based treatments. Future studies should investigate whether GP practice-based interventions are associated with changes in acceptance of primary medicine or psychotherapeutic services offered.

Compared to other studies, patients here showed good treatment compliance (37, 38). Additional

analyses of individual BAI score changes demonstrated that in the intervention group remission of symptoms of anxiety was achieved in approximately one third of the patients. Since this is twice as high compared to the control group, it is reasonable to assume that the intervention was effective. Future studies should evaluate patient characteristics associated with the acceptance and benefit of the intervention to facilitate decision-making for individual treatments. Based on the reduced amount of follow-up data on pharmacotherapy and on the limited quality of patient self-reporting, we do not believe that the intervention had an effect on the treatment with psychotropic medications.

Strengths of the study

In a large sample of patients receiving primary care, an intervention was evaluated which empowers and encourages patients to independently perform exposure

Key messages

- Panic disorder is a common condition in GP practices.
- General practitioners can successfully treat panic disorder patients with individually adaptable, behavioral therapy-oriented exercises.
- Practice-based case management ensures the implementation of the treatment and enables continuous monitoring of symptoms over time. General practitioners can directly respond to it.
- Interoceptive exposure exercises (so-called body exercises) are better suited for use in a GP practice setting than situational exposure exercises.
- Practice nurses (MFA) are as the “extended arm” of the general practitioners reliable partners in the treatment triangle doctor-patient-nurse.

exercises (21). To ensure transferability of its results, the study was conducted in single-GP practices or small group practices which are typical for the German primary care setting, accounting for the largest portion of healthcare services provided (39).

Disadvantages of the study

The open recruitment of about half of the patients could have introduced selection bias. However, this appears unlikely because no significant differences with regard to socioeconomic and clinical baseline data were found between patients who were included before and after practice randomization. In the intervention group, the proportion of missing follow-up data was higher compared to the control group, but altogether still similar to that in other studies on CBT-based interventions in primary care (13). The LMM analyses help to avoid an overestimation of the effects. In addition, we performed a sensitivity analysis based on multiple imputation of missing data points which confirmed the results of the primary analysis. Even though the BAI is a generic measure of anxiety, it can be used to assess symptoms typically associated with panic disorder; its validity and sensitivity to change have been proven in the primary care setting (31, 37). The reliability of the BAI was excellent in our sample. Waiting times for the intervention should not have affected symptom severity: On the one hand, the general practitioners in both groups were familiarized with the clinical care guidelines; on the other, patients of the control group benefited from participating in the study because they received well organized GP care and increased clinical attention (40).

Conclusion

GP practice teams (GP and practice nurse) can successfully treat patients with PDA using elements of CBT and continuous case management. The intervention was carried out in small GP practices which are the mainstay of primary care delivery in Germany. In this setting, resources are often limited and the implementation of complex collaborative care models is challenging.

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Availability of the data and the material

The data on which the results published in this study are based are subject to access restrictions and cannot be made publicly available. However, the data can be requested from the Principal Investigator (PI) of the study, Prof. Gensichen (Jochen.Gensichen@med.uni-muenchen.de) within the framework of an individual project agreement.

Study registration

Current Controlled Trials (www.isrctn.com/ISRCTN64669297)
German Clinical Trials Register (*Deutsches Register Klinischer Studien, DRKS*) (www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00004386)

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Ethics Committee and informed consent

The Ethics Committee of the Friedrich-Schiller University Jena granted approval of the study protocol on 17 August 2012 (no. 3484-06/12). All participating physicians and patients gave their written informed consent to participating in the study.

Conflict of interest

The authors declare no conflict of interest

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► Supplementary material

eMethods, eTables:
www.aerzteblatt-international.de/19m0159

Supplementary material to:

Panic Disorder in Primary Care

The Effects of a Team-based Intervention—a Cluster-Randomized Trial

by Jochen Gensichen, Thomas S. Hiller, Jörg Breitbart, Christian Brettschneider, Tobias Teismann, Ulrike Schumacher, Karoline Lukaschek, Mercedes Schelle, Nico Schneider, Michael Sommer, Michel Wensing, Hans-Helmut König, and Jürgen Margraf for the Jena-PARADIES study group

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eMETHODS

Detailed description of the methods

Study design and subjects

Jena-PARADIES (Patient Activation foR Anxiety DIsoRdErS) was a cluster-randomized intervention study with a two-arm parallel group design (intervention group versus treatment-as-usual(TAU) control group) (17). To prevent contamination of control group patients, GP practices were the randomization units (clusters).

Patients were screened by the teams of the participating GP practices, using the Overall Anxiety Severity and Impairment Scale (OASIS) (18) and the panic modules of the Patient Health Questionnaire (PHQ) (19). The general practitioner invited patients with suspicious scores for a diagnostic interview during which the patient's eligibility for participating in the study was verified using validated ICD-10 check lists (20).

Only adult patients with PDA (ICD-10: F41.0 or F40.01) were included in the study. The exclusion criteria were as follows: suicidality, psychotic or substance-related disorders, severe physical impairments, pregnancy or ongoing anxiety-specific psychotherapy. The general practitioners were responsible for including eligible patients and obtaining their informed consents to study participation.

Randomization

After a three-month recruitment period for each practice, cluster randomization of the GP practices was performed (allocation ratio 1:1). The randomization list was computer-generated and not known to the study team. The randomization was stratified according to practice location (urban versus rural). This stratification was made to account for the regional differences in access to specialist care. Three month after the first patients of a practice had been enrolled in the study—or earlier, if in the practice four patients had already been recruited—the practices were randomized (retrieval of allocation status from a centrally stored electronic randomization tool and communication of the allocation status to the practice team). At baseline examination, patients were not informed (blinded) about the allocation status of their GP practice.

Training of the practice teams

To facilitate patient recruitment and to harmonize the standard

treatment (TAU) provided by the various GP practices, the practice teams (the general practitioner and the practice nurse [*Medizinische Fachangestellte*, MFA]) received a basic training of 2.5 hours duration at the time of inclusion in the study. The basic training relied on recommendations from clinical guidelines (6). It comprised the use of the diagnostic instruments and the formalities of the patient inclusion procedure which were developed according to good clinical practice (GCP) guidelines. The practice nurses were specifically trained to conduct the screening of patients in the waiting room of the GP practice. Practice teams allocated to the study's intervention arm received in addition a 3-hour training how to conduct the study-related intervention and detailed treatment manuals.

Interventions

The practice team-supported exposure training comprised evidence-based elements of CBT (psychoeducation, interoceptive and situational anxiety exposure exercises) (21) as well as intervention elements from the chronic care model (22). Intervention group patients received a therapy companion book, providing information about psychoeducation and how to perform the exercises, and exposure log sheets. During a period of 23 weeks, 4 structured GP visits were scheduled; in the first three visits, an introduction to elements of cognitive behavioral therapy was given. Starting from the second GP visit, patients were encouraged to independently perform exposure exercises at least twice a week. To assess current symptoms of anxiety at regular intervals and to enhance treatment adherence, the practice nurse carried out checklist-based telephone monitoring (23). In case of sub-optimal monitoring results, the general practitioners could arrange for additional patient contacts and/or adaptations to be made to the exercise plan. Patients in the control group received treatment as usual, i.e. guideline-based psychosocial or psychopharmacological treatment (6, 24). The general practitioners were free to administer whatever treatment they deemed necessary and make referrals at their own discretion.

Endpoints

The primary endpoint was the clinical severity of the anxiety symptoms measured using the Beck Anxiety Inventory (BAI) (25). The patients used this instrument to rate how severely

affected they had been by 21 typical symptoms of anxiety (range 0–63) during the last week. The BAI is a standard instrument for measuring the intensity of symptoms of anxiety; it can be used to measure the typical symptoms of a panic disorder. The BAI has good psychometric features; its validity and sensitivity to changes have been proven in a primary care setting too (31, 37).

The secondary endpoints included

- number and severity of panic attacks, measured using 2 items (A1, A2) of the panic and agoraphobia scale (PAS) (26)
- agoraphobic avoidance behavior, measured using the mobility inventory (MI), “alone” subscale (27);
- depression measured using the Patient Health Questionnaire, depression subscale (PHQ-9) (19);
- patient evaluation of the medical care received, measured using the Patient Assessment of Chronic Illness Care (PACIC) (28).

Measurements were performed at baseline (T0), at 6-month follow-up (T1) and at 12-month follow-up (T2). Patient-side baseline variables were reported by the patients or by their general practitioners.

Sample size calculation

With a standard deviation of the BAI of 11 (2), a standardized effect size of 0.35 (i.e. a BAI mean difference of 3.85 points) could be demonstrated with a power of 80% in a patient-randomized study with 130 patients per treatment group, using the t test. Assuming an intracluster correlation of 0.07 (2) and a cluster size of 6, a design effect of 1.35 (correction factor for sample size adaption with cluster randomization) was calculated. When in addition a dropout rate of 20% was assumed, 222 patients from 37 practices per treatment group were required.

Statistical analyses

The statistical analyses were performed using the software SAS, version 9.4 (SAS Institute Inc, Cary, NC). The baseline characteristics of the study participants and additional variables were described using relevant descriptive statistics. The statistical tests were performed as two-sided tests; the significance level was set at $\alpha=0.05$. The primary hypothesis test (regarding the primary endpoint BAI) was regarded as confirmatory. All other statistical tests were exploratory in nature. The statistical analyses followed the intention-to-treat (ITT) principle (“analyzed as randomized”). For the analysis of intervention effects, linear mixed models (LMMs) and generalized LMMs, taking the hierarchical data structure into account (maximum likelihood method), were adapted (29). These models can correctly take missing data points into account; they deliver unbiased parameter estimates for data missing at random. (29). The patients nested in the GP practice were included in the LMM (which had been adapted for the primary analysis) as random factors; the practice location (urban versus rural), the treatment group (intervention versus control), the time of measurement (baseline [T0] versus 6-month follow-

up [T1] versus 12-month follow-up [T2]) as well as the interaction between the factors “treatment group” and “time of measurement” were included as fixed factors. Fixed-effects estimators are reported with 95% confidence intervals. The statistical test for clinical improvements referred to the interaction between the factors treatment group and time. To find out whether missing data had influenced the result of the primary analysis, we performed a sensitivity analysis based on multiple imputation of missing data points. The secondary endpoints were analyzed in a similar way: LMMs or generalized LMMs were adapted in such a way that the patients nested in the GP practices were included as random factors, while the treatment group (intervention versus control), the time of measurement (baseline [T0] versus 6-month follow-up [T1] versus 12-month follow-up [T2]) as well as the interaction between the factors “treatment group” and “time of measurement” were included as fixed factors. The corresponding explorative tests for clinical improvements again referred to the interaction between the factors treatment group and time.

Using the “clinical significance” approach (30), dichotomous measures for response to treatment and for remission were calculated. “Response” was defined as a statistically reliable BAI score decrease. “Remission” was defined as a BAI score decrease below the weighted midpoint between the empirical BAI score distribution in our sample (T0) and a comparable patient sample without anxiety disorders (30, 31). The data on remission after 12 months were used to calculate the number needed to treat (NNT).

Sensitivity analysis

To test whether missing data influenced the result of the primary analysis and thus to verify the robustness of this analysis, we performed a sensitivity analysis which substituted the missing data using a multiple imputation method. With this method, the missing data points on the primary endpoint (BAI) were estimated using the least-squares method. The multiple imputation was performed based on the input variables age, sex, education (year), partnership status (living alone versus with a partner), presence of comorbid agoraphobia (yes versus no), practice location (urban versus rural), as well as individual scores obtained at all time points of the questionnaires BAI, mobility inventory (MI), Panic and Agoraphobia Scale (PAS, Items A1 und A2), Patient Health Questionnaire (depression subscale, PHQ-9), EuroQoL (EQ-5D), and Patient Assessment of Chronic Illness Care (PACIC). Altogether, 5 datasets were imputed. The result of the sensitivity analysis supported the findings of the primary analysis: The reduction in the mean BAI scores was greater in the intervention group compared to the control group. The difference between the treatment groups with regard to the mean BAI score was at 6-month follow-up (T1) –2.8 points (95% CI: [–5.3; –0.2]) and at 12-month follow-up (T2) –3.6 points [–6.4; –0.7]. As in the primary analysis, a significant interaction of the factors “treatment group” and “time of measurement” was found in the sensitivity analysis ($p=0.026$).

eTable 1. Baseline Characteristics of Patients Who Did vs Did Not Complete 6 Months Follow-Up (T1 Dropout Analysis)

Characteristic	Control group (n = 189)		Intervention group (n = 230)	
	6 months follow-up completed (n = 163)	6 months follow-up not completed (n = 26)	6 months follow-up completed (n = 175)	6 months follow-up not completed (n = 55)
Mean age (SD), years	46.6 (15.0)	44.2 (13.9)	46.0 (13.3)	46.3 (16.7)
Available data, <i>n</i>	163	26	175	55
Female, <i>n</i> (%)	128 (78.5)	17 (65.4)	128 (73.1)	38 (69.1)
Available data, <i>n</i>	163	26	175	55
Median duration of education, (IQR), <i>y</i>	10 (10, 12)	10 (10, 12)	10 (9, 12)	10 (9, 11)
Available data, <i>n</i>	162	26	175	55
Employed, <i>n</i> (%)	97 (60.2)	17 (65.4)	114 (66.3)	34 (63.0)
Available data, <i>n</i>	161	26	172	54
Retired from work, <i>n</i> (%)	43 (26.7)	5 (19.2)	24 (13.8)	10 (18.5)
Available data, <i>n</i>	161	26	174	54
Living with partner, <i>n</i> (%)	101 (62.0)	13 (50.0)	113 (64.6)	31 (56.4)
Available data, <i>n</i>	163	26	175	55
Median long-term conditions (IQR), <i>n</i>	3 (1, 4)	2 (1, 5)	3 (2, 5)	3 (1, 5)
Available data, <i>n</i>	163	26	175	55
Comorbid agoraphobia, <i>n</i> (%)	122 (74.8)	13 (50.0)	137 (78.3)	43 (78.2)
Available data, <i>n</i>	163	26	175	55
Anxiety screening, mean OASIS score (SD)	12.4 (2.8)	12.9 (2.9)	12.4 (2.8)	12.8 (2.6)
Available data, <i>n</i>	161	25	173	53
Anxiety severity, mean BAI score (SD)	28.1 (12.5)	28.9 (12.3)	27.3 (12.3)	31.1 (12.1)
Available data, <i>n</i>	154	25	168	52
Avoidance behavior, mean MI score (SD)	2.31 (0.80)	2.27 (0.89)	2.19 (0.81)	2.39 (0.89)
Available data, <i>n</i>	132	20	153	45
Depression, mean PHQ-9 score (SD)	10.9 (5.9)	13.1 (5.7)	11.1 (5.6)	11.4 (5.6)
Available data, <i>n</i>	156	26	170	54
Quality of care, mean PACIC score (SD)	6.58 (2.66)	5.44 (2.82)	6.30 (2.50)	4.95 (2.26)
Available data, <i>n</i>	130	24	154	47

Abbreviations: BAI, Beck Anxiety Inventory; MI, Mobility Inventory (subscale 'alone'); IQR, Interquartile range; OASIS, Overall Anxiety Severity and Impairment Scale; PACIC, Patient Assessment of Chronic Illness Care (short form); PHQ-9, Patient Health Questionnaire (depression subscale).

eTable 2. Baseline Characteristics of Patients Who Did vs Did Not Complete 12 Months Follow-Up (T2 Dropout Analysis)

Characteristic	Control group (n = 189)		Intervention group (n = 230)	
	12 months follow-up completed (n = 150)	12 months follow-up not completed (n = 39)	12 months follow-up completed (n = 168)	12 months follow-up not completed (n = 62)
Mean age (SD), years	46.6 (14.7)	44.9 (15.4)	46.8 (13.3)	44.2 (16.1)
Available data, <i>n</i>	150	39	168	62
Female, <i>n</i> (%)	116 (77.3)	29 (74.4)	121 (72.0)	45 (72.6)
Available data, <i>n</i>	150	39	168	62
Median duration of education, (IQR), <i>y</i>	10 (9, 12)	10 (10, 12)	10 (9, 12)	10 (9, 10)
Available data, <i>n</i>	149	39	168	62
Employed, <i>n</i> (%)	91 (61.1)	23 (60.5)	107 (64.8)	41 (67.2)
Available data, <i>n</i>	149	38	165	61
Retired from work, <i>n</i> (%)	38 (25.5)	10 (26.3)	25 (15.0)	9 (14.8)
Available data, <i>n</i>	149	38	167	61
Living with partner, <i>n</i> (%)	93 (62.0)	21 (53.8)	110 (65.5)	34 (54.8)
Available data, <i>n</i>	150	39	168	62
Median long-term conditions (IQR), <i>n</i>	3 (1, 4)	2 (1, 5)	3 (2, 5)	3 (1, 5)
Available data, <i>n</i>	150	39	168	62
Comorbid agoraphobia, <i>n</i> (%)	113 (75.3)	22 (56.4)	131 (78.0)	49 (79.0)
Available data, <i>n</i>	150	39	168	62
Anxiety screening, mean OASIS score (SD)	12.4 (2.9)	12.8 (2.8)	12.4 (2.7)	12.9 (2.7)
Available data, <i>n</i>	150	36	167	59
Anxiety severity, mean BAI score (SD)	27.9 (12.5)	29.6 (12.3)	27.1 (12.1)	31.3 (12.5)
Available data, <i>n</i>	143	36	161	59
Avoidance behavior, mean MI score (SD)	2.29 (0.80)	2.35 (0.89)	2.17 (0.80)	2.47 (0.90)
Available data, <i>n</i>	122	30	151	47
Depression, mean PHQ-9 score (SD)	10.9 (5.8)	12.5 (6.0)	11.1 (5.7)	11.4 (5.4)
Available data, <i>n</i>	144	38	164	60
Quality of care, mean PACIC score (SD)	6.51 (2.67)	6.03 (2.88)	6.29 (2.44)	5.10 (2.51)
Available data, <i>n</i>	121	33	150	51

Abbreviations: BAI, Beck Anxiety Inventory; MI, Mobility Inventory (subscale 'alone'); IQR, Interquartile range; OASIS, Overall Anxiety Severity and Impairment Scale; PACIC, Patient Assessment of Chronic Illness Care (short form); PHQ-9, Patient Health Questionnaire (depression subscale).

eTable 3. Number of Panic Attacks (in the Past Week)^a

Visit		Control group (n = 189)		Intervention group (n = 230)		Total (n = 419)	
		<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
T0, baseline	Missing	4	.	1	.	5	.
	No panic attacks	47	25.4	47	20.5	94	22.7
	1 panic attack	59	31.9	68	29.7	127	30.7
	2 or 3 panic attacks	46	24.9	74	32.3	120	29.0
	4 to 6 panic attacks	25	13.5	25	10.9	50	12.1
	More than 6 panic attacks	8	4.3	15	6.6	23	5.6
T1, 6 months	Missing	29	.	57	.	86	.
	No panic attacks	67	41.9	84	48.6	151	45.3
	1 panic attack	39	24.4	59	34.1	98	29.4
	2 or 3 panic attacks	43	26.9	24	13.9	67	20.1
	4 to 6 panic attacks	6	3.8	4	2.3	10	3.0
	More than 6 panic attacks	5	3.1	2	1.2	7	2.1
T2, 12 months	Missing	42	.	65	.	107	.
	No panic attacks	62	42.2	88	53.3	150	48.1
	1 panic attack	44	29.9	47	28.5	91	29.2
	2 or 3 panic attacks	30	20.4	22	13.3	52	16.7
	4 to 6 panic attacks	8	5.4	4	2.4	12	3.8
	More than 6 panic attacks	3	2.0	4	2.4	7	2.2

^aPanic Disorder and Agoraphobia Scale (PAS), Item A1.

eTable 4. Severity of Panic Attacks (in the Past Week)^a

Visit		Control group (n = 189)		Intervention group (n = 230)		Total (n = 419)	
		<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
T0, baseline	<i>Missing</i>	4	.	6	.	10	.
	No panic attacks	46	24.9	41	18.3	87	21.3
	Usually mild	38	20.5	55	24.6	93	22.7
	Usually moderate	58	31.4	75	33.5	133	32.5
	Usually severe	35	18.9	41	18.3	76	18.6
	Usually extremely severe	8	4.3	12	5.4	20	4.9
T1, 6 months	<i>Missing</i>	36	.	63	.	99	.
	No panic attacks	60	39.2	74	44.3	134	41.9
	Usually mild	32	20.9	45	26.9	77	24.1
	Usually moderate	45	29.4	34	20.4	79	24.7
	Usually severe	13	8.5	10	6.0	23	7.2
	Usually extremely severe	3	2.0	4	2.4	7	2.2
T2, 12 months	<i>Missing</i>	44	.	68	.	112	.
	No panic attacks	59	40.7	85	52.5	144	46.9
	Usually mild	30	20.7	43	26.5	73	23.8
	Usually moderate	40	27.6	25	15.4	65	21.2
	Usually severe	16	11.0	7	4.3	23	7.5
	Usually extremely severe	0	0.0	2	1.2	2	0.7

^aPanic Disorder and Agoraphobia Scale (PAS), Item A2.

eTable 5. Premature Discontinuation of Treatment in the Intervention Group (n = 230) With Reasons^a

Premature discontinuation of treatment, <i>n</i> (%)	No	152 (66.1)
	Yes	78 (33.9)
Reason for premature discontinuation of treatment, <i>n</i> (%)	Motivation lost	13 (5.7)
	Therapeutic methods refused	7 (3.0)
	Burdening stressful life events (study-independent)	10 (4.3)
	Removal with change of primary care practice	8 (3.5)
	Non-adherence to intervention procedure	8 (3.5)
	Elective admission to hospital	3 (1.3)
	Practice team sickened or disbanded	18 (7.8)
	Patient deceased	1 (0.4)
	Unknown	10 (4.3)

^a"Premature discontinuation of treatment" in the intervention group was defined as having attended less than the first three appointments with the primary care physician (that conveyed the crucial CBT-oriented elements).

eTable 6. Descriptive Statistics Based on Available Raw Outcome Data

Timepoint, by outcome	Control group (n = 189)		Intervention group (n = 230)		Mean difference	Effect size of mean difference ^a	Effect size of difference in mean change to baseline ^b	Reliability of measure ^c
	<i>n</i>	<i>Mean (SD)</i>	<i>n</i>	<i>Mean (SD)</i>				
BAI^d								0.93
Baseline	179	28.2 (12.4)	220	28.2 (12.3)	0.0	0.0		
6 months	156	23.0 (13.0)	166	19.1 (12.4)	-3.9	0.31	0.22	
12 months	144	22.1 (13.3)	164	17.3 (12.5)	-4.8	0.37	0.25	
MI^e								0.96
Baseline	152	2.30 (0.81)	198	2.24 (0.83)	-0.06	-0.07		
6 months	135	2.18 (0.83)	143	1.92 (0.87)	-0.26	0.23	0.35	
12 months	128	2.07 (0.85)	146	1.78 (0.77)	-0.29	0.28	0.23	
PHQ-9^f								0.86
Baseline	182	11.2 (5.9)	224	11.2 (5.6)	0.0	0.0		
6 months	157	9.3 (5.8)	171	7.3 (4.8)	-2.0	0.35	0.42	
12 months	145	8.9 (5.7)	163	6.4 (5.0)	-2.5	0.44	0.51	
PACIC^g								0.91
Baseline	154	6.41 (2.71)	201	5.99 (2.51)	0.42	-0.16		
6 months	147	6.46 (2.79)	160	7.42 (2.54)	0.96	0.52	0.41	
12 months	135	6.06 (3.08)	147	7.17 (2.78)	1.11	0.54	0.46	

Abbreviations: BAI, Beck Anxiety Inventory; MI, Mobility Inventory (subscale 'alone'); PACIC, Patient Assessment of Chronic Illness Care (short form); PHQ-9, Patient Health Questionnaire (depression subscale).

^aStandardized between-group difference in observed mean scores.

^bStandardized between-group difference in observed mean change scores.

^cInternal consistency (standardized Cronbach's alpha) of questionnaire as measured in the current sample.

^dRange of possible scores, 0-63. Higher scores indicate higher levels of anxiety severity.

^eRange of possible scores, 1-5. Higher scores indicate severer agoraphobic avoidance behavior.

^fRange of possible scores, 0-27. Higher scores indicate severer depression symptoms.

^gRange of possible scores, 1-10. Higher scores indicate better quality of chronic illness care.

eTable 7. Changes in Panic Attack Frequency from Baseline to 6-Months Follow-Up ^a													
Allocation	Number of panic attacks (past week): Baseline	Number of panic attacks (past week): 6 months											
		<i>Missing</i>		0		1		2-3		4-6		>6	
		<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Control group (n = 189)	<i>Missing</i>	1	.	1	.	1	.	.	.	1	.	.	.
	0	7	.	27	17.2	10	6.4	3	1.9	.	.	.	.
	1	8	.	23	14.6	11	7.0	16	10.2	.	.	1	0.6
	2-3	7	.	10	6.4	13	8.3	14	8.9	2	1.3	.	.
	4-6	4	.	5	3.2	4	2.5	8	5.1	3	1.9	1	0.6
	>6	2	.	1	0.6	.	.	2	1.3	.	.	3	1.9
Intervention group (n = 230)	<i>Missing</i>	.	.	.	.	.	.	1	.	.	.	.	.
	0	11	.	25	14.5	9	5.2	1	0.6	1	0.6	.	.
	1	14	.	30	17.4	20	11.6	3	1.7	1	0.6	.	.
	2-3	20	.	21	12.2	19	11.0	12	7.0	1	0.6	1	0.6
	4-6	8	.	6	3.5	6	3.5	5	2.9	.	.	.	.
	>6	4	.	2	1.2	5	2.9	2	1.2	1	0.6	1	0.6

^a For each allocation, the shift table shows how many patients improved (highlighted in green), deteriorated (red), or had no change (yellow) from baseline to 6-month follow-up (post-intervention) regarding the number of panic attacks (in the past week), measured with the Panic and Agoraphobia Scale (PAS), Item A1.

eTable 8. Changes in Panic Attack Severity from Baseline to 12-Months Follow-Up ^a														
Allocation		Severity of panic attacks (past week): Baseline	Severity of panic attacks (past week): 12 months											
			<i>Missing</i>		No panic attacks		Very Mild		Moderate		Severe		Extremely severe	
			<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Control group (n = 189)	<i>Missing</i>	2	.	1	.	.	.	1	.	.	.	.	.	
	No panic attacks	9	.	24	15.9	7	4.6	5	3.3	1	0.7	.	.	
	Very Mild	5	.	16	10.6	9	6.0	7	4.6	1	0.7	.	.	
	Moderate	13	.	14	9.3	9	6.0	18	11.9	4	2.6	.	.	
	Severe	6	.	4	2.6	7	4.6	11	7.3	7	4.6	.	.	
	Extremely severe	1	.	1	0.7	.	.	3	2.0	.	.	3	2.0	
Intervention group (n = 230)	<i>Missing</i>	2	.	.	.	2	.	1	.	1	.	.	.	
	No panic attacks	8	.	22	13.5	9	5.5	2	1.2	.	.	.	.	
	Very Mild	18	.	18	11.0	12	7.4	7	4.3	.	.	.	.	
	Moderate	18	.	23	14.1	15	9.2	13	8.0	4	2.5	2	1.2	
	Severe	13	.	9	5.5	6	3.7	10	6.1	2	1.2	1	0.6	
	Extremely severe	4	.	2	1.2	1	0.6	1	0.6	3	1.8	1	0.6	

^a For each allocation, the shift table shows how many patients improved (highlighted in green), deteriorated (red), or had no change (yellow) from baseline to 6-month follow-up (post-intervention) regarding usual severity of panic attacks (in the past week), measured with the Panic and Agoraphobia Scale (PAS), Item A2.

eTable 9. Patients Reporting Intake of Any Psychiatric Medication*, ITT-sample			
	<i>Control group (n=189)</i> <i>n (%)</i>	<i>Intervention group (n=230)</i> <i>n (%)</i>	<i>Total (n=419)</i> <i>n (%)</i>
<i>T0</i>	108 (57.1)	121 (52.6)	229 (54.6)
<i>T1</i>	50 (26.5)	45 (19.6)	95 (22.7)
<i>T2</i>	38 (20.1)	37 (16.1)	75 (17.9)

*Medication includes any antidepressants, mood stabilizers, anxiolytics and neuroleptics.