Anzeilax, a Smartphone-based Digital Therapeutic for Generalized Anxiety Disorder: A Randomized Controlled Trial

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Chanmi Park[1, 2] MA; Hyunsil Song[1, 2] BA; Hanna Kim[1] BA; Eunji Kim[3] MA; Hye-Jeong Jo[3] BA; Jae-Jin Kim[3, 4] MD, PhD; Jee Hang Lee[5, 6] PhD; Jinwoo Kim[1, 2] PhD

[1]HAII Corp. Seoul KR
[2]Human Computer Interaction Lab, Department of Cognitive Science, Yonsei University Seoul KR
[3]Institute of Behavioral Science in Medicine, Yonsei University College of Medicine Seoul KR
[4]Department of Psychiatry, Yonsei University College of Medicine Seoul KR
[5]Institute for Advanced Intelligence Study Daejeon KR
[6]Department of human centered AI, Sangmyung University Seoul KR

Corresponding Author:
Jee Hang Lee PhD
Department of human centered AI, Sangmyung University
20 Hongjimun 2-gil, Jongno District
Seoul
KR

Abstract

Background: Individuals with generalized anxiety disorder (GAD) often face challenges with self-regulation and limited access to traditional therapy. While Acceptance and Commitment Therapy (ACT) has demonstrated both efficacy and effectiveness in promoting psychological flexibility, scalable solutions are necessary to address these barriers. This study introduces Anzeilax, an ACT-based digital therapeutic (DTx) that incorporates self-talk as a novel mechanism of action (MoA) to enhance psychological flexibility in the treatment of GAD.

Objective: This study aimed to evaluate the efficacy of Anzeilax in reducing anxiety symptoms in individuals with GAD.

Methods: A 10-week, parallel-group, superiority randomized controlled trial was conducted with 96 participants diagnosed with GAD (GAD-7 scores ?10, age ?19 years). The participants were randomly assigned (1:1) to receive either Anzeilax, a self-guided ACT-based DTx incorporating self-talk content alongside treatment-as-usual (n=48), or treatment-as-usual alone (n=48). Only the outcome evaluators were blinded to the group assignment. The primary outcome was the change in GAD-7 score from baseline to week 10. The secondary outcomes included the Beck Anxiety Inventory (BAI) for anxiety symptoms, the Penn State Worrying Questionnaire (PSWQ) for pathological worry, and the Hospital Anxiety and Depression Scale (HADS) for anxiety and depression symptoms. All self-report outcomes were assessed at baseline and at weeks 5, 10 (post-intervention), and 15 (follow-up).

Results: During the trial, 34 (71%) and 31 (65%) participants in the treatment group maintained at least 80% of the prescribed usage frequency at weeks 5 and 10, respectively. Based on the Full Analysis Set (FAS), participants using Anzeilax demonstrated significant improvement in anxiety symptoms compared to the control group. Analysis of the primary outcome at 10 weeks post-intervention compared to baseline exhibited a significant reduction in GAD-7 scores (adjusted mean difference: -2.26; 95% CI: -3.78 to -0.74, P=.002). Secondary outcomes at the same time point indicated consistent improvements, with significant group-by-time interactions observed in the GAD-7 (P=.008, Cohen d=0.60), BAI (P=.008, Cohen d=0.50), PSWQ (P=.002, Cohen d=0.62), and HADS-A (P=.014, Cohen d=0.50). These improvements were sustained throughout the 15-week follow-up period. While the differences in depressive symptoms between the two groups did not present statistical significance, notable improvements were observed in the treatment group.

Conclusions: Anzeilax demonstrated clinically meaningful efficacy in reducing anxiety symptoms when combined with treatment-as-usual. The results showed consistent improvements across multiple anxiety measures, with effects sustained through follow-up. The incorporation of context-sensitive self-talk within an ACT-based DTx framework offers a promising and accessible solution for treating individuals with GAD. Clinical Trial: ClinicalTrials.gov NCT06010654

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[1]Human Computer Interaction Lab, Department of Cognitive Science, Yonsei University, Seoul, Republic of Korea
[2]HAII Corp., Seoul, Republic of Korea
[3]Department of Human-Centered AI, Sangmyung University, Seoul, Republic of Korea
[4]Institute for Advanced Intelligence Study, Daejeon, Republic of Korea
[5]Institute of Behavioral Science in Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea
[6]Department of Psychiatry, Yonsei University College of Medicine, Seoul, Republic of Korea

Corresponding Author:

Jinwoo Kim, PhD
Human Computer Interaction Lab, Yonsei University
HAII Corp.
Rm 501, 428 Samil-daero,
Jongno-gu, Seoul, 03140
Republic of Korea
Phone: (+82) 10 6307 2528
Email: jinwoo@haii.io

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Trial Registration: ClinicalTrials.gov NCT06010654

Keywords: Generalized Anxiety disorder; Randomized Controlled Trial; Acceptance and Commitment Therapy; Self-talk; Digital Therapeutic; mHealth; Digital Health; Mental Health

Introduction

Generalized anxiety disorder (GAD) affects approximately 4% of the population [1,2] which is characterized by persistent and excessive worry that significantly disrupts daily functioning and diminishes quality of life [3,4]. Individuals with GAD often exhibit impaired self-regulation, which perpetuates excessive rumination and worry patterns [5]. This maladaptive cycle undermines their ability to adaptively engage with emotions across various contexts, whether positive, negative, or neutral [6,7].

The Acceptance and Commitment Therapy (ACT) [8] has emerged as an effective intervention for GAD which promotes psychological flexibility and cognitive defusion [9–11]. This approach enables individuals to observe and disengage from distressing thoughts while making value-aligned decisions [12]. However, traditional therapeutic approaches often encounter accessibility barriers due to logistical and scheduling constraints, emphasizing the need for scalable solutions [13]. The advent of smartphone-based digital therapeutic (DTx) has addressed this gap by making ACT-based interventions more widely accessible [14,15]. In addition, several studies have demonstrated significant reductions in anxiety symptoms through these platforms [16–21].

This study introduced *Anzeilax*, an innovative ACT-based DTx that incorporates self-talk as a mechanism of action (MoA) to enhance psychological flexibility and self-regulation. Self-talk – broadly defined as verbalizations or statements directed at oneself to serve self-regulatory functions [22] – is a foundational component of self-regulation theory. It allows individuals to interpret situations, guide their behavior, and regulate emotions [23]. Past studies

demonstrated the efficacy in enhancing focus and self-regulation across various domains, including sports psychology and test anxiety [24,25].

As a mechanism for guiding thoughts and actions, self-talk plays a pivotal role in self-regulation; positive or constructive self-talk enhances focus and motivation, whereas negative or critical self-talk hinders performance [26]. Within the ACT framework, self-talk aligns with the principle of cognitive defusion, which encourages individuals to recognize thoughts as transient mental events, rather than absolute truths dictating behavior [27,28]. This approach transforms self-talk into supportive internal dialogue, helping individuals distance themselves from unhelpful thoughts and refocus on meaningful, value-driven action, effectively bridging self-regulation theory and ACT principles.

Anzeilax adopts self-talk in a context-sensitive manner, tailoring its application to the users' emotional states. During negative emotional states, self-distancing strategies are employed to reduce the intensity of rumination, promote psychological flexibility and diminish the influence of maladaptive thought patterns [29]. Conversely, during positive states, self-referencing techniques are incorporated to foster adaptive emotional engagement, thereby enhancing motivation and alignment with personal goals. By addressing the challenges individuals with GAD face in adaptive emotional processing [30], this context-sensitive approach bridges theoretical insights from ACT and self-regulation theory with practical, personalized interventions.

We conducted a parallel-group, superiority randomized controlled trial (RCT) (ClinicalTrials.gov NCT06010654) to compare the efficacy of *Anzeilax* combined with treatment-as-usual (TAU) against TAU alone in individuals with GAD over a 10-week intervention period, with a 15-week follow-up assessment. Our primary hypothesis was that *Anzeilax* combined with TAU would demonstrate superior efficacy in reducing GAD symptoms compared to TAU alone at the 10-week post-intervention point. Secondary objectives included evaluating the effects of *Anzeilax* on specific anxiety symptoms, worry, and depression at both post-intervention and follow-up. Safety outcomes were also monitored to ensure the long-term sustainability of the intervention.

This study aimed to advance the field of DTx for GAD by evaluating a novel, patient-centered approach that integrates Acceptance and Commitment Therapy (ACT) principles with context-sensitive self-talk. Through this innovative combination, *Anzeilax* seeks to offer an accessible and effective solution for managing GAD symptoms.

Methods

Trial Design

A phase II, randomized (1:1), single blind (evaluator-blind), parallel-group superiority trial with a primary endpoint at 10 weeks after randomization was conducted. The trial protocol was approved by the Korea Ministry of Food and Drug Safety (protocol number: 1289) and registered prospectively with the Institutional Review Board (IRB) of Gangnam Severance Hospital, Yonsei University, South Korea (registration number: 2022-0961-020; project number: 3-2023-0018) and ClinicalTrials.gov (NCT06010654). The trial adhered to the ethical standards in accordance with the Declaration of Helsinki. (see Multimedia Appendix 1 for the CONSORT E-HEALTH Checklist of the trial).

Participants

This clinical trial included adults aged 19 years or older with at least a high school diploma. The participants were required to have been diagnosed with GAD according to the DSM-5 (ICD-10) code 300.02 (F41.1), had a score of 10 or higher on the GAD-7 scale (indicating moderate to severe anxiety), and currently taking the prescribed medication for GAD. Individuals with other anxiety disorders, such as panic, social anxiety, or major depressive disorder (MDD) accompanied by excessive worry (a key symptom of GAD) were also eligible. The participants had to fully understand the purpose, content, and process of the clinical trial and provide written consent to participate.

The participants were excluded if they met any of the following criteria: inability to read the consent form; lack of proficiency in using a smartphone; current or past psychiatric history (including schizophrenia, psychosis, bipolar disorder, or epilepsy); brain injury; cognitive impairment; neurological disorders; intellectual disability; substance or alcohol use disorder, suicidal intent, suicidal ideation, or self-harm within the past 6 months; recent (within the last 3 months) or current participation in cognitive behavioral therapy for anxiety, depression, or mood disorders; enrollment in another clinical study; or if the investigator deemed the participant unsuitable for the trial.

Intervention

Participants in the treatment group were given access to the *Anzeilax* app, a self-guided DTx application developed for iOS and Android platforms and launched in 2023 by HAII Corp. (see Multimedia Appendix 2). *Anzeilax* was designed for daily use over a 10-week intervention period and featured two main programs: *Self-Talk* and *Self-Talk Plus*.

The primary program, *Self-Talk*, delivered one piece of content daily, accompanied by an introductory explanation to enhance user comprehension and engagement. Upon completing *Self-Talk* exercises, participants gained access to *Self-Talk Plus*, which allowed them to express their current emotions by selecting descriptors such as weather icons and emotion words. Based on these context inputs, the program generated customized self-talk exercises for participants to practice independently.

Both *Self-Talk* and *Self-Talk Plus* included two types of exercises: reading ACT-based metaphorical content and self-verbalization, which involved vocalizing responses to guided questions. These practices require users to record their responses while reading or answering prompts and listen to their recordings as a final reflective step, reinforcing therapeutic content.

In addition to the main programs, users could access features such as log history, basic information, and reward badges through the app menu, providing additional motivation and tracking as they progressed through the program.

To enhance user comfort during the listening phase, *Anzeilax* incorporates a voice equalization feature designed to address the common discomfort associated with hearing one's recorded voice. Research on self-talk suggests that individuals often perceive their recorded voice as unfamiliar or uncomfortable due to the absence of the bone conduction component in the sound [31–33]. The voice equalization feature mitigates this discomfort by adjusting the audio frequencies: amplifying mid- and high-frequency bands while attenuating low-, low-mid-, and ultra-high-frequency bands. This process creates a more natural and pleasant auditory experience for users.

To promote consistent engagement, automated push notifications were tailored to adapt to individual usage patterns. Participants were instructed to use *Anzeilax* at least four days per week throughout the 10-week intervention period. If a participant's usage indicated a risk of falling below this threshold, a reminder notification with an encouraging message was sent. For participants who maintained regular usage, motivational messages were delivered to reinforce their engagement.

The frequency and content of these notifications were carefully calibrated to avoid overwhelming users with repetitive or excessive messaging, ensuring sustained adherence to the program without causing notification fatigue.

Study Procedure and Randomization

To facilitate recruitment, the RCT was publicized through multiple channels, including Seoul Metro advertisements, hospital postings, and psychiatric patient community websites. The participants applied for the trial using Google forms. After an initial online screening, the eligible participants underwent a video interview via Zoom with a researcher using the Mini-International Neuropsychiatric Interview [34] to confirm the diagnosis and inclusion criteria.

Prior to the trial, participants received verbal and written explanations of the study procedures and provided written informed consent during a face-to-face baseline assessment meeting. Allocation numbers were generated by the sponsor, sealed in opaque envelopes, and provided to the study researchers. Upon meeting eligibility requirements and providing consent, participants were randomly assigned to either the treatment group (*Anzeilax* and TAU) or the control group (TAU only) by drawing an envelope containing their allocation number.

TAU, applied to both groups, consisted of maintaining participants' existing treatment regimens, including current psychiatric medications. Medication management followed the pharmacological treatment guidelines for GAD established by the Korean Medical Association. Adjustments to medication type or dosage, as deemed necessary by the treating psychiatrist, were allowed and not restricted by the study protocol.

We note that the psychiatrists providing TAU were unaware of their patients' participation in the study. This ensured that TAU was prescribed independently of the research, maintaining

standard care without influence from the study protocol or trial considerations.

Each participant drew a slip marked "treatment group" or "control group" under the supervision of the Clinical Research Coordinator, who documented the randomization date and signed the slip. The randomization number, along with the participant screening number, served as the identification code throughout the trial. As a single-blind (evaluator-blind) study, the randomization records were managed by the principal investigator and a designated randomization officer.

Participants assigned to the treatment group were provided with personal login codes for *Anzeilax* and instructed to use the application at least four times per week over the 10-week intervention period. While participants could flexibly access the application based on their schedules, engagement was encouraged through an incentive system. Follow-up assessments for both groups were conducted at weeks 5, 10, and 15, with all post-baseline assessments administered online.

Participants in both groups received compensation for their involvement in the study. Each participant was provided a participation fee of 20,000 KRW ($15 USD) for the first visit and 10,000 KRW ($7.50 USD) for each online assessment (2nd, 3rd, and 4th assessments), totaling 50,000 KRW ($37.50 USD). Additionally, participants in the treatment group were eligible for up to 150,000 KRW ($112.50 USD) in extra compensation, depending on their level of engagement with the *Anzeilax* throughout the study. Upon completing the trial, participants in the control group were offered access to *Anzeilax*.

Sample Size

A sample size of 66 participants (33 per group) was required to detect a small to medium effect size (Cohen d=0.5) with 80% power between the groups. Accounting for an anticipated 30% attrition rate (19–45%) [20, 35, 36], an additional 15 participants per group were included, resulting in a total sample size of 96 participants (48 per group).

Measures

Assessments were conducted at four time points: baseline (week 0), mid-intervention (week 5), post-intervention (week 10), and at follow-up (week 15). Baseline measurements were completed in person at the hospital, while subsequent assessments were conducted online. The primary outcome measure was anxiety symptoms, assessed post-intervention using the GAD-7 scale [37], a validated tool for measuring the severity of generalized anxiety symptoms.

Secondary outcomes included specific domains of anxiety, evaluated using standardized measures. Cognitive and physical symptoms of anxiety were assessed with the Beck Anxiety Inventory (BAI) [38], worry severity was measured using the Penn State Worry Questionnaire (PSWQ) [39], and overall anxiety and depression symptoms were evaluated using the Hospital Anxiety and Depression Scale (HADS) [40].

Participant safety was monitored throughout the study period via the spontaneous reporting of adverse events. Adverse events were defined as any undesirable clinical or physical findings not present before the trial began, including anticipated side effects. Reported adverse events were classified as mild, moderate or severe based on their severity.

To evaluate participants' engagement and experience, adherence to the intervention was measured, offering valuable insights into their response to *Anzeilax* DTx and TAU. This metric was crucial for assessing the engagement levels and user satisfaction throughout the intervention period.

Statistical Analysis

The analysis was conducted using the Full Analysis Set (FAS) with adjustments made using the Last Observation Carried Forward method. Subsequently, analysis was performed on the per-protocol (PP) population. In cases where discrepancies were observed between the FAS and PP results, the FAS analysis was designated as the primary analysis method, with PP analysis serving as a supplementary approach. To assess consistency, the results of the PP analysis were compared with those of the FAS analysis.

For the primary outcome analysis, the GAD-7 scores were collected through surveys at the first visit (baseline) and after completion (week 10). For the treatment group, the values before (baseline) and after using *Anzeilax* (week 10) were summarized using descriptive statistics. For the control group, the values before starting the TAU (baseline) and after 10 weeks were summarized similarly. For the primary efficacy endpoint analysis of the GAD-7, the between-group comparison of the difference in the scores from baseline to 10 weeks were analyzed using the analysis of covariance (ANCOVA), with baseline values as a covariate. The significance level was set at a one-sided $P<.025$.

To evaluate the secondary outcome, changes over time, and between-group differences in symptom relief compared to baseline for the test and control groups, a repeated-measures analysis of variance (ANOVA) was conducted at 5-week intervals over a total of 15 weeks (10-week intervention and 5-week follow-up periods). The analysis was performed on the GAD-7, BAI, PSWQ, and HADS measurements taken at baseline, 5-week, 10-week, and 15-week follow-up. The significance level was set at a one-sided $P<.025$.

Results

Baseline Characteristics

Between August 14, 2023, and April 11, 2024, 2,034 people were screened for the trial. Of these, 1,723 were excluded because their anxiety levels were lower than 10 on the GAD-7. A total of 311 patients were assessed for eligibility, and 96 (5%) met all the inclusion criteria and were randomized. The sample comprised 96 adults randomized to either the treatment (n=48) or control (n=48) group, of whom 64% were females. The mean (SD) age was 30 (7.87) years, with a range of 19–60 years. Table 1 provides an overview of the demographics and baseline scores for primary and secondary outcomes by group. The post-intervention and follow-up assessments were completed on June 20 and July 25, 2024, respectively.

In the treatment group, 17 participants discontinued the intervention. Among those who completed the trial, the participants practiced an average of 63 and 81 *Self-Talk* and *Self-Talk Plus* sessions, respectively. The frequency of *Self-Talk Plus* practice ranged from 46 to 243. Self-verbalization, which involves vocalizing responses to guided questions, was the most frequently selected program type in *Self-Talk Plus* (reading ACT content: 1,029; self-verbalization: 1,467). In the control group, two participants were lost to follow-up. Thus, 77 participants (treatment arm, n=31; control arm, n=46) completed all the trial assessments (Figure 1).

Table 1. Baseline characteristics of study participants.

	Overall (n=96)	Treatment arm (n=48)	Control arm (n=48)	Chi-square (*df*)	*P* value
Age, mean (SD)	30 (7.87)	32.4 (8.73)	29.4 (6.73)	N/A	N/A
Gender, n (%)				X^2_1=0.45	.83
Male	35 (36)	17 (35)	18 (37.5)	N/A	N/A
Female	61 (64)	31(65)	30 (62.5)	N/A	N/A
Education, n (%)				X^2_3=3.21	.36
Doctoral degree	1 (1)	0	1 (2.1)	N/A	N/A
Master degree	10 (10.4)	6 (12.5)	4 (8.3)	N/A	N/A
Undergraduate degree	59 (61.5)	32 (66.7)	27 (56.3)	N/A	N/A
High school degree	26 (27.1)	10 (20.8)	16 (33.3)	N/A	N/A
Work status, n (%)				X^2_2=5.28	.71
Employed	49 (51)	30 (63)	19 (40)	N/A	N/A
Not employed	43 (45)	16 (33)	27 (56)	N/A	N/A
N/A	4 (4)	2 (4)	2 (4)	N/A	N/A
Anxiety history, mean (SD)				X^2_3=2.39	.5
Less than 1 year	8 (8.3)	3 (6.3)	5 (10.4)	N/A	N/A

1-5 years	57 (59.4)	30 (62.5)	27 (56.3)	N/A	N/A
6-10 years	22 (22.9)	9 (18.8)	13 (27.1)	N/A	N/A
Over 10 years	9 (9.4)	6 (12.5)	3 (6.3)	N/A	N/A
Psychiatric comorbidities, n (%)					
MDD[a]	50 (52)	27 (56)	23 (48)	X^2_1=0.67	.41
PD[b]	25 (26)	8 (17)	17 (35)	X^2_1=4.38	.04
SAD[c]	3 (3)	1 (2)	2 (4)	X^2_1=0.34	.56
Other	23 (24)	8 (17)	15 (31)	X^2_1=2.8	.09
Physical comorbidities, n (%)	21 (21.9)	9 (19)	12 (25)	X^2_1=0.55	.46
Outcomes, means (SD)					
Baseline GAD-7[d]	12.36 (3.49)	12.42 (3.57)	12.31 (3.45)	X^2_{14}=16.7	.27
Baseline BAI[e]	25.10 (10.02)	24.81 (11.4)	25.40 (8.54)	X^2_{36}=50.1	.06
Baseline PSWQ[f]	56.43 (4.7)	57.23 (4.64)	55.65 (4.68)	X^2_{20}=22.6	.31
Baseline HADS-A[g]	11.59 (3.8)	13.44 (3.67)	13.19 (2.63)	X^2_{15}=18.2	.25
Baseline HADS-D[h]	13.31 (3.18)	12.19 (4.10)	11.00 (3.43)	X^2_{16}=21.4	.16

[a]Major Depressive Disorder
[b]Panic Disorder
[c]Social Anxiety Disorder
[d]Generalized Anxiety Disorder-7
[e]Beck Anxiety Inventory
[f]Penn State Worry Questionnaire
[g]Hospital Anxiety and Depression Scale-Anxiety
[h]Hospital Anxiety and Depression Scale- Depression

Intervention Effects on the Primary Outcome

All statistical analyses were conducted using R (version 4.4.1; R core Team, 2024), a widely used open-source statistical computing software. The FAS and PP groups demonstrated reductions in GAD-7 scores from baseline to post-intervention (week 10). In the FAS population, the treatment group's mean GAD-7 score decreased from 12.42 (SD 3.57) at baseline to 8.83 (SD 3.99) at week 10, reflecting a reduction of 3.58 points (95% CI: -4.88 to -2.28). In comparison, the control group's score decreased from 12.31 (SD 3.45) at baseline to 11.04 (SD 4.29) at week 10, indicating a reduction of 1.27 points (95% CI: -2.35 to -0.19). In the PP population, the treatment group (n=31) exhibited a mean reduction of 4.94 points (95% CI: -6.52 to -3.36), with scores decreasing from 12.10 (SD 3.49) at baseline to 7.16 (SD 3.40) at week 10. However, the control group (n=46) showed a reduction of 1.33 points (95% CI: -2.45 to -0.21): , with scores declining from 12.37 (SD 3.49) at baseline to 11.04 (SD 4.37) at week 10 (Table 2).

The analysis of treatment effects using ANCOVA, controlling for baseline scores, revealed significant differences between the groups in both analysis sets. In the FAS, the adjusted mean

difference between groups was -2.26 points (95% CI: -3.78 to -0.74, *P*=.002) with a medium effect size (Cohen *d* = 0.61) (Figure 2). The PP analysis showed an even more pronounced treatment effect, with an adjusted mean difference of -3.74 points (95% CI: -5.41 to -2.07, *P*<.001) and a large effect size (Cohen *d* = 1.05) (Table 3) (see Multimedia Appendix 3).

Table 2. Changes in GAD-7 from baseline to post-intervention (week 10) in FAS and PP population.

	Baseline Mean (SD)	Post-intervention Mean (SD)	Δ Mean (95% CI)
FAS			
Treatment (n=48)	12.42 (3.57)	8.83 (3.99)	-3.58 (-4.88, -2.28)
Control (n=48)	12.31 (3.45)	11.04 (4.29)	-1.27 (-2.35, -0.19)
PP			
Treatment (n=31)	12.10 (3.49)	7.16 (3.40)	-4.94 (-6.52, -3.36)
Control (n=46)	12.37 (3.49)	11.04 (4.37)	-1.33 (-2.45, -0.21)

Table 3. Post-intervention outcomes for GAD-7 in FAS and PP population.

	Adjusted mean difference (SE) (95% CI)	*P* value	Effect size (Cohen *d*)
FAS (Treatment vs. Control)	-2.26 (0.77) (-3.78, -0.74)	.002	0.61
PP (Treatment vs. Control)	-3.74 (0.84) (-5.41, -2.07)	<.001	1.05

Intervention Effects on Secondary Outcome

The secondary outcome measures, including GAD-7, BAI, PSWQ, and HADS subscales for anxiety and depression, were analyzed using repeated-measures ANOVA to examine group-by-time interactions across four time points: baseline, week 5, week 10 (post-intervention), and week 15 (follow-up) (Table 4) (Figure 3).

The analysis of GAD-7 scores revealed a significant group-by-time interaction through post-intervention ($F_{1.95,\ 183.60}$=4.32, *P*=.008) and follow-up (*P*=.009) The treatment group demonstrated greater reductions from baseline (mean 12.42, SD 3.57) to week 10 (mean 8.83, SD 3.99), compared to controls from baseline (mean 12.31, SD 3.45) to week 10 (mean 11.04, SD 4.29), with a medium effect size (Cohen *d*=0.60). Both groups showed initial reductions through mid-intervention week 5; however, the trajectory diverged thereafter. While the treatment group continued to show decreasing GAD-7 scores, the control group demonstrated a rebound effect after week 5, followed by a slight reduction after post-intervention.

The analysis of anxiety symptoms using the BAI revealed a significant group-by-time

interaction through post-intervention ($F_{1.99, 187.11}$= 4.22, *P*=.008) and follow-up (*P*=.004). Despite similar baseline scores in the treatment group, mean 24.81 (SD 11.4), and control group, mean 25.40 (SD 8.54), the treatment group showed substantial reductions through week 10, mean 17.77 (SD 10.6), which were maintained at week 15, mean 17.58 (SD 8.93). The control group showed minimal changes from baseline, mean 25.40 (SD 8.54), to week 10, mean 23.46 (SD 9.99), and week 15, mean 23.44 (SD 10.9). The estimate of mean change difference between groups increased from post-intervention (-5.69, 95% CI -9.92 to 1.45) to week 15 follow-up (-5.85, 95% CI -9.95 to -1.76), indicating a growing treatment effect over time. The change-based effect size was medium (Cohen *d*=0.50).

The PSWQ showed a significant group-by-time interaction through post-intervention ($F_{1.92, 180.93}$= 6.26, *P*=.002) and at follow-up (*P*=.007). The treatment group demonstrated reductions from baseline, mean 57.23 (SD 4.64), to week 10, mean 54.35 (SD 4.84), whereas control group scores remained stable from baseline, mean 55.65 (SD 4.68), to week 10, mean 55.73 (SD 4.93), yielding a medium effect size (Cohen *d*=0.62).

For the HADS, the anxiety subscale showed significant group-by-time interactions through post-intervention ($F_{1.96, 183.96}$= 3.66, *P*=.014) and follow-up (*P*=.039). The treatment group demonstrated greater reductions from baseline, mean 13.44 (SD 3.67), to week 10, mean 10.67 (SD 3.85), compared to controls from baseline, mean 13.19 (SD 2.63), to week 10, mean 12.17 (SD 3.82), with a medium effect size (Cohen *d*=0.50). Although the depression subscale (HADS-D) showed no significant group-by-time interaction through post-intervention ($F_{1.97, 184.92}$= 1.68, *P*=.096) or follow-up (*P*=.101), the treatment group demonstrated notable improvements from baseline, mean 12.19 (SD 4.10), to week 10, mean 10.23 (SD 4.63), compared to more modest changes in the control group from baseline, mean 11.00 (SD 3.43), to week 10, mean 10.25 (SD 4.08), with a small effect size (Cohen *d*=0.30).

Table 4. Impact of the intervention on the secondary outcome measures (FAS).

	Treatment Mean (SD)	Control Mean (SD)	Estimate of mean change difference (95% CI)	*P* value (Group x time)	Effect size (Cohen *d*)
GAD-7[a]					
Baseline	12.42 (3.57)	12.31 (3.45)	0.1 (-1.34, 1.55)		
Mid-intervention (Week 5)	9.77 (3.78)	10.31 (3.89)	-0.54 (-2.12, 1.03)	.008	0.60
Post-intervention (Week 10)	8,83 (3.99)	11.04 (4.29)	-2.21 (-3.91, -0.51)		
Follow-up (Week 15)	8.58 (3.83)	10.21 (4.76)	-1.62 (-3.4, 0.15)	.009	N/A
BAI[b]					

Baseline	24.81 (11.4)	25.40 (8.54)	-0.58 (-4.72, 3.55)		
Mid-intervention (Week 5)	21.10 (11.0)	23.79 (10.8)	-2.69 (-7.17, 1.79)	.008	0.50
Post-intervention (Week 10)	17.77 (10.6)	23.46 (9.99)	-5.69 (-9.92, -1.45)		
Follow-up (Week 15)	17.58 (8.93)	23.44 (10.9)	-5.85 (-9.95, -1.76)	.004	N/A
PSWQ[c]					
Baseline	57.23 (4.64)	55.65 (4.68)	1.58 (-0.33, 3.5)		
Mid-intervention (Week 5)	54.83 (4.94)	56.15 (5.06)	-1.31 (-3.37, 0.74)	.002	0.62
Post-intervention (Week 10)	54.35 (4.84)	55.73 (4.93)	-1.38 (-3.38, 0.63)		
Follow-up (Week 15)	55.08 (4.94)	55.06 (7.31)	0.02 (-2.54, 2.58)	.007	N/A
HADS-A[d]					
Baseline	13.44 (3.67)	13.19 (2.63)	0.25 (-1.06, 1.56)		
Mid-intervention (Week 5)	11.96 (3.75)	12.83 (3.47)	-0.88 (-2.36, 0.61)	.014	0.50
Post-intervention (Week 10)	10.67 (3.85)	12.17 (3.82)	-1.5 (-3.08, 0.08)		
Follow-up (Week 15)	11.19 (4.18)	12.21 (4.34)	-1.02 (-2.77, 0.73)	.039	N/A
HADS-D[e]					
Baseline	12.19 (4.10)	11.00 (3.43)	1.19 (-0.36, 2.74)		
Mid-intervention (Week 5)	11.10 (4.65)	10.33 (3.73)	0.77 (-0.96, 2.5)	.096	0.30
Post-intervention (Week 10)	10.23 (4.63)	10.25 (4.08)	-0.02 (-1.81, 1.77)		

Follow-up (Week 15)	10.42 (4.54)	10.44 (4.21)	-0.02 (-1.82, 1.78)	.101	N/A

[a]Generalized Anxiety Disorder-7
[b]Beck Anxiety Inventory
[c]Penn State Worry Questionnaire
[d]Hospital Anxiety Depression Scale-Anxiety
[e]Hospital Anxiety Depression Scale-Depression

Safety and Adherence

Safety and adherence analyses were conducted only for the treatment group. Throughout the study period, no severe adverse events were reported by any participants receiving *Anzeilax*. Adherence to *Anzeilax* was defined as completing at least 80% of the prescribed usage frequency (20 sessions at 5 weeks and 40 sessions at 10 weeks), as measured using the app usage log data. During the trial, 34 (71%) and 31 (65%) participants in the treatment group maintained at least 80% of the prescribed usage frequency at weeks 5 and 10, respectively.

Discussion

Principal Findings

This study demonstrated the superior efficacy of *Anzeilax*, a novel ACT-based DTx incorporating context-sensitive self-talk, when combined with TAU for the treatment of GAD. Significant between-group differences observed in both FAS and PP analyses, with particularly strong outcomes in the PP analysis. While the adjusted mean difference was slightly below the established GAD-7 minimal clinically important difference (MCID) of four points [41], the results indicated meaningful clinical improvement in anxiety symptoms, supported by consistent positive outcomes across secondary measures.

The intervention's effectiveness was demonstrated by improvements across multiple anxiety measures, notably a substantial reduction in BAI scores (Cohen d=0.50). The concurrent reduction in GAD-7 and BAI highlights a broad therapeutic impact, as these instruments assess complementary dimensions of anxiety. The GAD-7 focuses on cognitive and emotional symptoms, whereas the BAI captures physical manifestations [42]. This comprehensive improvement suggests potential applications beyond the GAD to conditions with prominent physical symptoms, such as panic disorder [43].

The significant improvement in PSWQ highlights the treatment's efficacy in addressing pathological worry, a core feature of GAD. The PSWQ is specifically designed to distinguish pathological worry from normal anxiety by measuring the excessive, pervasive, and uncontrollable nature [44]. Although the GAD-7 assesses broader anxiety symptoms, it offers a more nuanced evaluation of the cognitive worry component central to GAD. The synchronal improvements in both measures demonstrate the comprehensive therapeutic impact of *Anzeilax* on general anxiety symptoms and specific cognitive mechanisms underlying pathological worry.

Although past research on ACT manifested a positive expectation in reducing depressive symptoms [45-47], our results were inconsistent with those findings. Several factors may account for this outcome. First, the fully automated approach used in this study may have contributed to the discrepancy. In previous research, therapists were likely to actively involved in the treatment program [19,48], whereas we employed a fully automated approach without human interaction. Given that therapeutic alliance and human contact are critical components in addressing depressive symptoms [49–51], this methodological difference may have influenced the results. Second, the inclusion of participants without comorbid MDD may have affected the findings. Specifically, 44% of participants in the treatment group (n=21) and 52% in the control group (n=25) did not have MDD as a comorbid condition. This suggests that not all participants exhibited depressive symptoms substantial enough to contribute meaningfully to the analysis. These findings underscore the importance of conducting a post-hoc analysis focusing specifically on participants with comorbid MDD. Such an analysis could provide more targeted insights into the effectiveness of *Anzeilax* for managing depressive symptoms.

To evaluate the lasting effect of *Anzeilax*, follow-up assessments were conducted five weeks after post-intervention. The therapeutic effects exhibited differential patterns across outcome measures. The treatment group maintained reductions in anxiety symptoms as measured by GAD-7 and BAI, whereas PSWQ and HADS-anxiety scores showed some rebound during the follow-up period. This divergence may reflect the distinct dimensions of anxiety assessed by each measure: the GAD-7 assesses core GAD symptoms, the BAI emphasizes physical manifestations of anxiety, HADS-A focuses on general emotional tension and fear, and PSWQ evaluates worry persistence. The latter dimensions may be less stable due to the chronic and dynamic nature of these symptoms. Notably, these findings suggest that *Anzeilax* provides comprehensive effectiveness across various anxiety dimensions during active use, while maintaining particularly strong effects on core anxiety symptoms even after discontinuation.

The findings are consistent with *Anzeilax*'s therapeutic mechanism, which integrates ACT principles with context-sensitive self-talk to enhance psychological flexibility, modulate anxiety-related cognitive and behavioral processes within a contextual behavioral science framework [52]. While *Anzeilax* is designed to improve individuals' relationship with worry rather than eliminate it completely, participants may experience recurring worry loops when not actively engaging with the DTx. Although the 10-week intervention period appears sufficient to initiate cognitive shift through self-talk practices, more deeply ingrained worry habits may require extended or more intensive intervention to sustain consistent improvement during follow-up periods.

The positive outcomes observed in this study can be attributed to the innovative integration of self-talk within the ACT framework. By employing context-sensitive self-talk strategies, *Anzeilax* appeared to enhance the effectiveness of cognitive defusion techniques central to the ACT. The structured vocalization process during negative emotional states likely facilitates psychological distancing from anxious thoughts, whereas self-referencing techniques during positive states reinforced adaptive coping patterns.

This dual approach, rooted in the self-regulation theory and ACT principles, effectively addresses the challenges individuals with GAD face in emotional processing and regulation. Additionally, the self-talk strategy encouraged users to actively engage with the *Anzeilax* program by verbalizing its content aloud and listening to their own words [53,54]. This deliberate action not only reinforced the therapeutic concepts, but also fostered deeper immersion in the intervention. By transforming passive engagement into active participation, this approach may significantly enhance the delivery and effectiveness of ACT's core mechanisms, potentially contributing to therapeutic improvement in individuals with GAD.

Anzeilax is a non-invasive treatment method with minimal risk of adverse events or device-related effects. The absence of adverse events during our trial suggests that *Anzeilax* has a favorable safety profile when used as prescribed for GAD treatment. However, as a self-guided DTx, implementing a systematic reporting mechanism for technical issues will be essential when the product becomes available to the public.

Our findings have several important clinical implications. The digital format of *Anzeilax* enhances accessibility, while sustained follow-up results indicate durable benefits for anxiety management. The integration of self-talk offers patients a practical and actionable strategy for managing their symptoms and observed improvements across anxiety-specific and general emotion regulation measures suggest potentially broader benefits for overall emotional well-being.

Limitations

This study had some limitations. First, the single-blind design (evaluator-blind) meant that the participants were aware of their group assignments, potentially introducing a response bias in self-reported outcomes. Although the sustained effects observed during the follow-up period suggest a genuine therapeutic effect rather than expectancy effects, future studies would benefit from implementing an active control condition using a sham device to minimize such bias. Given the recurring nature of psychological disorders, future studies should examine the sustainability of therapeutic gains beyond the 15-week follow-up period. Additionally, to better understand the intervention's MoA, studies should aim to differentiate the specific contributions of context-sensitive self-talk from the standard ACT components.

Conclusions

In conclusion, this study provides evidence of the efficacy of *Anzeilax* and demonstrates that the integration of context-sensitive self-talk within an ACT-based DTx framework can effectively reduce anxiety symptoms in individuals with GAD. Consistent improvements across multiple measures of anxiety and worry, coupled with the maintenance of these gains at follow-up, suggest that this approach offers a promising scalable solution for the treatment of GAD. The absence of severe adverse events and reasonable adherence rates further support the feasibility and safety of implementing *Anzeilax* in clinical practice.

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Author contributions

J.-J.K. designed the study; C.P. and J.K. led the conceptualization of the intervention. E.K. and H.-J.J. performed the data collection. C.P., H.S. and H.K. conducted data analysis.; J.K. and J.H.L. supervised data analysis and manuscript writing. C.P. and H.S. wrote the original manuscript. J.H.L., J.-J.K and J.K. reviewed, revised and edited the paper. All authors approved the final version for submission. J.K. led the whole project. Funding acquisition was led by J.K..

Conflicts of Interest

HAII Corp. provided research support and contributed to the study conceptualization, trial design, implementation and manuscript preparation. J.K. is CEO of HAII Corp.. C.P., H.S. and H.K. are employees of HAII Corp..

Abbreviations

ACT: Acceptance and Commitment Therapy

ANCOVA: Analysis of covariance

ANOVA: Analysis of variance

BAI: Beck Anxiety Inventory

DTx: Digital Therapeutic

FAS: Full Analysis Set

GAD: Generalized Anxiety Disorder

GAD-7: Generalized Anxiety Disorder-7

HADS: Hospital Anxiety and Depression Scale

IRB: Institutional Review Board

MCID: Minimal clinically important difference

MDD: Major depressive disorder

MoA: Mechanism of action

PD: Panic disorder

PP: Per-Protocol

PSWQ: Penn State Worry Questionnaire

RCT: Randomized controlled trial

SAD: Social anxiety disorder

TAU: Treatment-as-usual

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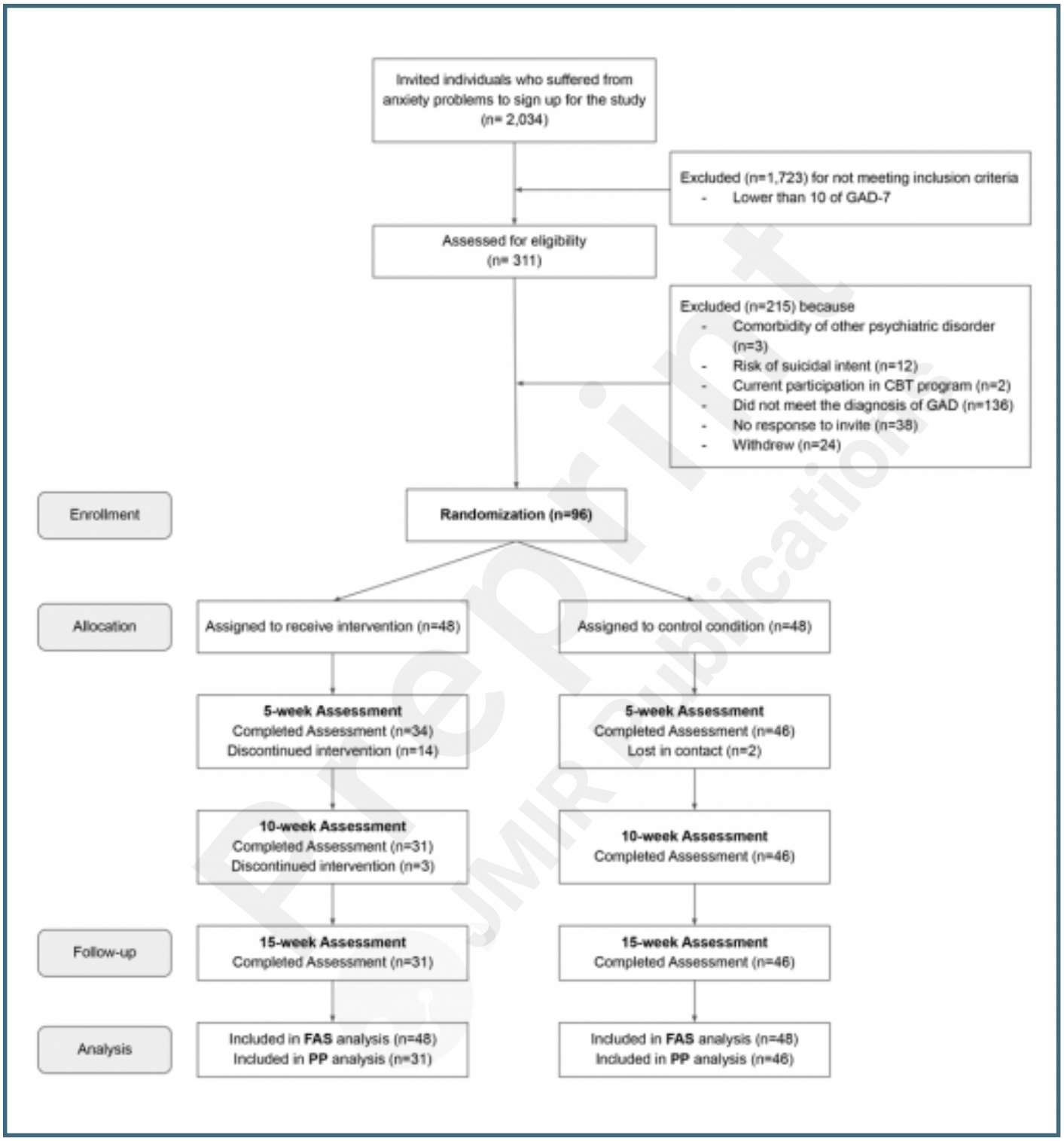
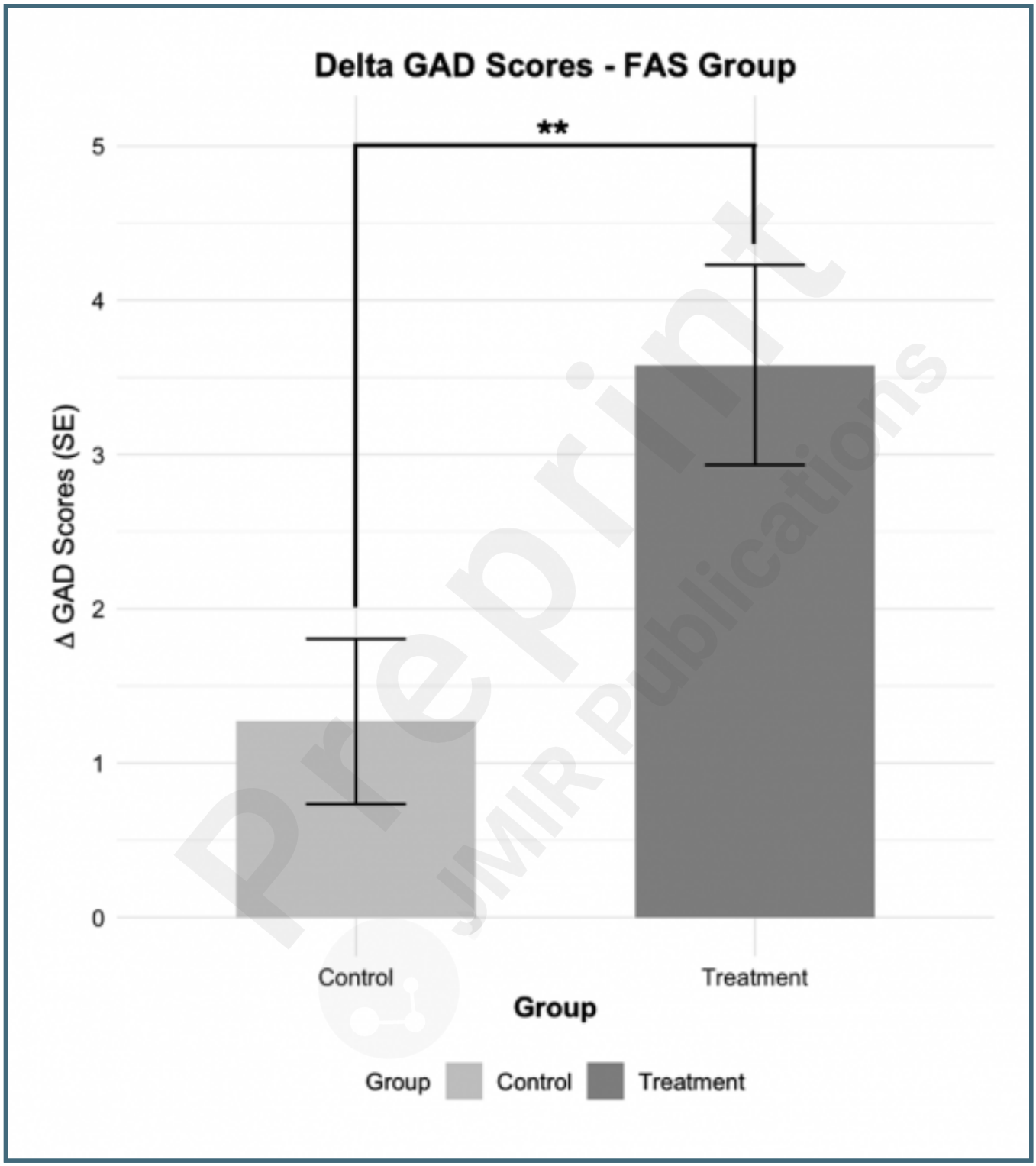
Supplementary Files

Figures

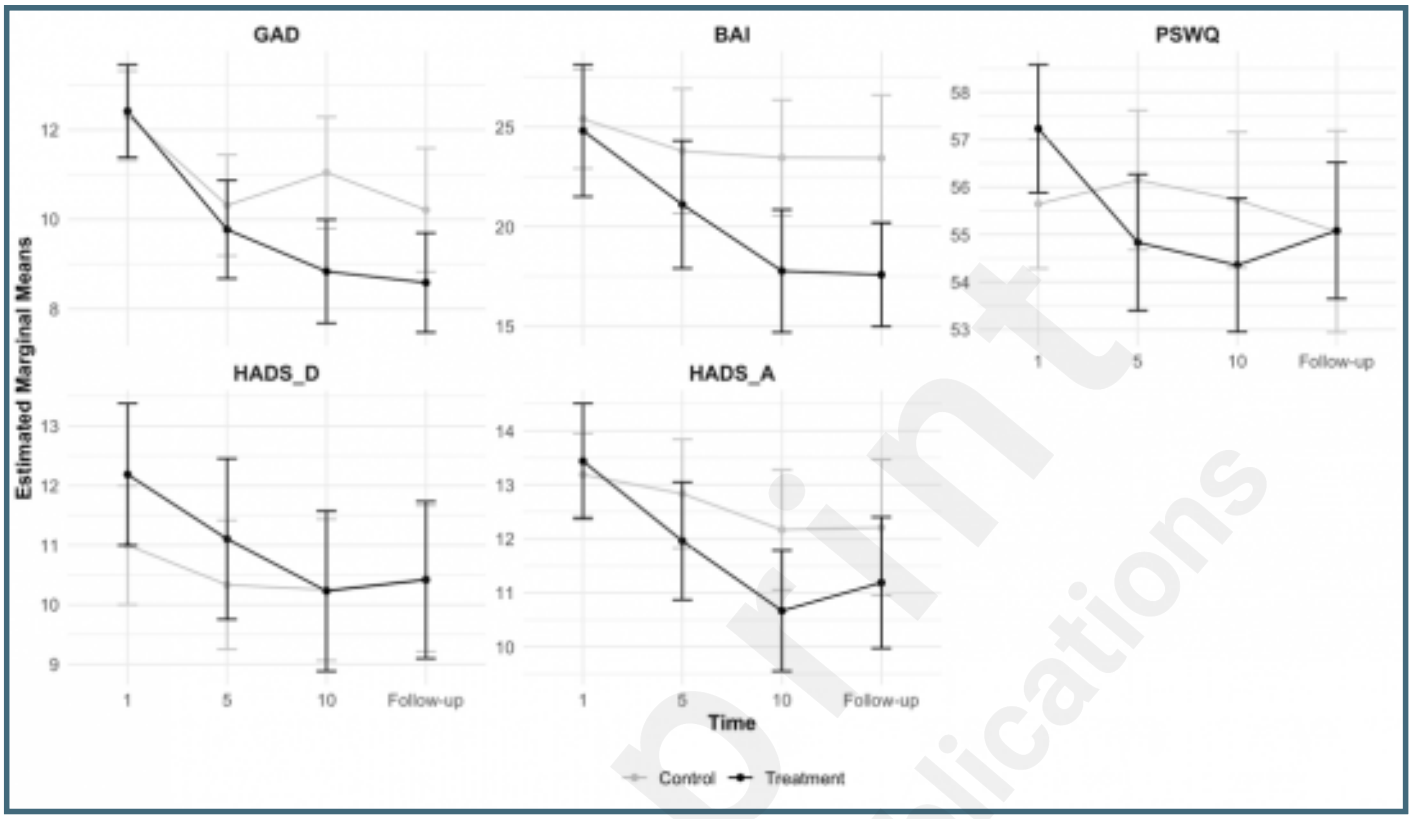
Consort flow diagram of participants.



Comparison of the adjusted mean difference in GAD-7 between treatment and control (week 10) groups in FAS.



Changes in mean BAI, PSWQ, HADS-Anxiety, HADS-Depression between treatment and control groups in FAS.



Multimedia Appendixes

CONSORT E-HEALTH Checklist (V 1.6.1).
URL: http://asset.jmir.pub/assets/f6bab0c3abf7df702e5e97cefd5c338a.pdf

A snapshot of Anzeilax.
URL: http://asset.jmir.pub/assets/99186f45ce82253aaab65b36a3588416.pdf

Supplementary analysis.
URL: http://asset.jmir.pub/assets/3b302c10d96dc2e923c578cf4dd7087e.pdf