Evaluation of an Online-Based Self-Help Program for Patients With Panic Disorder - A Randomized Controlled Trial

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Abstract

Background: Panic disorder, with and without agoraphobia, can be a highly debilitating disorder leading to functional impairments, increased risk of developing comorbidities, and a reduced quality of life. Panic disorder comes with a higher economic burden than other anxiety disorder, mainly due to absenteeism.

Objective: The present study evaluated the effectiveness of a minimally-guided online self-help intervention for panic disorder with or without agoraphobia. As our primary hypotheses, we expected the intervention to improve both panic symptoms and well-being.

Methods: German-speaking patients (N=156) between 18 and 65 with internet access and a diagnosis of panic disorder or agoraphobia with panic disorder were recruited for this randomized controlled trial. The intervention group (N=84) received access to a 12-week online self-help program. The waitlist control group (N=72) received care as usual during the study period and was offered the prospect of using the program after 12 weeks.

Results: Changes in PAS revealed a significant effect in favor of the intervention group (t (df=110.1)=-2.22, padj=.027) with a small to moderate effect size (d=-0.37, 95%-CI: -0.70; -0.04). No significant effect was found for the second primary outcome WHO-5 (t (df=149.8)=1.35, padj=.088) or the secondary outcomes functioning, mental health literacy, working ability and healthcare use).

Conclusions: The presented online intervention can help reduce the core symptomatology of panic disorder with or without agoraphobia. Diminished effects may be due to higher illness burden in the intervention group and possibly the COVID pandemic which caused unique challenges to patients suffering from panic disorder. Regarding well-being and the secondary outcomes, superiority towards the control group was not established. Therefore, further research and intervention adaptations may be warranted to improve these outcomes. Clinical Trial: https://drks.de/search/en/trial/DRKS00023800

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Abstract

Objectives: The present study evaluated the effectiveness of a minimally-guided online self-help intervention for panic disorder with or without agoraphobia. As our primary hypotheses, we expected the intervention to improve both panic symptoms and well-being.

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Results: Changes in PAS revealed a significant effect in favor of the intervention group (t (df=110.1)=-2.22, p_{adj}=.027) with a small to moderate effect size (d=-0.37, 95%-CI: -0.70; -0.04). No significant effect was found for the second primary outcome WHO-5 (t (df=149.8)=1.35, p_{adj}=.088) or the secondary outcomes functioning, mental health literacy, working ability and healthcare use).

Conclusions: The presented online intervention can help reduce the core symptomatology of panic disorder with or without agoraphobia. Diminished effects may be due to higher illness burden in the intervention group and possibly the COVID pandemic which caused unique challenges to patients suffering from panic disorder. Regarding well-being and the secondary outcomes, superiority towards the control group was not established. Therefore, further research and intervention adaptations may be warranted to improve these outcomes.

Keywords: Randomized Controlled Trial, Internet-Based Interventions, Panic Disorder, Agoraphobia With Panic

Public health implications: Web-based self-help interventions can decrease the symptom burden for patients with panic disorder with or without agoraphobia. These findings provide the basis for implementing the intervention into routine clinical care.

Introduction

Panic disorders involve recurring sudden panic attacks and a constant fear of experiencing more episodes. These attacks come with physical symptoms like breathing issues, palpitations, sweating, and nausea, as well as psychological symptoms such as derealization and a fear of losing control or dying [1-2]. Agoraphobia, which affects 35-65% of people with panic disorder [3], involves excessive fear and avoidance of situations where escape may be difficult, like public transport, and help may not be readily available in case of a panic attack. Both panic disorder with and without agoraphobia are closely related and often seen as part of a continuum [4].

Panic disorders, with or without agoraphobia, come with functional impairments and reduced well-being, increasing the risk of other mental disorders [5-8]. They also impose a significant economic burden, surpassing that of other anxiety, mood, or alcohol-related disorders [9]. These costs include hospital treatments, healthcare visits, and, most notably, absenteeism, which accounts for 60% of all expenses [10]. Thus, it is crucial to offer effective and timely treatment for panic disorders for both societal and individual well-being.

Regarding psychotherapeutic treatments, recently CBT and short-term psychodynamic therapy have been identified as treatments of choice [11]. CBT targets fear and avoidance behavior by psychoeducation, exposure therapy, cognitive restructuring, mindfulness, and acceptance interventions leading to large effect sizes compared to a waitlist group (g=0.96; [12]). Also, effects remain superior to treatment as usual for six months follow-up [13]. Psychopharmacology yields small to moderate effect sizes in comparison to placebo and similar to CBT [14]. Though, compared to pharmacotherapy, CBT shows longer-term treatment effects, better cost-efficacy, and higher patient acceptance [15].

An analysis of treatment barriers in anxiety disorders [16] showed that 81.8% of patients with panic disorders contemplate treatment. Still, only 67.3% seek help at least once in their life, and this

number is even lower in patients with agoraphobia (70.1% vs. 36.9%). Frequently reported barriers to help-seeking include self-reliance, presumed ineffectiveness, high waiting periods, or problems with the practitioner [16]. Further, negative attitudes and lack of knowledge and appropriate beliefs about mental health are associated with less help-seeking behavior [17].

During treatment waiting periods, it is recommended to offer patients self-help programs based on CBT [18], since technology-based treatment alternatives can help surpass the aforementioned barriers [19]. Most of these alternatives are based on CBT, since it is well suited for online intervention delivery due to its highly structured, directive, standardized nature and its focus on psychoeducation and homework [20].

A systematic review and meta-analysis including 27 studies on internet-based CBT (iCBT) for panic disorder [21] showed high effectiveness for reducing symptoms of panic disorder (g=1.16) and agoraphobia (g=0.91) compared to waitlist. While most literature addresses guided forms of iCBT with therapeutic support, unguided, self-directed iCBT programs have also shown large pre-post effect sizes for treating panic disorders (e.g., d=0.70-1.06; [22]). Studies found no significant differences in panic disorder symptom reduction, completion rates, and satisfaction between guided and unguided iCBT ([22-23]. Additionally, neither frequency of a supportive attendant [24-25] nor the experience or training of the support person [26] seem to significantly influence panic disorder symptom reduction during iCBT. Of particular note is the benefit of iCBT to the healthcare system, as it is a cost-effective treatment alternative with similar efficacy to face-to-face CBT [27-28]. Also, iCBT can help to bridge the waiting periods for face-to-face psychotherapy, which on average lasts several months in Germany and has further increased since the beginning of the corona pandemic [29-30].

In sum, there is evidence for the benefits of internet-based treatments even with little guidance regarding core symptom reduction. However, little research can be found investigating

broader effects on well-being, functioning, mental health literacy, working ability, and health care use. These seem particularly relevant to assess effects on cost-effectiveness.

Objectives

This study aimed to evaluate a 12-week online self-help program (*Selfapy*) for panic disorder patients within the German healthcare system. We assessed its effectiveness in reducing panic symptoms, functioning impairments, absenteeism, and healthcare use. We conducted a randomized controlled trial comparing the self-help intervention group (IG) with a waitlist control group (CG) that received care as usual. This approach mimics the typical wait times for psychotherapy in Germany, providing insights into real-world conditions for panic disorder patients seeking treatment reflecting current routine care.

Hypotheses

Based on previous research, the primary outcomes focus on disorder-specific symptom burden (panic and agoraphobia symptoms) and well-being. The secondary hypotheses target daily functioning, work capacity, and the efforts and burdens of patients for the healthcare sector. Additionally, the program's effect on mental health literacy was observed because of its connection to barriers to help-seeking behavior [17]. Lastly, changes in comorbid anxiety and depression symptoms as well as negative effects of the program beyond symptomatology, are being explored.

Primary hypotheses

The primary outcomes that were tested against the control group after 12 weeks.

a. A greater reduction in self-rated panic and agoraphobia symptomatology in the IG compared to the CG.

b. A greater improvement in well-being in the IG compared to the CG.

Secondary hypotheses

a. A greater decrease in self-reported difficulties in daily life in the IG compared to the CG.

b. A greater improvement in work capacity in the IG compared to the CG.

c. A greater improvement in self-assessed health literacy in the IG compared to the CG.

d. A greater reduction in the extent of health care use in the IG compared to the CG.

Exploratory hypotheses

a. A greater decrease in anxiety symptoms compared to the CG.

b. A greater decrease in comorbid depressive symptoms compared to the CG.

c. No more negative treatment effects in the IG compared to the CG

Methods

Study design

The trial was preregistered beforehand (https://drks.de/search/en/trial/DRKS00023800) and a study protocol was published [31]. Before randomization, a structured diagnostic interview (DIPS-OA, [32-33]) was conducted with every participant via video calls. Concerning DSM-IV-TR criteria, the DIPS-OA was found to have acceptable interrater (.78) and retest (.76) reliability for anxiety disorders [34]. Eligible patients were randomly assigned to the intervention group (IG) or control group (CG) in a 1:1 ratio without stratification. Randomization was conducted by a team member who was not involved in the analysis. Patients in the IG could use the intervention immediately after randomization, while the CG could only access the intervention after a waiting period of 12 weeks. Interim and final evaluations occurred 6 (T2) and 12 (T3) weeks after the baseline assessment (T1).

Recruitment

Announcements for study participation were published in the whole of Germany via a university email newsletter, social media, and on flyers in clinics, pharmacies, and practices of

medical doctors and psychotherapists. After an online pre-screening, participants were invited to choose an appointment for a remote diagnostic interview assessing the inclusion and exclusion criteria. All participants received an allowance of 30€ after completing the questionnaires (T1 and T3). Altogether 4361 people started the online screening, of whom 156 (3.58%) were included in the trial.

Inclusion and exclusion criteria

Video calls were conducted with all subjects who checked the pre-screening criteria to assess inclusion and exclusion criteria, during which eligibility was assessed via the DIPS-OA. Trained psychologists conducted all interviews under supervision by a certified psychotherapist (CBT).

Eligible subjects were those who 1) were between 18 and 65 years of age, 2) had sufficient knowledge of the German language, 3) had uninterrupted Internet access, 4) provided electronic informed consent to participate in the study, and 5) met criteria for a diagnosis of panic disorder with or without agoraphobia.

Subjects were excluded if they did not meet any of the inclusion criteria or met any of the following criteria: 1) past or current diagnosis of bipolar disorder, 2) past or current diagnosis of psychotic disorder, 3) current diagnosis of substance dependence, 4) current diagnosis of a severe major depressive episode, and 5) acute suicidality. The criteria were chosen, because they could interfere with the successful implementation of the course.

Intervention

The online self-help program for the treatment of panic disorder and agoraphobia with panic disorder (*Selfapy*). The program is based on evidence-based methods and exercises derived from CBT, as well as elements from Mindfulness-Based Therapy (e.g., [35-36]). The online intervention consists of core modules, which include mandatory exercise content, and a subsequent set of optional specialization areas that are individually selectable (for a complete overview, see [31]). Each module

covers a specific topic, such as *exposure*, *mindfulness*, or *problem-solving* training. The modules contain informative texts, videos, audio, and interactive exercises and can be used via the web as well as on mobile devices.

Participants completed the online program independently, with a psychologist monitoring for safety concerns like suicidality through messaging. Active communication only occurred for safety reasons. The intervention group had immediate access to the 12-week self-help treatment and were advised to spend 15-20 minutes daily on it. The control group received no treatment for 12 weeks but could seek other assistance beyond this trial, such as medication or therapy, to mimic routine care. All concurrent treatments were self-reported.

Control group

To control for regression to the mean the participants in the CG did not receive the intervention during the study period. Regardless of group allocation, all participants could seek other forms of treatment, including medication and face-to-face psychotherapy to mirror care as usual as closely as possible. The CG received the study intervention after study completion (=after 12 weeks), since 12 weeks is a common waiting time for psychotherapy in Germany [29], leading to increased external validity of this trial.

Participants characteristics

The sociodemographic characteristics of all participants are displayed in Table 1 (see additional information in OSM 1). Altogether, 59 (38.3%) participants were diagnosed with panic disorder, whereas 96 (61.7%) participants fulfilled the diagnostic criteria of agoraphobia with panic disorder[1]. Regarding comorbidities, 47 (30.1%) participants also fulfilled the diagnostic criteria for Generalized Anxiety Disorder, which was the most prominent comorbid disorder (see OSM 45). Comorbid depression rates were relatively low, with only 9 (5.8%) participants fulfilling the

[1] Due to a technical problem, the information on the assignment to one of the two diagnoses was lost for one person in the IG.

diagnostic criteria for Major Depressive Disorder. It is important to note that the low comorbidity rate can be attributed to this study's exclusion criteria, which specifically excluded individuals with severe depression.

Table 1

Sociodemographic characteristics of the study cohort at baseline

	Treatment (*N*=82)		Control (*N*=74)		Total Sample (*N*=156)	
Characteristics	***N***	**%**	***N***	**%**	***N***	**%**
Sex						
Female	65	79.27	56	75.68	121	77.56
Male	16	19.51	17	22.97	33	21.15
Non-binary	1	1.22	1	1.35	2	1.29
Age in years (*M, SD)*	35.1	11.5	35.0	11.1	35.0	11.3
Health care use						
Psychotherapy	35	42.68	26	35.14	61	39.10
pharmacotherapy	27	32.93	23	31.08	50	32.05

Note.

Safety Monitoring and Ethical Standards

All participants provided informed consent, and the study was approved by the ethics committee at Heidelberg University (Ethics Committee-No. AZ Prüß 2021 1/1). Suicidal thoughts were assessed at multiple time points (T1, T2, and T3) using a Likert scale. If participants rated their thoughts as 1 or higher (indicating they had thoughts of wanting to harm themselves) for the past two weeks, they were contacted by phone or email, and an emergency plan was established. For individuals contacted due to suicidality, their questionnaire participation was halted to prioritize immediate support. Suicidal incidents occurred three times, all within the control group

Outcomes

Measures were conducted at three different points in time: Before the start of the intervention (T1, baseline), after six weeks (T2, during treatment), and 12 weeks after the beginning of the intervention (T3, posttreatment). At each measurement time point the primary, secondary and exploratory outcomes were assessed.

Primary outcome measures

The change in panic symptoms was evaluated using the *Panic and Agoraphobia Scale* (*PAS*; [37]). In our data, we calculated McDonald's omega [38] as a reliability measure with ω=0.86 at T1. Wellbeing was assessed by the five-item *World Health Organization Well-being Index* (*WHO-5*; [39]). The reliability of the *WHO-5* was high, with ω=0.87 at T1.

Secondary outcome measures

Functioning in daily life was measured by the *Work and Social Adjustment Scale* (*WSAS*; [40]) assessing professional and personal functioning. Reliability was good with ω=0.79 at T1.

Work capacity was measured with the *iMTA Productivity Cost Questionnaire* to assess the amount of lost working hours in the last four weeks due to absenteeism or distress-related impaired work capabilities (*iPCQ*; [41]).

Mental health literacy was measured with the *Mental Health Literacy Scale* (*MHLS*; [42]) with high reliability (ω=0.85 at T1).

The extent of therapy-related efforts and burdens of patients (*Client Sociodemographic and Service Receipt Inventory - CSSRI*; [43]) was collected on three subscales: *CSSRI-partly inpatient* to assess partly inpatient treatment, *CSSRI-complementary* to assess complementary services (e.g., self-help groups), and *CSSRI-ambulant* to assess outpatient services (e.g., psychotherapy treatment,

medical treatment).

Additional outcome measures

Adverse treatment effects were assessed with the *Negative Effects Questionnaire* (*NEQ*; [44]). The *NEQ* contains 32 items and showed high reliability (ω=0.89 at T3). Also, general symptoms of anxiety were assessed using the *Beck Anxiety Inventory* (*BAI*; [45]) with ω=0.89 at T1. Depressive symptoms were collected with the *Patient Health Questionnaire-9* (*PHQ-9*; [46]) with ω=0.74 at T1.

More detailed descriptions of the outcomes can be found in the study protocol.

A priori sample size planning

The between-group effect size estimate was based on recent meta-analytic evidence for effect sizes in unguided online psychological interventions for anxiety disorders (d=0.45; e.g., [47]). This effect was used as the basis for sample size determination. For the planned mixed model with two measurement time points with a general correlation structure [48], a directed hypothesis, a group allocation of 1:1, a power of 0.80, and an alpha level of 0.025 after Bonferroni-Holm correction, a total of 156 patients (78 per group) were needed. The number of cases was calculated using the *R*-tool longpower [49]. For the secondary outcomes, we calculated a minimal detectable effect size of d=-0.46 with 80% power and an alpha level of 0.0125 (Bonferroni-Holm adjustment) based on a post-hoc power analysis of the WSAS with *simr* [50].

Randomization and blinding

Participants meeting the criteria were randomly assigned to either:

(a) Immediate access to the online panic disorder intervention group (IG).

(b) Delayed access to the online intervention, starting after 12 weeks (CG).

Randomization in a non-stratified 1:1 ratio, performed after the diagnostic interview, was done by a researcher not involved in the project, ensuring the interviewers were unaware of group assignments (Allocation Sequence Concealment). Participants were informed of their group via email. They were told that the waiting time would be randomly varied. Thus, patients in the CG did not know that there were only two groups with respect to the waiting period. Data collection, evaluation, and statistical analysis were done blindly. A team member not involved in analysis coded the group variable, and analysis scripts were prepared before knowing the actual data.

Statistical analyses

The statistical analyses were conducted following the study protocol [31]. The analyses were performed with *R*, version 4.2.0 [51].

Adhering to ITT principles, none of the enrolled participants were generally excluded. Missing values were replaced by Multivariate Imputation by Chained Equations (MICE; with n=5 imputations; [52]) based on the control arm, using the variables age and gender as predictors in addition to the T1 outcome measurements. Four additional sensitivity analyses are reported in the appendix: A completer analysis using only patient data with completed T1 and T3 measures, last-observation-carried-forward (LOCF), baseline-observation-carried-forward (BOCF), and a reference-based-multiple imputation (J2R; [53]). In addition to these analyses, a "per-protocol" sample sensitivity analysis was defined for exploratory analyses, including all IG patients who completed at least 4 of the 12 modules.

The confirmatory analysis of the primary endpoints consisted of calculating a mixed model with two measurement time points and a general correlation structure [48]. A random effect for the subject was calculated (random intercept), and three fixed effects (group, time, and the interaction of these two effects). The two measurement times were nested within subjects. The treatment effect regarding all outcomes was estimated as the fixed interaction effect after the final (T3) assessment. Secondary confirmatory outcomes were calculated only after success in the primary analysis on

continuous outcome measures, using the same mixed model with a random intercept for the subject.

Independent *t*-tests and χ2-tests were used to estimate differences between groups in pre-treatment sample characteristics. Also, *t*-tests were used to identify differences in adverse effects in the NEQ at T2 and T3.

To assess the magnitude of the treatment effects, the fixed interaction effect of time and group was divided by the root of the summed variances of the random effects [54]. Effect sizes can be roughly interpreted according to Cohen's *d*: Effect sizes of 0.20 are considered small, 0.50 moderate, and 0.80 large [55].

The *CSSRI* questionnaire was split into the three most relevant subscales (*CSSRI-partially inpatient*, *CSSRI-outpatient*, and *CSSRI-complementary*) that were also subject to Bonferroni-Holm adjustment by dividing by 3, 2, and 1, respectively.

Due to highly skewed data, the *iPCQ* and the *CSSRI partially inpatient* scales were log10-transformed. The *CSSRI-outpatient* and *CSSRI-complementary* scales were dichotomized because of rare extreme outliers, in which case a transformation is not recommended [56]. For these dichotomized measures, the analysis was adapted to a mixed logistic regression model with random intercept and three fixed effects (group, time, and group*time). For these analyses, odds ratios were calculated as the effect size.

The additional outcome measures, *BAI* and *PHQ-9*, were analyzed using the same model as the primary and secondary outcomes.

Data and code

All data and analysis code have been made publicly available at the OSF repository and can be accessed at [57]. Materials about the content of the online intervention are reported in the study protocol [31].

Results

Participants flow

Recruitment occurred from February 12, 2021, to March 21, 2022. A total of 604 clinical interviews were conducted, leading to 292 participants being excluded based on inclusion and exclusion criteria. Additionally, 156 participants joined another trial on generalized anxiety disorder [58]. The remaining 156 participants were randomized into the Intervention Group (IG, N=84) and Control Group (CG, N=74). Sociodemographic differences between the groups were not significant.

More IG participants (35.8%) had a current diagnosis of social phobia compared to CG (15.1%, $\chi 2$=8.59, p=.005). However, more CG participants had a past diagnosis of social phobia (5.5%) than IG (0%, $\chi 2$=4.56, p=.048). No other diagnosis differences were observed (see OSM 45). Current psychopharmacology ($\chi 2$=0.061, p=.805) and psychotherapy ($\chi 2$=0.931, p=.335) also did not differ between groups. The control group had lower anxiety levels at baseline for the BAI (t(df=153.8)=2.30, p=.023). No group differences were found in primary or secondary outcomes.

Missing data

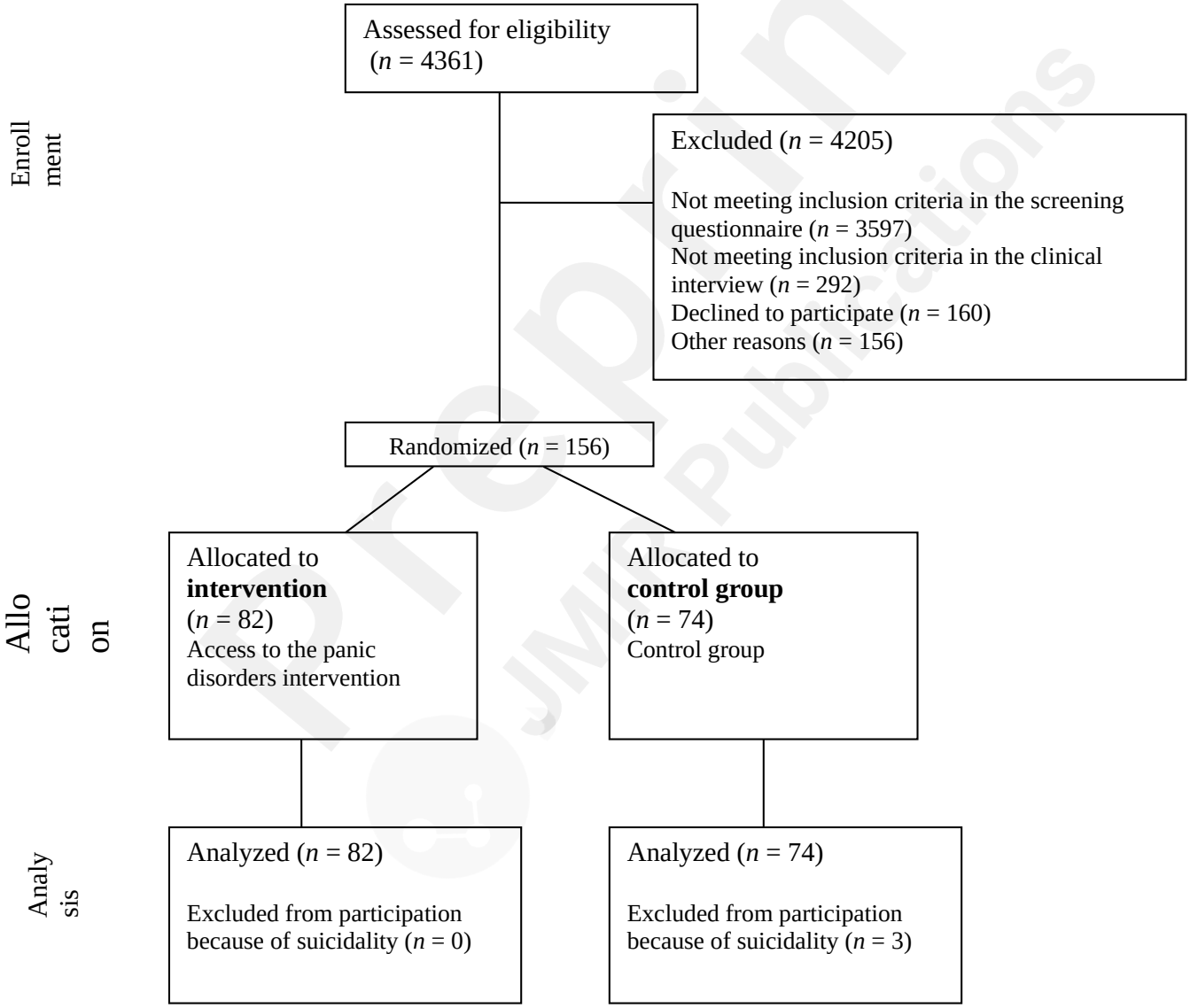
Non-completion rates were 16.0% (n=25) for the PAS (first primary outcome) and 18.6% (n=29) for the WHO-5 (second primary outcome) at T3. Therefore, 70 (85.4%) in the IG and 61 (82.4%) participants in the CG completed the *PAS* at posttreatment. Similarly, 68 (82.3%) participants in the IG and 59 (79.7%) in the CG completed the WHO-5 posttreatment.

Logistic regression analyses showed that participant dropout for the *WHO-5* was not associated with any of the following baseline variables: group allocation, sex, age, work capacity, medication intake, or the baseline values of any of the primary or secondary outcomes. For the *PAS*, dropout was not associated with group allocation, age, work capacity, psychotherapy, or the baseline values of any primary or secondary outcomes. However, female sex (p=.024) and medication intake (p=.048) were associated with reduced dropout for the *PAS*.

Figure1

CONSORT flow diagram

Note. Deviations from the sample size occurred for some of the secondary and additional outcomes due to partial missingness.



Since none of the baseline outcomes were associated with dropout, the empirical data supported missing at random (MAR) instead of missing not at random (MNAR). Therefore, as determined in the study protocol, MICE analysis was conducted as our primary analysis.

Adverse events

During the trial, three participants from the control group reported suicidality and had to be

excluded from the study. Trained psychologists immediately contacted them. They were excluded from further data collection, but all previous data was still used.

Adherence

Due to a technical problem, usage data was missing for one person in the IG. Based on data from 81 participants, the IG completed an average of 7.3 (*sd*=3.9) modules out of the total 12 modules. 26 (32.1%) participants completed the whole course, and 73 (90.1%) underwent the first four modules, which was chosen as a sensitivity analysis to assess a basic amount of engagement.

Primary Outcomes

Descriptive statistics for the primary outcome measures (PAS and WHO-5) for each assessment point are shown in the appendix for completer and ITT samples (MICE, LOCF, BOCF, and J2R imputation). On average, severe levels of panic and agoraphobia were reported at baseline (*M*=34.56; *sd*=8.31; scores range from 13 to 66). Moreover, low well-being was reported at baseline (*M*=2.87; *sd*=0.97; scores range from 0.0 to 4.2).

Regarding the main interaction effect of the group allocation variable at T3 (see Table 2), the *PAS* measure ($t(df=110.1)=-2.22$, $p=.014$) reached significance after alpha adjustment. The interaction effect time*group was small to moderate (*d*=-0.37, 95%-CI: -0.70; -0.04). Within-group T1-T3 effect sizes for *PAS* were moderate in the IG (*d*=-0.58, 95%-CI: -0.77; -0.39) and small in the CG (*d*=-0.21, 95%-CI: -0.42; 0.00). However, this was not the case for the WHO-5 measure ($t(df=149.8)=1.35$, $p=.088$; see Table 2). The interaction effect was small (*d*=0.22; 95%-CI: -0.10; 0.53). Within-group effects were small to moderate in the IG (*d*=0.30, 95%-CI: 0.06; 0.53) and minimal in the CG (*d*=0.08, 95%-CI: -0.11; 0.28) for *WHO-5*. All imputations and effects can be seen in OSM 2-8.

Table 2

Bonferroni-Holm adjustment for the primary outcomes (MICE imputed)

Primary Outcome	*t (df)*	*p* (one-sided)	Adjustment factor	Adjusted *p*	Effect size *d* (95%-CI)

PAS	-2.22 (*df*=110.1)	.014	2	.027*	-0.37 (-0.70; -0.04)
WHO-5	1.35 (*df*=149.8)	.088	1	.088	0.22 (-0.10; 0.53)

Note. * indicates $p \leq .05$, ** indicates $p \leq .01$, *** indicates $p \leq .001$.

For *PAS*, the interaction effect time*group was small to moderate (*d*=-0.37, 95%-CI: -0.70; -0.04), and for *WHO-5*, it was small (*d*=0.22, 95%-CI: -0.10; 0.53). Within-group T1-T3 effect sizes for *PAS* were moderate in the IG (*d*=-0.58, 95%-CI: -0.77; -0.39) and small in the CG (*d*=-0.21, 95%-CI: -0.42; 0.00).

Minimal clinical important difference

The Reliable Change Index (RCI; [59]) was used to calculate reliable improvement or deterioration. Regarding the *PAS*, 33.6% of IG and 16.8% of CG patients improved reliably from T1 to T3. In contrast, 6.1% deteriorated in the IG and 9.2% in the CG. Therefore, a significant difference was found ($p < .001$).

For the WHO-5, improvement (28.3% versus 11.4%) favored the IG. However, deterioration (12.7% versus 11.4%) was stronger in the CG. A significant difference was identified (*p*=.002).

Sensitivity analyses for per-protocol sample (four completed modules)

Additionally, per-protocol sensitivity analyses were conducted for both primary outcomes, including only the 73 participants (90.1%) that underwent at least the first four modules. Because no hypotheses were specified, the effects are calculated as two-tailed tests without alpha adjustment. A significant group*time interaction (*t*=-3.25, *p*=.001) was found for the *PAS* with a moderate effect size (*d*=-0.50; 95%-CI: -0.80, -0.20). Regarding the *WHO-5*, no significant interaction was found (*t*=1.80, *p*=.074).

Secondary outcomes

Since a significant effect was found for at least one of the primary outcomes, the secondary

outcomes were analyzed with confirmatory tests[2].

Descriptive statistics, effect sizes, and significance levels can be found in the OSM 12-40. None of the interaction effects was significant after the Bonferroni-Holm adjustment (see Table 3).

For the WSAS, a small to moderate within-group (T1-T3) effect was found in the IG (*d*=-0.35; 95%-CI: -0.54; -0.17) and a minimal effect in the CG (*d*=-0.13 95%-CI: -0.29; 0.04). For the MHLS, iPCQ, and the CSSRI subscales no significant interaction effects were identified. For the CSSRI outpatient questionnaire, there was a significant within-group effect (T1-T3) in both the IG (*d*=-0.46; 95%-CI: -0.28; -0.06) and the CG (*d*=-0.34; 95%-CI: -0.55; -0.12).

[2] Due to the dichotomization in the secondary outcomes *CSSRI-partial inpatient* and *CSSRI-complementary*, the J2R imputation was not possible.

Table 3

Linear mixed model and Bonferroni-Holm adjustment for the secondary outcomes based on MICE imputation (T1-T3)

	Group*Time					
Outcome	***t***	***df***	***p* (one-sided)**	**adjustment factor**	**adjusted *p*-value**	**Effect size *d* (95% CI)**
WSAS	-1.72	105.1	.043	4	.172	-0.22 (-0.48; 0.03)
MHLS	-0.76	231.6	.224	2	.449	-0.09 (-0.34; 0.15)
iPCQ	-1.37	206.8	.086	3	.258	-0.21 (-0.51; 0.09)
CSSRI outpatient	0.48	231.6	1.00	1*1[a]	1.00	0.07 (-0.22; 0.37)
CSSRI partly inpatient	-0.56	6.2	.293	1*3[a]	.879	0.24[b] (0.00; 30.16)
CSSRI complementary	-0.30	6.5	.388	1*2[a]	.776	0.16[b] (0.00; 28134)

Note. * indicates p ≤ .05, ** indicates p ≤ .01, *** indicates p ≤ .001. [a] The additional factors are due to the additional alpha adjustments of the *CSSRI* subscales. [b] Effects are odds ratios. MICE, Multiple Imputation by Chained Equations. *WSAS, Work and Social Adjustment Scale; MHLS, Mental Health Literacy Scale; CSSRI, Client Sociodemographic, and Service Receipt Inventory*

Additional outcomes

For the *BAI*, a significant interaction was found at T3 ($t(df$=206.8)=-4.12, $p < .001$) with a moderate to large effect size (d=-0.60 95%-CI: -0.89; -0.32). Within-group effects (T1-T3) were large in the treatment group (d=-0.82 95%-CI: -1.05; -0.60) and small in the intervention group (d=-0.22 95%-CI: -0.39; -0.05).

For the *PHQ-9*, also a significant interaction was found ($t(df$=257.4)=-3.20, $p < .001$) with a small to moderate effect size (d=-0.41 95%-CI: -0.66; -0.16). Within-group effects (T1-T3) were small (d=-0.25 95%-CI: -0.42; -0.09) in the IG and showed minimal to small deterioration in the CG (d=0.15 95%-CI: -0.03; 0.34). Regarding adverse effects, no difference was found between the groups (t=-1.14, p=.255; see Table 5 and OSM 43 and 44).

Table 4

Linear mixed model and effect sizes for the exploratory outcomes BAI and PHQ-9 – MICE imputed, T3-T1

	Group*Time			
Outcome	***t***	***df***	***p* (two-sided)**	**Interaction effect (95% CI)**
BAI	-4.12	206.8	< .001***	-0.60 (-0.89; -0.32)
PHQ-9	-3.20	257.4	<.001***	-0.41 (-0.66; -0.16)

Note. * indicates p ≤ .05, ** indicates p ≤ .01, *** indicates p ≤ .001. a. Effect sizes for the dichotomized outcomes are reported as odd's ratio. MICE, Multiple Imputation by Chained Equations. BAI, Beck Anxiety Inventory; PHQ-9, Patient Health Questionnaire-9.

Table 5

Most common negative effects

	Intervention group (*N*=82)	
Negative effects	***N***	**%**
Unpleasant memories resurfaced	38	46.3
I had more problems with my sleep	15	18.3
I felt like I was under more stress	17	20.7
I experienced more unpleasant feelings	14	17.1
I felt more worried	11	13.4
I experienced more anxiety	11	13.4
I felt more dejected	10	12.2
I stopped thinking help was possible	6	7.3
I lost faith in myself	6	7.3
I experienced more hopelessness	5	6.1

Discussion

The present study compared the effectiveness of an online-based self-help iCBT for patients with panic disorder with or without agoraphobia with the current care situation of affected treatment-seeking individuals over 12 weeks.

In this trial, a significantly greater reduction in panic and agoraphobia symptoms was found for patients using the online intervention. No effects were found regarding the well-being of the patients. Also, no effects were found regarding the secondary hypotheses, namely daily functioning, work capacity, mental health literacy, and healthcare-related burdens. In the additional outcomes, significantly greater reductions in anxiety symptoms and depression were identified in favor of the online intervention.

Within our study, effect sizes for panic and agoraphobia symptoms were moderate within the groups (d=0.58) and small to moderate for the interaction effect (d=0.37). These interaction effects are smaller than the ones reported [21] with g=1.04 for panic and g=0.64 for agoraphobia when the treatment length was between five to twelve weeks.

The smaller effect sizes in our study may be attributed to several factors. Firstly, even though randomization occurred, the IG was more severely burdened than the CG with higher anxiety levels in the *BAI*, higher rates of social phobia (35.8% vs. 15.1%), marginal higher rates of generalized anxiety disorder (38.4% vs. 23.3%), and marginal higher rates of depression (9.8% vs. 1.4%). Secondly, the study was conducted from March 2021 to February 2022, which corresponds to the COVID-19 pandemic. Preliminary evidence suggests that the severity of panic disorder symptoms increased during COVID-19 (d=0.85 during the first wave; [60] Langhammer et al., 2022). This could be plausible, since respiratory difficulties are common symptoms of panic and SARS-CoV-2, possibly leading to breath-related fear conditioning and associated hypervigilance, which could trigger and exacerbate panic symptoms [61] in both the treatment and control group. In summary, higher illness burden in the IG may have confounded the differential effects on panic and

agoraphobia symptoms as well as well-being while the COVID-19 pandemic might have diminished effects in both groups.

Regarding the secondary hypotheses, several reasons for the lack of effects come to mind. First, this trial was not specifically powered for the secondary outcomes, especially due to the Bonferroni-Holm adjustment. The minimal effect size for 80% power and alpha=.0125 was calculated at *d*=0.46 based on a post-hoc power analysis of the WSAS, so that only moderate to large effects could be detected. Second, the iPCQ and CSSRI subscales had a strong floor effect [62] due to the rare occurrence of additional treatments respective lost working hours at baseline. For the iPCQ, 45.8% of participants reported zero lost work hours. For the CSSRI-partly inpatient subscale, 83.3% reported no inpatient appointments, and for the CSSRI complementary subscale, 86.7% reported no complementary treatments at baseline. Lower but substantial numbers were found for no ambulant treatment in the CSSRI outpatient (32.0%). Similarly, the MHLS had a ceiling effect with a baseline mean of 4.4 and a range from 3.3 to 5.0 on a scale from 1 to 5. Third, the CSSRI subscales assessed additional treatment use over the last three months, and therefore the use was measured from the beginning of the intervention. Therefore, the measurement included a timeframe in which the intervention had barely started. Similarly, the iPCQ was assessed for the last six weeks, which could cause a similar problem.

In conclusion, the lack of effects on the secondary outcomes could be due to several reasons, including insufficient power, substantial floor and ceiling effects, and long measurement times.

Implications for future research

In the current literature, substantial effects of iCBT for panic disorder and agoraphobia are identified [21]. However, most studies focus on panic and agoraphobia symptomatology, and there is little to no research on well-being and functioning. Yet, these measures are essential as they provide a more holistic perspective on recovery [63-64]. Further, as 60% of the financial burden is due to absenteeism [10] and additional costs are resulting from treatment, work capacity and health care use

allow an estimation of the costs associated with panic disorder. This current study found small effects on well-being (d=0.22), functioning (d=0.22), and work capacity (d=0.21), but lacked the power to validate these effects. Therefore, studies with higher statistical power are needed for reliable results. Also, modules specifically addressing these outcomes (e.g., well-being, work-related problems) could be integrated into iCBT to broaden the effects.

There is some evidence for the cost-effectiveness of panic disorder prevention via face-to-face therapy [65]. Therefore, iCBT seems even more suitable for preventative measures, as it is readily available at disorder onset and cheaper than traditional CBT [27].

Another important line of future research should focus on predictors of treatment effects. Although there are some preliminary findings for moderators (alliance [66] and impairment [67]), further research is warranted to enable clinicians to design more effective treatment courses.

Limitations

The study had several limitations. First, no active control group was chosen, as this reflects current routine care in Germany where patients have to wait up to several months for their treatment. However, this only allows conclusions in comparison to German routine care and provides no differential effect sizes to other interventions. Second, since some patients were recruited via social media and not from a mental health provider, this study may only partly reflect routine care. However, all patients underwent clinical interviews with trained master psychologists to secure clinical diagnoses and significant symptom severity to ensure sufficiently burdened patients. Third, this analysis lacked follow-up data, which is essential to test the effects' durability and assess effects with more extended time frames (e.g., *CSSRI*, *iPCQ*).

However, this study provides evidence for the effectiveness of the online-based intervention in conditions comparable to routine care. The design allowed for a balance between high internal validity due to randomization and blinding of the investigators and high external validity owing to inclusive exclusion criteria that only excluded comorbidities that would affect the use of the

intervention, while allowing for additional support such as psychotherapy and medication. Further, this trial investigated vital outcomes such as well-being, everyday functioning, work capacity, and healthcare burdens, providing valuable insights into the intervention‘s impact.

Declarations

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Contributor Roles Taxonomy (CRediT)

Christopher Lalk: formal analysis, investigation, software, writing - original draft, **Teresa G. Väth**: writing - original draft, formal analysis, **Sofie Hanraths:** writing - original draft, formal analysis, **Luise Pruessner**: writing - review and editing, **Christina Timm**: writing - review and editing, **Steffen Hartmann**: writing - review and editing, **Sven Barnow**: writing - review and editing, **Julian Rubel**: supervision, methodology, project administration, writing - review and editing

External organizations

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Abbreviations

BOCF: baseline Observation carried forward

CBT: cognitive Behavior Therapy

CG: control Group

DIPS-OA: diagnostisches Interview psychischer Störungen – open Access

iCBT: internet-based cognitive Behavior Therapy

J2R imputation: jump to reference imputation

IG: intervention Group

LOCF: last Observation carried forward

MICE: Multivariate Imputation by chained Equations

RCI: reliable Change Index

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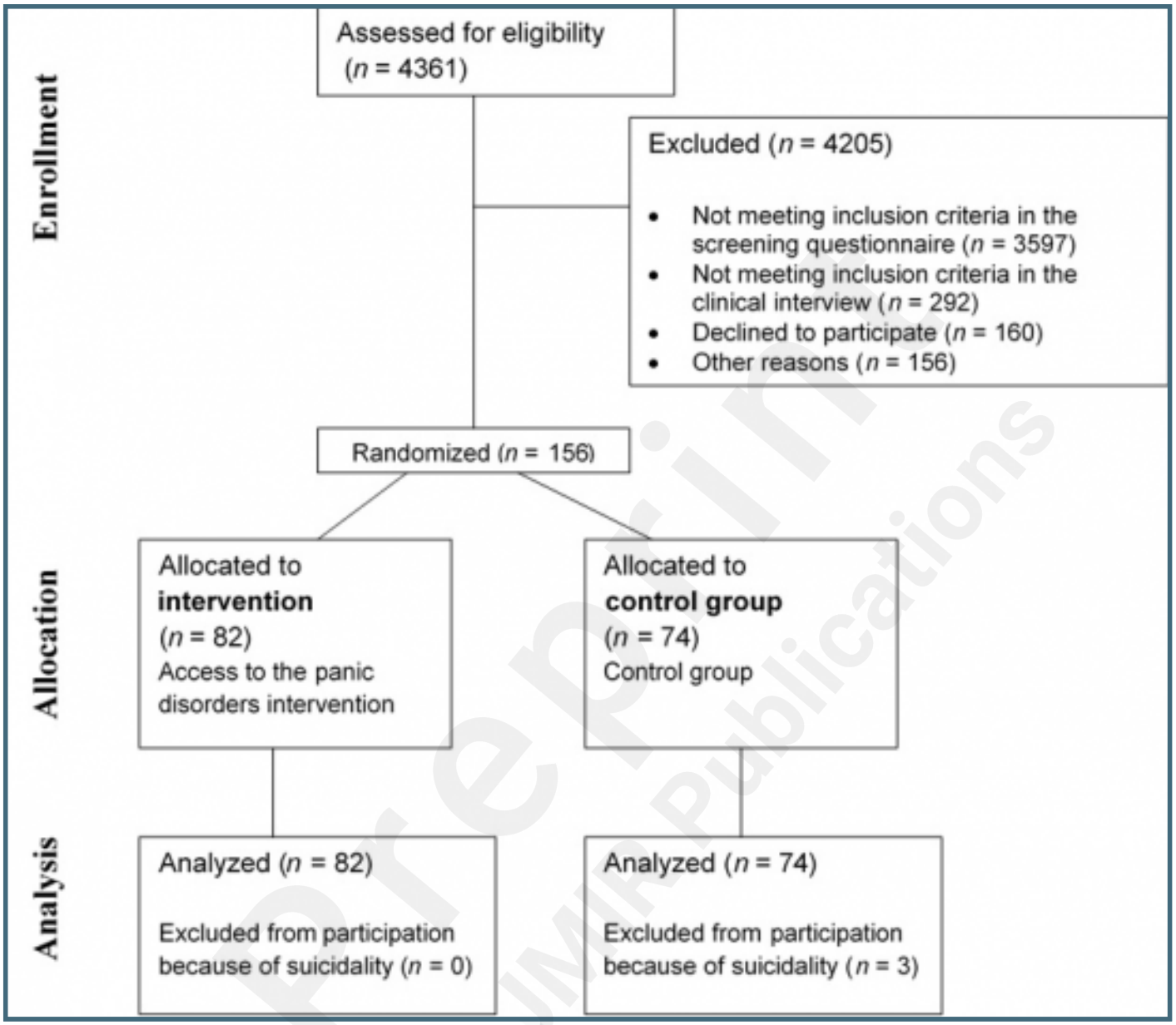
Supplementary Files

Figures

Flow Diagramm. Some numbers were different for secondary or exploratory outcomes.



Multimedia Appendixes

Online Support Material.
URL: http://asset.jmir.pub/assets/fa35e9007d2a7c5e1cd24a8b2761450f.docx

TOC/Feature image for homepages

Computer therapy.