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# Clinician guidance in digital therapeutics for panic disorder: Meta-analytic dissection and implications for regulatory framing and scalable deployment

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ABSTRACT

*Background:* Digital therapeutics (DTx) have emerged as scalable and accessible treatment modalities for panic disorder.

*Objective:* This study aimed to identify the extent to which clinician guidance impacts the digital intervention effectiveness for panic disorder across multiple clinical outcomes.

*Methods:* This study included 40 randomized controlled trials of digital intervention for panic disorder published up to March 2025. Eligible studies enrolled adults with a primary diagnosis of panic disorder (with or without agoraphobia) and compared a digital therapeutic intervention against active (therapist-led or treatment-as-usual) or passive (waitlist or no-treatment) controls. Outcomes were the Panic Disorder Severity Scale (PDSS), Agoraphobic Cognitions Questionnaire (ACQ), and Body Sensations Questionnaire (BSQ). Random-effects meta-analyses, subgroup analyses, sensitivity analyses, and mixed-effects meta regressions were conducted. The moderator variables included the comparator type, guidance format (clinician-guidance or self-guided), intervention modality, and region.

*Results:* Self-guided DTx demonstrated a moderate effect size on PDSS (Hedges' g =0.31, 95 % confidence interval [CI]: 0.05–0.68), whereas clinician-guided interventions exhibited stronger effects (g =0.95, 95 % CI: 0.44–1.46). These findings indicate that well-structured self-guided interventions can address symptom domains, involving panic frequency and physiological distress. Conversely, cognitive-focused outcome assessment using ACQ and BSQ revealed that only clinician-guided interventions yielded statistically significant and clinically meaningful improvements (ACQ: g =0.46, 95 % CI: 0.15–0.76; BSQ: g =0.67, 95 % CI: 0.30–1.05), whereas self-guided formats exhibited negligible effects (ACQ: g =0.11; BSQ: g =0.27).

*Conclusions:* This meta-analysis revealed that self-guided digital interventions effectively reduce the overall symptom severity in panic disorder, whereas clinician involvement exerts a notably stronger influence on cognition-related outcomes. These findings support a domain-specific and context-sensitive understanding of guidance. Accordingly, the DTx design and policy should match the mechanistic pathways through which psychological change will occur.

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## 1. Introduction

Digital therapeutics (DTx), defined as evidence-based software-driven interventions designed to prevent, manage, or treat medical disorders (DigitalTherapeuticsAlliance, 2025), are rapidly transforming the field of mental health care (Torous et al., 2021). In contrast to conventional therapy models that depend on in-person sessions, DTx platforms, including mobile cognitive behavioral therapy (CBT) applications, virtual reality exposure therapy (VRET), and conversational agents, provide scalable (Rathbone et al., 2017), accessible (Pot-Kolder et al., 2020), and potentially cost-efficient alternatives for both patients and healthcare systems (Jankovic et al., 2022; Naslund et al., 2022). These interventions have gained momentum despite increasing demands for mental health services, particularly in underserved or resource-limited settings where clinical personnel are scarce and geographical barriers limit care access. DTx scalability and standardization have drawn substantial interest from regulatory bodies, including the United States Food and Drug Administration (US FDA) and the European Medicines Agency (EMA), currently recognizing DTx as a distinct therapeutic modality eligible for market authorization under the software-as-a-medical-device framework (IMDRF, 2013).

DTx are frequently promoted for their independent administration and potential as standalone treatments; however, several clinical trials have indicated improved success when these interventions are accompanied by clinician guidance (Oey et al., 2023; Seo et al., 2024). Randomized studies and meta-analyses reveal that guided DTx, particularly those incorporating therapist-facilitated CBT components, consistently demonstrate higher engagement (Akdemir et al., 2024), adherence (Musiat et al., 2022), and effect sizes (ESs) compared with unguided versions (Moshe et al., 2021). Consequently, clinician involvement is frequently associated with improved treatment engagement and outcome, which may benefit from interpersonal support (Andersson & Titov, 2014; Karyotaki et al., 2021; Musiat et al., 2022). However, this interpretation may obscure a crucial distinction. From a regulatory and scalability perspective, clinical guidance is not mandated as a required component; rather, it can function in multiple ways; (a) as a uniform enhancer of outcomes, (b) as a moderator whose influence varies by outcome domain, comparator type, or delivery modality, or (c) as a confounding factor that complicates interpretation due to overlaps with design elements such as comparator intensity or attrition (USFDA, 2017, 2018). Noteworthily, the regulatory context requires that DTx can produce clinically reproducible meaningful results in terms of clinical validation regardless of its use of DTx as a standalone or adjunctively in a therapeutic context (Lutz et al., 2022).

The discrepancy between efficacy-oriented research frameworks and vague regulatory requirements causes a significant tension that requires both empirical and conceptual resolution. Meta-analyses and randomized trials consistently reveal that guided interventions outperform unguided interventions, thereby reinforcing the notion that therapist involvement is crucial for therapeutic success (Cuijpers et al., 2019; Karyotaki et al., 2021). This interpretation overlooks the broader implementation context of DTx deployment. The presence of guidance prompts essential inquiries regarding scalability, cost-effectiveness, and practical applicability, particularly in systems experiencing workforce shortages and geographic disparities (Gega et al., 2022; Naslund et al., 2022). Consequently, a thorough analysis of guidance effects is crucial for identifying scientific interpretations of efficacy and for informing regulatory pathways and payer decisions that increasingly require evidence of independent effectiveness.

This study empirically investigates the complex role of clinician guidance as a potential moderator, rather than a presumed enhancer, in patients with panic disorder (with or without agoraphobia). Clarifying this distinction is critical for both scientific and regulatory reasons: it determines whether guidance should be considered an indispensable element of digital CBT or a context-dependent design feature that can be intentionally incorporated where it adds value, while preserving the stand-alone integrity required for scalable deployment. Panic disorder involves discrete, intense panic attacks marked by physiological symptoms (e.g., palpitations, shortness of breath) and a range of secondary cognitive–behavioral symptoms, including anticipatory anxiety, avoidance, and catastrophic misinterpretations of bodily sensations (Roy-Byrne et al., 2006). This dual structure—combining biologically driven panic and learned maladaptive responses—creates heterogeneity in symptoms and treatment targets (Association, 2013; Barlow, 2002). While clinical trials often prioritize overall severity measures such as panic frequency and intensity for regulatory endpoint, CBT therapeutic processes emphasize cognitive restructuring and behavioral change targeting distortions and avoidance patterns (Barlow, 2002; CHMP; EMA, 2005; Roy-Byrne et al., 2006). This divergence makes panic disorder an ideal model to assess how clinician guidance may differentially affect behavioral and cognitive outcomes in digital CBT. Panic disorder has been extensively investigated through several randomized controlled trials (RCTs) that focus on internet-based CBT (ICBT), mobile applications, and virtual reality (VR) interventions (Apolinário-Hagen, 2019; Jung et al., 2025). The heterogeneity of symptoms and the density of research render panic disorder a suitable model for assessing the independent and interactive effects of clinician guidance in the delivery of digital CBT.

While existing meta-analyses have focused on overall treatment efficacy or psychotherapy comparisons in panic disorder, none have systematically examined how clinician guidance moderates digital therapeutic effectiveness across specific symptom domains. A meta-analytic approach is warranted to systematically quantify the influence of clinician guidance in DTx for panic disorder, considering the variability in guidance formats and the significance of standalone approval in policy contexts. This study investigates the impact of this distinction on regulatory interpretation, particularly concerning standalone approval pathways that require DTx to demonstrate efficacy without professional oversight. The primary question of this study was "To what extent does clinician guidance impact the effectiveness of digital interventions across various symptom domains?" The primary hypothesis posits that clinician guidance improves outcomes, although its effects vary in terms of outcome type and study design and may be unnecessary in certain circumstances. Our findings are intended to guide clinical deployment strategies, as well as regulatory and market-access frameworks, that prioritize scalability and health system efficiency.

## 2. Materials and methods

### 2.1. Protocol and registration

This systematic review and meta-analysis complied with the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines and conformed to the registered online procedure at PROSPERO (CRD42023457618). The study protocol was prospectively registered prior to data extraction and analysis. Any minor protocol amendments were documented and reported in accordance with PROSPERO requirements.

### 2.2. Study selection criteria

The Population, Intervention, Comparison, Outcomes, and Study framework was employed to develop the search strategy (Table 1). The literature search was performed for the inclusion of the following study categories: RCTs that compare single- or multicomponent interventions against no intervention, placebo, or standard care. Further, the reference lists of the included original research and previous reviews were manually assessed to discover any further acceptable investigations. To mitigate the risk of publication bias, both eligible published and unpublished studies were evaluated for inclusion.

**Table 1**
PICO-S framework for the eligibility of the study.

| Criteria | Eligible groups |
|---|---|
| Population (P) | Panic disorder with or without agoraphobia |
| Intervention (I) | Digital therapeutics, including digital health, digital medicine, Cognitive behavioral therapy (CBT), internet-based, online, virtual reality, mobile app, smartphone, chatbot, eHealth, and software as a medical device |
| Comparison (C) | (1) active controls (therapist-led interventions or standard care therapy as usual) and (2) passive controls (waitlist or no interventions and follow-ups). |
| Outcomes (O) | Clinical outcome: reducing panic disorder symptoms |
| Study Design (S) | Randomized controlled trials |

#### 2.2.1. Participants

Eligible study participants were aged 18 years or over with a primary diagnosis of panic disorder with or without agoraphobia based on any standard operationalized criteria— Diagnostic and Statistical Manual of Mental Disorders (DSM) up to the fifth version, and International Classification of Diseases, tenth version (ICD-10). Studies were required to clearly document diagnostic criteria used for participant inclusion. Studies enrolling participants with comorbid conditions were eligible if panic disorder was the primary diagnosis

#### 2.2.2. Interventions

Interventions are mainly focused on DTx, including medical devices, cell phones (smartphones), any device using applications through the internet, or any other technology or mobile devices. Digital interventions had to be specifically designed to target panic disorder symptoms as a primary therapeutic focus. Treatment through medicine, standard of care, or no interventions and follow-ups could be considered as eligible interventions to be selected for this study if several intervention treatment groups are observed.

#### 2.2.3. Comparators

Control conditions were classified as (1) active controls (therapist-led interventions or standard care therapy as usual) and (2) passive controls (waitlist or no interventions and follow-ups). Active controls included any evidence-based psychological or pharmacological treatment provided as comparison conditions. Passive controls represented conditions where participants received no active intervention during the study period.

#### 2.2.4. Outcomes

Eligible studies were those that reported at least 1 mental health outcome, including the Panic Disorder Severity Scale (PDSS), Panic and Agoraphobia Scale (PAS), Agoraphobic Cognitions Questionnaire (ACQ), Body Sensations Questionnaire (BSQ), and Anxiety Sensitivity Index (ASI), and provided the outcome data required to calculate the ES to reduce panic disorder symptoms as a primary outcome. The PDSS provides a comprehensive index of overall clinical severity by assessing multiple dimensions, including the frequency and intensity of panic attacks, anticipatory anxiety, phobic avoidance, and functional impairment. It is generally regarded as the gold standard in both clinical and research settings for measuring treatment response and disorder severity following the DSM-based criteria. The ACQ measures the intensity of maladaptive cognitions that are frequently associated with panic episodes, such as catastrophic fears of dying, losing control, or going insane. These cognitive distortions are crucial to the pathophysiology of panic disorder and are the primary targets of CBT, making the ACQ a valid index of the cognitive-level treatment response. BSQ captures the degree of fear or sensitivity toward somatic sensations typically associated with panic attacks, including palpitations, dizziness, and chest tightness. Interoceptive sensitivity plays a central role in the maintenance of panic disorder; thus, the BSQ provides a crucial physiological dimension for assessing clinical change, especially in response to exposure-based interventions.

### 2.3. Search strategy

We conducted a systematic literature search of PubMed (MEDLINE), Embase, APA PsycINFO, Cochrane Library, and Web of Science databases, up to March 30, 2025. A search was conducted with the PICO framework for the titles and abstracts of the literature. The full search terms used in each database are provided in Supplementary table 1.

### 2.4. Study selection and data extraction

Two authors independently assessed the titles and abstracts of the references identified by the electronic search strategies to check whether the study was relevant concerning the following predefined inclusion criteria. Any uncertainties during the initial screening were flagged for discussion during the full-text review stage. Inclusion criteria were (a) participants were aged 18 years or over with a primary diagnosis of panic disorder with or without agoraphobia following any standard operationalized criteria (Research Diagnostic Criteria, DSM up to the fifth version, and ICD-10); (b) treatment was designed to reduce panic disorder symptoms as a primary outcome; (c) panic disorder symptoms were evaluated using a validated self-report or investigator-report measure, including the PDSS, PAS, ACQ, BSQ, ASI, etc.; (d) active treatment including DTx was delivered; (e) adopted an RCT design.

Two authors reviewed the full text of all studies that were identified by at least one author. The inclusion of studies that have been assessed differently by the two authors was reviewed in light of the discussion, and an additional author was involved, if necessary. Pilot-tested and prespecified data extraction forms were employed to extract relevant data from the original articles, including diagnosis criteria, age of study participants, geographical region where the study was conducted, type and contents of the intervention, comparison groups with the intervention group, and primary and secondary outcomes. Identified articles were first screened through the contents of the abstract by independent reviewers and then proceeded to the second review through the full text review, also by independent reviewers. Regarding the final selection of the studies, two reviewers had an alignment discussion for the appropriateness of the study inclusion.

### 2.5. Quality assessment

A modified version of the Cochrane Risk of Bias 2.0 instrument for RCTs was utilized to assess the quality of the included studies (Sterne et al., 2019). Five distinct domains were assessed: (1) the randomization process; (2) deviations from the intended interventions; (3) missing outcome data; (4) outcome measurement; and (5) selection of the reported result. The risk of bias was assessed and reported as “low risk,” “some concerns,” or “high risk of bias.”

### 2.6. Statistical analysis

R software (version 4.4.1) was used for analyses. Pair-wise meta-analyses with a random-effects model were conducted for every comparison of at least two studies. The treatment effect was measured by comparing the mean scores before and after treatment and using the difference between each study arm’s pre- and post-treatment scores of reported outcome measures to calculate Hedges g, which is the ES. Intention-to-treat data were favored over per-protocol data when both data were available (López-López et al., 2018). Employing a random-effects model, the ES of the separate investigations were combined and displayed in forest plots along with the pooled prediction interval of ES. In cases where the original study used a multiple-arm RCT design, including mutually exclusive intervention groups compared with a common comparator, each comparison between an intervention arm

and the control arm was considered an independent ES estimate. Accordingly, these comparisons were entered as distinct entries in the meta-analysis and were individually represented. The Cochrane Q test, with a statistical significance of $P < 0.05$ and $I^2$ statistics, was used for heterogeneity assessment. Low, medium, and high heterogeneity are generally indicated by $I^2$ values of 25 %, 50 %, and 75 %, respectively. The Egger's test of the intercept was conducted with a one-tailed significance level of α of 0.05, and publication bias was analyzed by investigating the funnel plot.

The categorical variables were subjected to subgroup analysis and meta-regression using the same variables. The subgroup analyses involved stratified ES estimation across each variable, whereas the combined subgroup categories were used to assess the interaction effects. Meta-regression was conducted using mixed-effects models to estimate the independent contribution of each variable to the between-study heterogeneity. We applied a stepwise selection approach to construct an optimal model. To address potential effect size dependencies from multiple comparisons within studies, we conducted sensitivity analyses using study-level aggregation and robust variance estimation (RVE) with CR2 small-sample correction.

## 3. Results

Overall, 983 studies were identified through the systematic search of PUBMED, EMBASE, Web of Science, Cochrane Library, and PsycINFO after deleting 700 duplicated records. An additional 48 studies were manually searched from the citations of the relevant articles. Finally, 40 studies were included in the systematic review and meta-analysis (Fig. 1).

Table 2 presents the study characteristics. This study included 40 studies published up to March 2025 and conducted in Asia, Europe, Australia, and other regions. These studies reported various outcomes of panic disorder and anxiety, including the PDSS, PAS, ACQ, BSQ, and ASI.

Among the 40 studies, 23, 21, and 15 reported the PDSS, ACQ, and BSQ as primary or secondary outcome measures, respectively. To evaluate the multidimensional assessment of the clinical improvement of panic disorder, we conducted a meta-analysis of the PDSS, ACQ, and BSQ, which represent symptom severity, cognitive distortions, and somatic hypervigilance, with the reported results for each outcome, respectively. Each meta-analysis was conducted using all available studies that reported the respective outcome measure.

### 3.1. PDSS

Table 3 summarizes the results of the overall meta-analysis and subgroup analyses for changes in panic disorder severity as measured with the PDSS. The pooled ES for the outcome of the pre- and post-treatment difference of PDSS exhibited a statistically significant difference between the intervention and control groups across all 28 comparisons (g: 0.72; 95 % confidence interval [CI]: 0.36–1.08) (Table 3). These results indicate that the studied digital treatment options have proven to be clinically valid treatments, as represented by PDSS metric improvement.

Subgroup analyses revealed substantial differences in terms of comparator type, guidance format, intervention modality, and region.

For the outcome of the pre- to post-treatment change in PDSS, the pooled ES across 11 comparisons involving active comparators revealed no statistically significant difference between the digital interventions and control conditions (g= −0.06; 95 % CI: −0.28–0.17). Compared with active controls, including CBT, DTx were noninferior to traditional treatments. No significant heterogeneity among the pooled studies was found using the Cochranes Q test and $I^2$ statistics ($I^2$: 15.05 %; Q:14.45; df:10; *p*-value =0.1533). The funnel plot and Egger's test indicate no publication bias.

In contrast, when compared against passive control groups (e.g.,

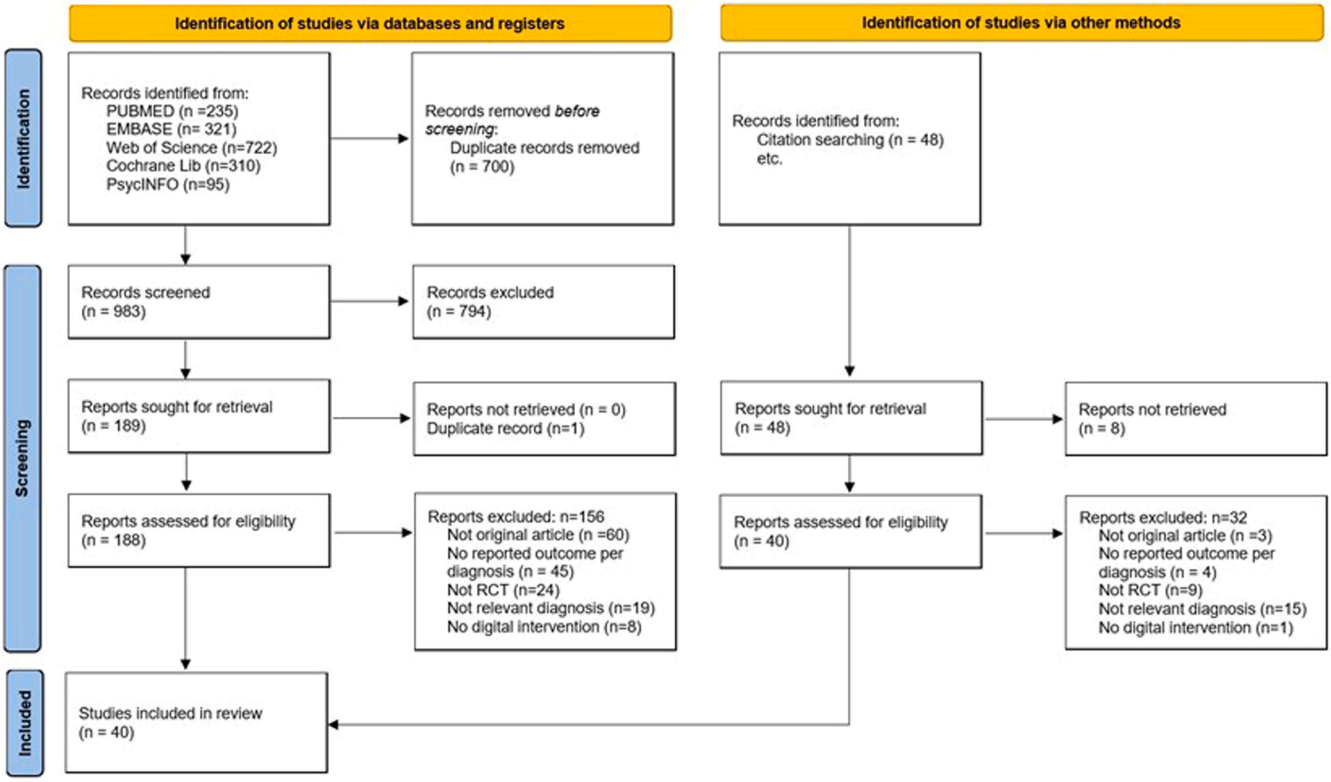


**Fig. 1. PRISMA flow diagram for the literature review,** Note. PRISMA flow diagram showing the study selection process for the systematic review and meta-analysis. A total of 983 unique records were screened after duplicate removal. Following title/abstract screening and full-text eligibility assessment, 40 randomized controlled trials evaluating digital therapeutics for panic disorder were included in the final analysis.

**Table 2**
Characteristics of the included studies.

| Study | | Primary diagnosis | Diagnosis criteria | Age | Treatment comparison | | | | | Outcome measures | Country |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Intervention | | Sample size | Control | Sample size | | |
| 1 | Schultz et al., 2025 (Schultz et al., 2025) | Panic disorder | DSM-V[1] | 18–80 years | App-based Internet-based CBT (ICBT) program with self-guided virtual reality exposure therapy (VRET) | 8 modules in 12 weeks | 63 | Care as usual | 61 | BAI[2], PAS[3], BDI-II[4], CSQ[5], AAQ[6], and WHOQOL-BREF[7] | Germany |
| 2 | Spies et al., 2025 ( Spies et al., 2025) | Panic disorder with or without agoraphobia | DSM-V | ≥ 18 years | Smartphone-based self-management tool (mindable™) | Daily treatment for 8 weeks | 57 | Waitlist | 50 | PAS, WHOQOL-BREF, **ACQ**[8], SDS[9], and CSQ-I | Germany |
| 3 | Kim et al., 2024 ( Kim et al., 2024) | Panic disorder | DSM-V | 20–65 years | A smartphone-based app for treating the clinical symptoms of panic disorder, panic symptoms, depressive symptoms, and anxiety | 20 sessions in 4 weeks | 25 | Control | 25 | **PDSS**[10], HAM-A[11], and GAD−7[12] | Korea |
| 4 | Stech et al., 2021 ( Stech et al., 2021) | Panic disorder | DSM-V | ≥ 18 years | Internet-delivered exposure therapy program | 6 lessons in 8 weeks | 35 | ICBT | 34 | **PDSS**, MI[13], PHQ−9[14], WSAS[15], and DOR[16] | Australia |
| 5 | Shin et al., 2021 ( Shin et al., 2021) | Panic disorder | DSM-V | 19–60 years | 4-week VR-based CBT with a total of 12 sessions | 12 sessions in 4 weeks | 33 | Waitlist | 21 | **PDSS**, HRSD[17], STAI_S[18], STAI_T[19], KIDS_SR[20], PSS[21], KSAD[22], ASI[23], HADS[24], APPQ[25], and **BSQ**[26] | Korea |
| 6 | Ebenfeld et al., 2021 (Ebenfeld et al., 2021) | Panic disorder with or without agoraphobia | Symptom criteria | ≥ 18 years | Guided, hybrid web-based training program (GET.ON™) based on CBT | 6 modules in 6 weeks | 45 | Waitlist | 47 | **BSQ**, PAS, HAM-A, **ACQ**, MI, CES-D[27], SF−12[28], CSQ-I | Germany |
| 7 | Oh et al., 2020 (Oh et al., 2020) | Panic disorder with or without agoraphobia | DSM-V | 19–60 years | Mobile app-based interactive CBT using a chatbot (Todaki) | Daily interaction in 4 weeks | 21 | Traditional treatment (book group) | 20 | **PDSS**, HADS, APPQ, **BSQ,** and **ACQ** | Korea |
| 8 | Ciuca et al., 2018 ( Ciuca et al., 2018) | Panic disorder | DSM-IV | 18–65 years | ICBT<br>Paxonline Program for Panic Disorder (PAXPD); guided (via real-time video sessions) | 16 modules in 12 weeks | 36 | Unguided self-help treatment<br>waitlist control | 37<br>38 | **PDSS, BSQ, ACQ**, PHQ−9, WSAS PACQ, and BVS[29] | Romania |
| 9 | Schröder et al., 2017 (Schröder et al., 2017) | Panic disorder | Symptom criteria | 18–65 years | Confid, established cognitive–behavioral interventions for anxiety | 16 modules in 4 weeks | 61 | Care as usual | 67 | PAS, BAI, BSI−18[30], PHQ−9, and BSPS[31] | Germany |
| 10 | Christoforou et al., 2017 (Christoforou et al., 2017) | Agoraphobia | Symptom criteria | ≥ 18 years | A novel mobile app designed to target agoraphobia (called Agoraphobia Free) | 10 sessions in 12 weeks | 86 | Stress-free (general CBT) | 84 | PAS | UK |
| 11 | Berger et al., 2017( Berger et al., 2017) | Panic disorder with or without agoraphobia | DSM-IV | ≥ 18 years | Unguided ICBT was provided by a novel transdiagnostic ICBT programme ('velibra™'). | 6 sessions in 9 weeks | 33 | Control | 30 | **BSQ, ACQ**, MI, SF−12, BAI, SIAS[32]/ SPS[33], DASS−21[34], BDI-II, BSI[35], and PSWQ[36] | Switzerland, Germany, and Austria |
| 12 | Dear et al., 2016 ( Dear et al., 2016) | Panic disorder | DSM-IV | 18–64 years | ICBT treatment | 5 sessions in 8 weeks | 33 | General CBT | 28 | Mini-SPIN[37], GAD−7, PHQ−9, **PDSS-SR**, K10[38], SDS, and NEO-FFI | Australia |
| 13 | Oromendia et al., 2016 (Oromendia et al., 2016) | Panic disorder with or without agoraphobia | DSM-IV | 18–60 years | Web-based treatment program (free from anxiety) | 8 modules in 8 weeks | 27 | Treatment with psychological support or waitlist group | 27, 25 | **PDSS**, ASI, BAI, SDS, and BDI-II | Spain |
| 14 | Ivanova et al., 2016 (Ivanova et al., 2016) | Diagnosed with social anxiety | DSM-IV | ≥ 18 years | Internet-delivered ACT-based treatment program and a smartphone application | 8 modules in 10 weeks | 13 | Unguided treatment or waitlist group | 14, 12 | **PDSS**, GAD−7, PHQ−9, QOLI[39], and LSAS-SR[40] | Sweden |

(*continued on next page*)

**Table 2** (*continued*)

| Study | | Primary diagnosis | Diagnosis criteria | Age | Treatment comparison | | | | | Outcome measures | Country |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Intervention | | Sample size | Control | Sample size | | |
| | | disorder and/or panic disorder | | | | | | | | | |
| 15 | Fogliati et al., 2016 (Fogliati et al., 2016) | Panic disorder | DSM-IV | 18–64 years | ICBT for panic disorder (DS-CBT) | 5 sessions in 8 weeks | 68 | General CBT | 64 | **PDSS**, PHQ−9, GAD−7, MINI-SPIN, K−10, SDS, and NEO-FFI-N[41] | Australia |
| 16 | Allen et al., 2016 ( Allen et al., 2016) | Panic disorder with or without agoraphobia | DSM-IV | ≥ 18 years | ICBT | 5 sessions in 8 weeks | 27 | Control | 36 | **PDSS**, PHQ−9, K−10, NEO-FFI-N, and WHODAS-II[42] | Australia |
| 17 | Dear et al., 2015 ( Dear et al., 2015) | Panic disorder | DSM-IV | 18–64 years | ICBT | 5 sessions in 8 weeks | 50 | General CBT | 42 | GAD−7, PHQ−9, Mini-SPIN, **PDSS-SR**, K10, SDS, and NEOFFIN | Australia |
| 18 | Pitti et al., 2015 ( Pitti et al., 2015) | Agoraphobia with/without panic disorder | ICD−10 | Mean age: 39 years | VRET + CBT + Paroxetine | 4 sessions in 11 weeks | n.r* | CBT+Paroxetine or Paroxetine | n.r | **BSQ, ACQ**, BAI, BDI-II, and AGPH[43] | Spain |
| 19 | Meyerbroeker, et al., (2013) ( Meyerbroeker et al., 2013) | Panic disorder with agoraphobia | DSM-IV | 18–65 years | VRET | 10 sessions in 8 weeks | 23 | Exposure in vivo | 21 | **PDSS**, MI, **BSQ,** and **ACQ** | Netherlands |
| 20 | Malbos et al., 2013( Malbos et al., 2013) | Panic disorder with agoraphobia | DSM-IV | 24–72 years | VRET | 10 sessions in 10 weeks | n.r | VR and cognitive therapy | n.r | ASI, **ACQ**, MI, PA, SSQ[44], DASS, and PQ | Australia |
| 21 | Pelissolo et al., 2012 (Pelissolo et al., 2012) | Panic disorder with agoraphobia | DSM-IV | Mean age: 37 years | VRET | 10 sessions in 12 weeks | 43 | CBT | 44 | **PDSS**, STAI_S, STAI_T, SDS, BDI, FQ[45], CAS[46], HARS[47], DES[48], PPGAS[49], WSA[50], and GAF[51] | France |
| 22 | Malbos et al., 2011 (Malbos et al., 2011) | Panic disorder with agoraphobia | DSM-IV | No information | VRET | 8 sessions in 10 weeks | 5 | VRET and cognitive therapy | 5 | DASS, ASI, **ACQ**, Mia, PA, BAT[52], SUD[53], HR[54], pNN50[55], and PQ[56] | Australia |
| 23 | Johnston et al., 2011 (Johnston et al., 2011) | Panic disorder with or without agoraphobia | DSM-IV | ≥ 18 years | Transdiagnostic Internet-Delivered Treatment with Clinical Support | 8 lessons in 10 weeks | 46 | Coaching-assisted ICBT or waitlist | 47, 46 | GAD−7, DASS−21, PSWQ, SIAS−6/ SPS−6, **PDSS-SR**, PHQ−9, and SDS | Australia |
| 24 | Lorenzo et al., 2011 (Lorenzo et al., 2011) | Agoraphobia with/without panic | DSM-IV and ICD−10 | 20–61 years | VRET + CBT | 11 lessons | 22 | CBT or waitlist | 22, 20 | **BSQ, ACQ**, BAI, and AI[57] | Spain |
| 25 | Titov et al., 2010 ( Titov et al., 2010) | Panic disorder | DSM-IV | ≥ 18 years | Transdiagnostic ICBT program | 6 lessons in 8 weeks | 42 | Control | 44 | GAD−7, PSWQ, SPSQ, **PDSS-SR**, PHQ−9, K10, SDS, DASS−21, and NEO-FFI-N | Australia |
| 26 | Wims et al., 2010 ( Wims et al., 2010) | Panic disorder with agoraphobia | DSM-IV | ≥ 18 years | ICBT program (the Panic program) | 6 sessions in 8 weeks | 29 | Waitlist | 25 | **PDSS**, MI, **ACQ, BSQ,** PA, PHQ−9, and SDS | Australia |
| 27 | Ruwaard et al., 2010 (Ruwaard et al., 2010) | Panic disorder with or without agoraphobia | DSM-IV | ≥ 18 years | Web-based therapist-assisted CBT of panic symptoms | 7 modules in 11 weeks | 27 | Waitlist | 31 | **PDSS, ACQ, BSQ**, MI, and DASS | Netherlands |
| 28 | Bergström et al., 2010 (Bergström et al., 2010) | Panic disorder with or without agoraphobia | DSM-IV | ≥ 18 years | ICBT | 10 modules in 10 weeks | 50 | CBT | 54 | **PDSS**, CGI[58], MADRS[59], ASI, and SDS | Sweden |
| 29 | Klein et al., 2009 ( Klein et al., 2009) | Panic disorder with or without agoraphobia | DSM-IV | ≥ 18 years | Panic online (PO) program: frequent contact | 8 weeks | 23 | PO program - infrequent contact | 28 | **PDSS, ACQ,** PA[60], BVS, DASS, ASP[61], WHOQOL, TCS[62], TAQ[63], and TSQ[64] | Australia |

(*continued on next page*)

**Table 2** (*continued*)

| Study | | Primary diagnosis | Diagnosis criteria | Age | Treatment comparison | | | | | Outcome measures | Country |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Intervention | | Sample size | Control | Sample size | | |
| 30 | Kiropoulos et al., 2008 (Kiropoulos et al., 2008) | Panic disorder with or without agoraphobia | DSM-IV | 18–70 years | PO program | 12 weeks | 43 | CBT | 38 | **PDSS, ACQ**, PA, BVS, DASS, ASP, WHOQOL, TCS, TAQ, and TSQ | Australia |
| 31 | Botella et al., 2007 ( Botella et al., 2007) | Panic disorder with or without agoraphobia | DSM-IV | ≥ 18 years | VRET | 9 sessions in 9 weeks | 12 | CBT or waitlist | 12<br>13 | **PDSS,** ASI, FQA[65], BDI, and MSG[66] | Spain |
| 32 | Richards et al., 2006 (Richards et al., 2006) | Panic disorder with or without agoraphobia | DSM-IV | 18–70 years | PO program + stress management | 8 weeks | 11 | PO program or control | 12<br>9 | **PDSS, ACQ**, PA, BVS, DASS, ASP, and WHOQOL | Australia |
| 33 | Klein et al., 2006 ( Klein et al., 2006) | Panic disorder with or without agoraphobia | DSM-IV | 18–70 years | PO program | 6 weeks | 19 | Manualized Workbook Care or Control | 18<br>18 | **PDSS, ACQ**, PA, BVS, DASS, and ASP | Australia |
| 34 | Carlbring et al., 2006 (Carlbring et al., 2006) | Panic disorder with or without agoraphobia | DSM-IV | 18–60 years | ICBT and weekly telephone calls | 10 modules in 10 weeks | 30 | Waitlist | 30 | **BSQ, ACQ,** MI, BAI, BDI, MADRS, and QOLI | Sweden |
| 35 | Choi et al., 2005 ( Choi et al., 2005) | Panic disorder with agoraphobia | DSM-IV | Mean age: 35 years | VRET + CBT | 4 sessions in 4 weeks | 20 | Pain control program | 20 | BDI, STAI, ASI, PBQ[67], **ACQ,** and **BSQ** | Korea |
| 36 | Carlbring et al., 2005 (Carlbring et al., 2005) | Panic disorder with or without agoraphobia | DSM-IV | 18–60 years | Internet-administered self-help plus minimal therapist contact via email | 10 modules in 10 weeks | 25 | CBT | 24 | **BSQ, ACQ**, MI, BAI, BDI, MADRS, QOLI, and Free from PD[68] | Sweden |
| 37 | Vincelli et al., 2003 (Vincelli et al., 2003) | Panic disorder with agoraphobia | DSM-IV | 35–53 years | Experiential cognitive therapy that integrates the use of virtual reality (VR) in a multicomponent CBT strategy | 8 sessions in 24 weeks | 4 | CBT or waitlist | 4, 4 | BDI-II, STAI, PA, and FQ[69] | Italy |
| 38 | Carlbring et al., 2003 (Carlbring et al., 2003) | Panic disorder | DSM-IV | 18–60 years | Internet-based multimodal treatment package based on CBT | 6 modules | 11 | Applied relaxation (AR) | 11 | **BSQ, ACQ**, MI, BAI, BDI, QOLI, and panic diary | Sweden |
| 39 | Klein et al., 2001 ( Klein & Richards, 2001) | Panic disorder | DSM-IV | Mean age: 40 and 46 years in women and men | Brief internet-based treatment | 3 weeks | 11 | Self-monitoring | 12 | PA, SEQ[70], BVS, and ASI | Australia |
| 40 | Carlbring et al., 2001 (Carlbring et al., 2001) | Panic disorder | DSM-IV | 18–60 years | Internet-based multimodal treatment package based on CBT | 6 modules in 7–12 weeks | n.r | Waitlist | n.r | **BSQ, ACQ,** MI, BAI, BDI, QOLI, and MADRS-SR | Sweden |

Note: *n.r = not reported, 1. DSM-V = Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, 2. BAI = Beck Anxiety Inventory, 3. PAS = Panic and Agoraphobia Scale, 4. BDI-II = Beck Depression Inventory-II, 5. CSQ = Client Satisfaction Questionnaire, 6. AAQ = Agoraphobic Avoidance Questionnaire, 7. WHOQOL-BREF = World Health Organization Quality of Life – BREF, 8. ACQ = Agoraphobic Cognitions Questionnaire, 9. SDS = Sheehan Disability Scale, 10. PDSS = Panic Disorder Severity Scale, 11. HAM-A = Hamilton Anxiety Rating Scale, 12. GAD-7 = Generalized Anxiety Disorder 7-item Scale, 13. MI = Mobility Inventory, 14. PHQ-9 = Patient Health Questionnaire-9, 15. WSAS = Work and Social Adjustment Scale, 16. DOR = Disability Outcome Rating, 17. HRSD = Hamilton Rating Scale for Depression, 18. STAI_S = State-Trait Anxiety Inventory – State, 19. STAI_T = State-Trait Anxiety Inventory – Trait, 20. KIDS_SR = Korean Inventory of Depressive Symptomatology – Self Report, 21. PSS = Perceived Stress Scale, 22. KSAD = Korean Social Avoidance and Distress Scale, 23. ASI = Anxiety Sensitivity Index, 24. HADS = Hospital Anxiety and Depression Scale, 25. APPQ = Albany Panic and Phobia Questionnaire, 26. BSQ = Body Sensations Questionnaire, 27. CES-D = Center for Epidemiologic Studies Depression Scale, 28. SF-12 = 12-item Short Form Health Survey, 29. BVS = Body Vigilance Scale, 30. BSI-18 = Brief Symptom Inventory-18, 31. BSPS = Brief Social Phobia Scale, 32. SIAS=Social Interaction anxiety scale, 33. SPS = social phobia scale, 34. DASS-21 = Depression Anxiety Stress Scales – 21 items, 35. BSI = Brief Symptom Inventory, 36. PSWQ = Penn State Worry Questionnaire, 37. MINI-SPIN = Mini-Social Phobia Inventory, 38. K10 = Kessler Psychological Distress Scale – 10 items, 39. QOLI = Quality of Life Inventory, 40. LSAS-SR = Liebowitz Social Anxiety Scale-Self Report, 41. NEO-FFI-N = NEO Five-Factor Inventory – Neuroticism subscale, 42. WHODAS-II = WHO Disability Assessment Schedule II, 43. AGPH = Agoraphobia Severity Rating, 44. SSQ = Simulator sickness questionnaire, 45. FQ = Fear Questionnaire, 46. CAS = Chambless Agoraphobic Cognitions Scale, 47. HARS = Hamilton Anxiety Rating Scale – Revised, 48. DES = Dissociative Experiences Scale, 49. PPGAS = Panic Phobia and Generalized Anxiety Scale, 50. WSA = Work and Social Adjustment, 51. GAF=Global Assessment of Functioning, 52. BAT=Behavioral Avoidance Test, 53. SUD= Subjective unit of Discomfort, 54. HR = Hear Rate, 55. pNN50 = Proportion of NN50 divided by the total number of NN intervals, 56. PQ = Presence Questionnaire, 57. AI=Agoraphobia Inventory, 58. CGI=Clinician Global Impression, 59. MADRS = Montgomery–Åsberg Depression Rating Scale, 60. PA=panic attacks, 61. ASP = Anxiety Sensitivity Profile, 62. TCS = Treatment Credibility Scale, 63. TAQ = Therapist Alliance Questionnaire, 64. TSQ = Treatment Satisfaction Questionnaire, 65. FQA = Fear Questionnaire – Agoraphobia subscale, 66. MSG = Maladjustment Scale-global, 67. PBQ = Panic Belief Questionnaire, 68. Free from PD = Free from Panic Disorder measure, 69. FQ = Fear Questionnaire, 70. SEQ = Subjective Experience Questionnaire

waitlist or no treatment), digital interventions demonstrated a significant treatment advantage, with a large, pooled ES derived from 17 comparisons (g= 1.21; 95 % CI: 0.77–1.64). This indicates that DTx was substantially more effective than the absence of intervention. However, considerable heterogeneity was detected across these studies ($I^2$: 76.70 %; Q: 65.41; df:16, $p$-value <0.0001), indicating variability in the treatment effects. The active control analysis revealed no indication of publication bias based on the funnel plot symmetry and Egger's regression test.

Similarly, clinician-guided interventions produced significantly greater effects (g =0.95, 95 % CI: 0.44–1.46) compared with self-guided interventions, which yielded a nonsignificant trend (g =0.31, 95 % CI: 0.05–0.68). ICBT demonstrated a robust effect (g =0.83, 95 % CI: 0.45–1.21) when stratified by intervention type, whereas VR-based interventions were not associated with a significant change in PDSS scores (g =0.16, 95 % CI: –0.73–1.06). Regionally, studies conducted in Europe demonstrated slightly higher effects (g =0.81) compared with those in non-European countries (g =0.65), with both estimates reaching statistical significance.

Additional interaction analyses revealed that the most significant ES was achieved by the combination of passive comparators and clinician-guided delivery (g =1.55, 95 % CI: 1.01–2.09). Conversely, studies that combined active comparators with any intervention or guidance format typically exhibited negligible effects. Noteworthily, heterogeneity was consistently high in the majority of subgroup comparisons, with $I^2$ values exceeding 50 % in several instances. This indicates that the residual between-study variability was not accounted for solely by the subgroup characteristics. These findings emphasize that both methodological features (e.g., comparator type and guidance) and intervention characteristics (e.g., platform, region) systematically moderate the observed effects of digital interventions on panic disorder symptoms.

Highly significant heterogeneity among the pooled studies was observed using the Cochranes Q test and $I^2$ statistics ($I^2$: 82.76 %; Q:148.55; df,27; $p$-value <0.0001) (Fig. 2).

Considering the heterogeneity of the studies, the results need to be analyzed separately when the control group is an active control (including CBT) with some evidence of clinical effectiveness. This is particularly important when compared with studies using passive control, including a waitlist group with no treatment, in comparison to the DTx. The results for active and passive controls are significantly different for the studies conducted by Botella et al. and Klein et al. (Fig. 2).

Table 4 shows the meta regression analysis that investigated potential moderators of treatment ESs across the included studies. The intercept represents the estimated average ES (Hedges' g) for studies that used ICBT, a passive control comparator, conducted outside the European Union (non-EU), and were delivered with clinician guidance. Compared with passive controls, studies using active comparators revealed significantly smaller ESs (β =–1.070, $p < 0.001$), indicating a lower relative treatment effect in those trials. Further, self-guided interventions were associated with substantially reduced treatment effects in comparison to those that were clinician-guided (β =–0.617, $p = 0.024$). This did not achieve conventional levels of statistical significance (β =–0.660, $p = 0.088$); however, VR-based interventions demonstrated a trend toward reduced ESs compared with ICBT. No significant difference in the ES was observed between studies conducted in the EU versus non-EU regions ($p = 0.508$). These results indicate that the comparator type and guidance modality substantially influenced the observed efficacy of DTx interventions for panic disorder.

Sensitivity analyses using robust variance estimation confirmed the robustness of these findings (Supplementary Table 2), with convergent results across all analytical approaches.

### 3.2. ACQ

The meta-analysis of 25 comparisons that assessed changes in agoraphobic cognitions as measured by the ACQ caused a statistically significant but modest overall effect (Hedges' g = 0.35, 95 % CI: 0.10–0.61, $p = 0.0066$), with moderate heterogeneity ($I^2$ =58.45 %) (Table 5).

Subgroup analyses indicated that the effects of studies using passive comparators were substantially greater (g =0.61, 95 % CI: 0.27–0.95, $p = 0.0004$), whereas those using active comparators exhibited negligible effects (g =0.05, $p = 0.72$). In a similar direction, clinician-guided interventions were associated with significantly greater improvements (g =0.46, $p = 0.0036$) than self-guided interventions, which had non-significant results (g =0.11, $p = 0.61$).

The effects of ICBT were significant (g =0.41, $p = 0.0092$) when stratified by intervention type, whereas VR-based interventions did not (g =0.21, $p = 0.39$). A regional difference was observed. Studies conducted in Europe demonstrated significantly greater improvements (g =0.48, $p = 0.0026$) compared with those conducted in non-European regions, which did not yield significant effects (g =0.12, $p = 0.57$).

Interaction analyses further highlighted that the combination of passive comparator and clinician guidance yielded the largest effect (g = 0.88, 95 % CI: 0.57–1.19, $p < 0.0001$), whereas other combinations, particularly those involving active comparators, failed to produce significant ACQ score improvements.

These results indicate that digital interventions may provide modest benefits in the modification of agoraphobic cognitions; however, the extent of these effects is significantly affected by the design features of the study, particularly the comparator type and delivery format.

Table 6 presents the meta-regression analysis that investigated potential moderators of treatment ESs for ACQ across the included studies. The intercept of the model reflected the estimated ES for studies using an ICBT intervention, a passive comparator, conducted outside of Europe, and with clinician guidance. Under these conditions, the mean ES was moderate and statistically significant ($g$ =0.58, SE =0.24, $p = 0.015$).

Relative to the reference group, ESs were significantly smaller in studies using active comparators (β =–0.556, $p = 0.033$), conducted with self-guided treatment (β =–0.729, $p = 0.008$). In contrast, studies conducted in Europe revealed significantly larger effects (β =0.430, $p = 0.106$). VR-based interventions showed a non-significant trend toward smaller effects compared with ICBT (β =–0.273, $p = 0.371$).

Robust variance estimation analyses yielded consistent results (Supplementary Table 3), confirming the stability of the observed effects.

### 3.3. BSQ

The meta-analysis for the BSQ included 18 comparisons. The overall pooled ES was moderate and statistically significant (Hedges' $g$ =0.52, 95 % CI: 0.20–0.84, $p = 0.0016$), with substantial heterogeneity ($I^2$ =66.03 %).

Subgroup analyses revealed that studies using passive comparators yielded significantly larger effects ($g$ =0.76, $p < 0.0001$) than those using active comparators, which exhibited negligible effects ($g$ =0.05, $p = 0.8133$). Similarly, clinician-guided interventions were associated with greater reductions in somatic anxiety symptoms ($g$ =0.67, $p = 0.0005$) compared with self-guided interventions, which did not reach statistical significance ($g$ =0.27, $p = 0.3579$).

ICBT exhibited a significant effect (g =0.61, $p = 0.0091$) when stratified by the type of intervention, whereas VR-based therapies had smaller, non-significant effects (g =0.33, $p = 0.08$). Regionally, European studies demonstrated a robust effect ($g$ =0.67, $p = 0.0003$), whereas studies conducted in other regions yielded null findings ($g$

**Table 3**
Summary results of the meta-analysis and subgroup analyses for the Panic Disorder Severity Scale.

| | Number of comparisons | Hedges` g | 95 % CI (g) | p-value | | $I^2$ |
|---|---|---|---|---|---|---|
| **Overall** | | | | | | |
| | 28 | 0.72 | (0.36–1.08) | < 0.0001 | *** | 82.76 % |
| **Comparator** | | | | | | |
| Active | 11 | −0.06 | (−0.28–0.17) | 0.6198 | | 15.05 % |
| Passive | 17 | 1.21 | (0.77–1.64) | < 0.0001 | *** | 76.70 % |
| **Guidance** | | | | | | |
| Self-guided | 10 | 0.31 | (−0.05–0.68) | 0.0936 | | 60.39 % |
| Clinician-guided | 18 | 0.95 | (0.44–1.46) | 0.0002 | *** | 84.99 % |
| **Intervention** | | | | | | |
| ICBT | 23 | 0.83 | (0.45–1.21) | < .0001 | *** | 82.06 % |
| VR | 5 | 0.16 | (−0.73–1.06) | 0.719 | | 80.74 % |
| **Region** | | | | | | |
| Europe | 12 | 0.81 | (0.26–1.36) | 0.0037 | ** | 81.77 % |
| Other regions | 16 | 0.65 | (0.16–1.14) | 0.0088 | ** | 84.13 % |
| **Comparator * Intervention** | | | | | | |
| Active • ICBT | 8 | 0 | (−0.23–0.23) | 0.9788 | | 0.00 % |
| Active • VR | 3 | −0.22 | (−1.01–0.58) | 0.5904 | | 61.93 % |
| Passive • ICBT | 15 | 1.27 | (0.84–1.71) | < 0.0001 | *** | 74.11 % |
| Passive • VR[a] | 2 | 0.72 | (−1.39–2.83) | 0.5031 | | 89.23 % |
| **Comparator * Region** | | | | | | |
| Active • Europe[a] | 4 | −0.14 | (−0.68–0.40) | 0.6057 | | 51.57 % |
| Active • Other regions | 7 | −0.02 | (−0.27–0.24) | 0.8974 | | 0.00 % |
| Passive • Europe | 8 | 1.29 | (0.79–1.79) | < 0.0001 | *** | 63.67 % |
| Passive • Other regions | 9 | 1.15 | (0.42–1.88) | 0.0021 | ** | 83.83 % |
| **Comparator * Guidance** | | | | | | |
| Active • self-guided[a] | 4 | −0.06 | (−0.36–0.23) | 0.6812 | | 0.00 % |
| Active • clinician-guided | 7 | −0.01 | (−0.43–0.40) | 0.95 | | 49.45 % |
| Passive • self-guided | 6 | 0.61 | (0.11–1.11) | 0.0165 | * | 53.09 % |
| Passive • clinician-guided | 11 | 1.55 | (1.01–2.09) | < 0.0001 | *** | 75.28 % |

*p*-values: * < 0.05; ** < 0.01; *** < 0.001.
a. Analyses based on fewer than five studies are reported but should be interpreted with caution, as effect size estimates may be unstable and associated with inflated variance

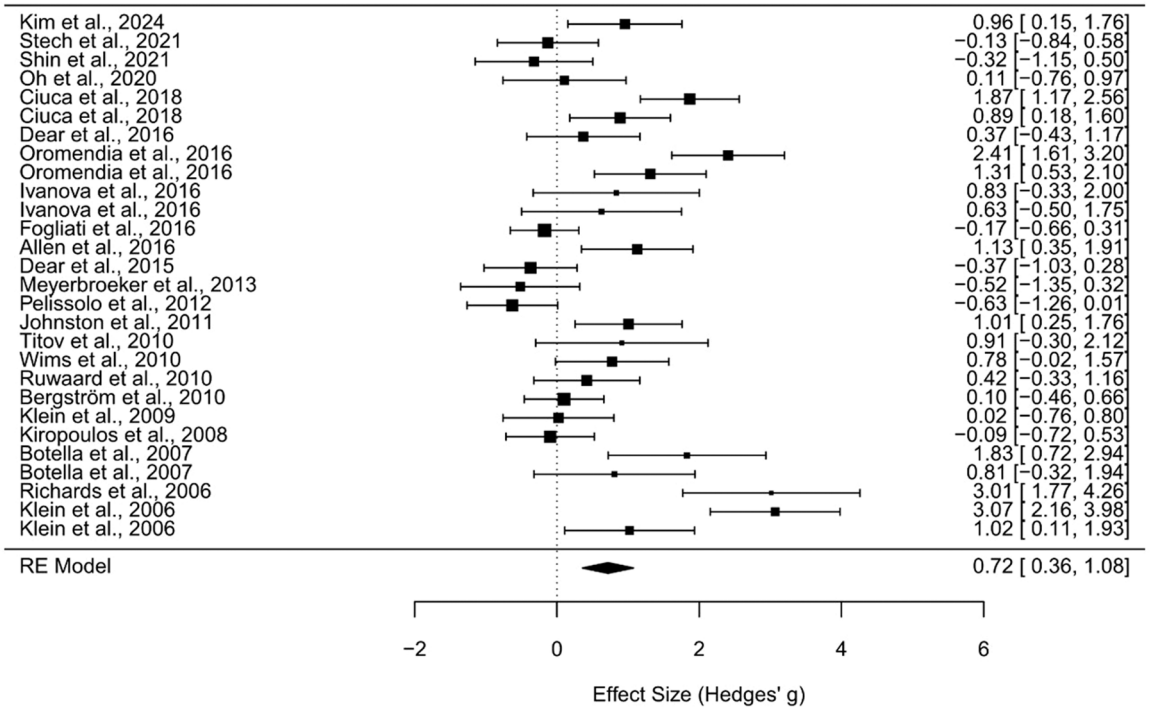


**Fig. 2. Forest plot comparing the pre- and post-treatment differences of the Panic Disorder Severity Scale between the intervention and control groups in the pooled analysis,** Note: Forest plot of effect sizes (Hedges' g) from 23 randomized controlled trials evaluating digital therapeutics (DTx) for panic disorder. The plot displays 29 effect size estimates with 95 % confidence intervals, and a pooled effect size calculated using a random-effects (RE) model. Square sizes represent the weight of each estimate in the meta-analysis.

**Table 4**
Meta-Regression Analysis on Treatment Effect Sizes for the Panic Disorder Severity Scale.

| Variables | Estimate (β) | Standard Error | p-value |
|---|---|---|---|
| intercept | 1.404 | 0.239 | < 0.000001 |
| Active comparator (vs. passive) | −1.070 | 0.275 | < 0.001 *** |
| EU region (vs. Others) | 0.190 | 0.287 | 0.508 |
| Self-guided (vs. clinician-guided) | −0.617 | 0.273 | 0.024* |
| VR Intervention (vs. ICBT) | −0.660 | 0.387 | 0.088 |

*p*-values: * < 0.05; ** < 0.01; *** < 0.001.

=0.02, $p = 0.9207$).

Interaction analyses further highlighted that the largest effect was observed in studies combining passive comparators with clinician guidance ($g$ =0.92, $p < 0.0001$). In contrast, all combinations involving active comparators failed to yield significant effects across the subgroup strata.

These results indicate that the study design factors, especially the comparator type and delivery format, substantially moderated the effectiveness of digital interventions in reducing somatic anxiety symptoms.

A meta-regression analysis was conducted to identify potential sources of heterogeneity in the treatment effects on somatic anxiety symptoms, utilizing the study-level moderators presented in Table 8. The model encompassed the comparator type, same as that of meta-regression for BSQ.

The intercept indicated the estimated ES for the reference condition—studies employing a passive comparator, conducted outside Europe, administered by clinicians, and utilizing ICBT—and was not statistically significant (g =0.348, $p = 0.338$).

The use of active comparators among the moderators was associated with a significantly reduced ES (β =–0.888, $p = 0.005$), indicating that the treatment effects were considerably smaller when the digital interventions were assessed against the active control conditions. Research in the European region demonstrated significantly larger effects than those conducted in other areas (β =0.713, $p = 0.028$). In contrast, neither self-guided interventions (β =–0.381, $p = 0.181$) nor VR-based interventions (β =0.042, $p = 0.898$) were significant predictors of the ES.

The results indicate that the study design characteristics, specifically the comparator type and region, significantly affect the effectiveness of digital interventions in mitigating bodily fear and interoceptive anxiety.

These findings were corroborated by robust variance estimation sensitivity analyses (Supplementary Table 4).

## 4. Discussion

The role of clinician involvement in therapeutic benefit has direct implications for regulatory assessment and the scalable implementation of DTx. This study systematically quantified the effect of clinician guidance on the effectiveness of DTxs for panic disorder. Employing a comprehensive meta-analytic framework, this study analyzed RCTs of digital interventions for panic disorder to investigate the effects of clinician involvement on the treatment effectiveness across multiple

**Table 6**
Meta-regression analysis on treatment effect sizes for the Agoraphobic Cognitions Questionnaire.

| Variables | Estimate (β) | Standard Error | p-value |
|---|---|---|---|
| intercept | 0.575 | 0.236 | 0.015 |
| Active comparator (vs. passive) | −0.556 | 0.262 | 0.033* |
| EU region (vs. Others) | 0.430 | 0.266 | 0.106 |
| Self-guided (vs. clinician-guided) | −0.729 | 0.275 | 0.008** |
| VR Intervention (vs. ICBT) | −0.273 | 0.305 | 0.371 |

*p*-values: * < 0.05; ** < 0.01; *** < 0.001.

**Table 5**
Summary results of the meta-analysis and subgroup analyses for the Agoraphobic Cognitions Questionnaire.

| | Number of comparisons | Hedges` g | 95 % CI (g) | *p*-value | | $I^2$ |
|---|---|---|---|---|---|---|
| **Overall** | | | | | | |
| | 25 | 0.35 | (0.10–0.61) | 0.0066 | ** | 58.45 % |
| **Comparator** | | | | | | |
| Active | 11 | −0.05 | (−0.33–0.23) | 0.7163 | | 6.89 % |
| Passive | 14 | 0.61 | (0.27–0.95) | 0.0004 | *** | 63.91 % |
| **Guidance** | | | | | | |
| Self-guided | 7 | 0.11 | (−0.32–0.54) | 0.6077 | | 54.76 % |
| Clinician-guided | 18 | 0.46 | (0.15–0.76) | 0.0036 | ** | 57.07 % |
| **Intervention** | | | | | | |
| ICBT | 17 | 0.41 | (0.10–0.72) | 0.0092 | ** | 64.09 % |
| VR | 8 | 0.21 | (−0.26–0.68) | 0.3865 | | 45.57 % |
| **Region** | | | | | | |
| Europe | 15 | 0.48 | (0.17–0.80) | 0.0026 | ** | 60.40 % |
| Other regions | 10 | 0.12 | (−0.29–0.53) | 0.5716 | | 48.80 % |
| **Comparator • Intervention** | | | | | | |
| Active • ICBT | 5 | −0.04 | (−0.42–0.33) | 0.8291 | | 8.81 % |
| Active • VR | 6 | −0.07 | (−0.54–0.40) | 0.7673 | | 20.76 % |
| Passive • ICBT | 12 | 0.57 | (0.19–0.95) | 0.0033 | ** | 68.07 % |
| Passive • VR[a] | 2 | 0.93 | (0.33–1.53) | 0.0025 | ** | 0.00 % |
| **Comparator • Region** | | | | | | |
| Active • Europe | 5 | 0.14 | (−0.26–0.54) | 0.5012 | | 0.00 % |
| Active • Other regions | 6 | −0.19 | (−0.64–0.26) | 0.4029 | | 29.74 % |
| Passive • Europe | 10 | 0.63 | (0.22–1.05) | 0.0029 | ** | 70.97 % |
| Passive • Other regions[a] | 4 | 0.55 | (−0.04–1.14) | 0.0691 | | 38.27 % |
| **Comparator • Guidance** | | | | | | |
| Active • self-guided[a] | 2 | −0.02 | (−0.67–0.64) | 0.9622 | | 0.00 % |
| Active • clinician-guided | 9 | −0.05 | (−0.39–0.28) | 0.7513 | | 18.85 % |
| Passive • self-guided | 5 | 0.16 | (−0.42–0.74) | 0.5896 | | 70.14 % |
| Passive • clinician-guided | 9 | 0.88 | (0.57–1.19) | < 0.0001 | *** | 26.59 % |

*p*-values: * < 0.05; ** < 0.01; *** < 0.001.
a. Analyses based on fewer than five studies are reported but should be interpreted with caution, as effect size estimates may be unstable and associated with inflated variance

**Table 7**
Summary results of the meta-analysis and subgroup analysis for the Body Sensations Questionnaire.

| | Number of comparisons | Hedges` g | 95 % CI (g) | *p*-value | | $I^2$ |
|---|---|---|---|---|---|---|
| **Overall** | | | | | | |
| | 18 | 0.52 | (0.20–0.84) | 0.0016 | ** | 66.03 % |
| **Comparator** | | | | | | |
| Active | 6 | −0.05 | (−0.46–0.36) | 0.8133 | | 20.37 % |
| Passive | 12 | 0.76 | (0.40–1.11) | < 0.0001 | *** | 62.75 % |
| **Guidance** | | | | | | |
| Self-guided | 7 | 0.27 | (−0.31–0.85) | 0.3579 | | 71.45 % |
| Clinician-guided | 11 | 0.67 | (0.30–1.05) | 0.0005 | *** | 60.16 % |
| **Intervention** | | | | | | |
| ICBT | 11 | 0.61 | (0.15–1.07) | 0.0091 | ** | 75.35 % |
| VR | 7 | 0.33 | (−0.04–0.70) | 0.0809 | | 21.19 % |
| **Region** | | | | | | |
| Europe | 14 | 0.67 | (0.31–1.04) | 0.0003 | *** | 66.43 % |
| Other regions[a] | 4 | −0.02 | (−0.44–0.40) | 0.9207 | | 0.00 % |
| **Comparator • Intervention** | | | | | | |
| Active • ICBT[a] | 2 | −0.51 | (−1.17–0.15) | 0.1268 | | 0.00 % |
| Active • VR[a] | 4 | 0.14 | (−0.29–0.58) | 0.5196 | | 0.00 % |
| Passive • ICBT | 9 | 0.81 | (0.38–1.24) | 0.0002 | *** | 68.43 % |
| Passive • VR[a] | 3 | 0.57 | (−0.09–1.23) | 0.0927 | | 43.15 % |
| **Comparator • Region** | | | | | | |
| Active • Europe | 5 | 0.04 | (−0.44–0.51) | 0.8765 | | 26.77 % |
| Active • Other regions | NA | NA | NA | | | |
| Passive • Europe | 9 | 0.95 | (0.58–1.33) | < 0.0001 | *** | 57.71 % |
| Passive • Other regions[a] | 3 | 0.1 | (−0.37–0.58) | 0.6671 | | 0.00 % |
| **Comparator • Guidance** | | | | | | |
| Active • self-guided[a] | 2 | −0.51 | (−1.17–0.15) | 0.1268 | | 0.00 % |
| Active • clinician-guided[a] | 4 | 0.14 | (−0.29–0.58) | 0.5196 | | 0.00 % |
| Passive • self-guided | 5 | 0.52 | (−0.11–1.14) | 0.104 | | 69.63 % |
| Passive • clinician-guided | 7 | 0.92 | (0.49–1.35) | < 0.0001 | *** | 56.25 % |

*p*-values: * < 0.05; ** < 0.01; *** < 0.001.
a. Analyses based on fewer than five studies are reported but should be interpreted with caution, as effect size estimates may be unstable and associated with inflated variance

outcome areas, assessing whether clinician guidance is crucial or a modifiable contextual factor. The results suggest that clinician guidance may be particularly associated with improvements in cognition-related domains, whereas self-guided interventions appear to have more modest but still meaningful effects on overall symptom intensity of panic disorder. While these patterns to the possibility that clinician guidance plays a role that extends beyond merely improving engagement or adherence; rather, it may differ in effect on treatment mechanisms based on the specific target of change (Mohr et al., 2013). These results emphasize the need to expand beyond the binary categories of guided and unguided delivery, moving toward a more complex understanding of how physician input affects treatment efficacy across multiple domains (Andersson & Titov, 2014; Cuijpers et al., 2010).

The current findings regarding overall symptom intensity, as assessed with the PDSS, corroborate previous evidence indicating that self-guided DTx yielded significant reductions in panic-related symptoms(Carlbring et al., 2001; Klein et al., 2009). Concurrently, our findings revealed that clinician-guided interventions demonstrated larger ESs, and several self-guided interventions produced outcomes within a range that may be considered clinically meaningful. Considering the nature of the PDSS—which encompasses aspects such as panic attack frequency and severity, avoidance behaviors, and functional impairment—these results indicate that certain symptom domains can be meaningfully addressed even in the absence of clinician guidance, particularly when supported by well-structured self-guided DTx (Furukawa et al., 2009).

In contrast, when the outcomes were assessed using cognitive-focused instruments, such as the ACQ and the BSQ, the trend significantly varied. Clinician-guided DTx yielded substantial benefits, whereas self-guided formats exhibited minimal to no effect. This divergence aligns with theoretical and neurobiological models indicating that meaningful cognitive change requires not only content exposure but also active engagement with complex thought processes, real-time feedback, and therapeutic alliance establishment (Kazdin,

**Table 8**
Meta-Regression Analysis on Treatment Effect Sizes for Body Sensations Questionnaire.

| Variables | Estimate (β) | Standard Error | *p*-value |
|---|---|---|---|
| Intercept | 0.348 | 0.363 | 0.338 |
| Active comparator (vs. passive) | −0.888 | 0.318 | 0.005*** |
| EU region (vs. Others) | 0.713 | 0.325 | 0.028** |
| Self-guided (vs. clinician-guided) | −0.381 | 0.285 | 0.181 |
| VR Intervention (vs. ICBT) | 0.042 | 0.327 | 0.898 |

*p*-values: * < 0.05; ** < 0.01; *** < 0.001.

2007). These are components for which clinician guidance is well-positioned to facilitate, not necessarily as the sole mechanism of action, but as a potentially crucial enabler of cognitive transformation (Horvath et al., 2011). This role is well-recognized in traditional psychotherapeutic models, such as CBT, where therapist involvement is frequently central to fostering metacognitive information and cognitive restructuring (Beck, 2011). Accordingly, our findings are consistent with the possibility that guidance effects may differ by outcome domain, suggesting that the efficacy of DTx could depend not only on what is delivered but also on how clinician involvement facilitates deeper psychological processing. These domain-specific patterns may reflect engagement-dependent mechanisms, where complex cognitive restructuring benefits from the sustained participation that clinician guidance facilitates. Future research should examine these mechanisms alongside long-term follow-up outcomes.

The present results suggest that clinician guidance can meaningfully influence the therapeutic efficacy of DTx, highlighting its potential importance as a key consideration in regulatory frameworks. Regulatory bodies, including the FDA and EMA, mandate that therapies demonstrate the capacity to produce clinically significant and reproducible outcomes (Boesen et al., 2021; CHMP;EMA, 2005; USFDA, 2017). The effects of clinician guidance across domains and its role in the treatment

context should not be inherently excluded or deemed essential; instead, it should be assessed as a design element contingent upon the nature of the intervention and the desired outcomes (EMA, 2023; USFDA, 2023a, 2023b). The characteristics of domain-specific influences, once deemed less significant in assessing the psychiatric efficacy of existing drugs (Montero-Espinoza, 2025), indicate that DTx guidelines should consider the mechanistic attributes of the treatment content. Furthermore, the impact of clinician guidance should be recognized as conditional rather than essential or irrelevant. Our findings suggest that guidance may be particularly supportive in achieving certain outcome types, such as cognitive change, while self-guided approaches may still yield meaningful improvements in symptom severity. This understanding corresponds with the focus of regulatory authorities on real-world efficacy, reproducibility, and well-defined therapeutic claims, facilitating the development of more customized regulatory assessment strategies (Sverdlov et al., 2018; Wang et al., 2023).

The scalability and practical implementation of DTx present significant challenges in addition to obtaining regulatory approval (Linardon et al., 2019; Torous et al., 2019). Several DTx targeting conditions, such as insomnia, substance use disorders, and depression, have been withdrawn from the market or have not attained lasting adoption (Firth et al., 2017). Multiple factors affected these outcomes, such as insurance reimbursement, healthcare provider awareness, and digital literacy; however, the lack of clarity in clinician guidance within real-world contexts was identified as a notable barrier (Kendziorra et al., 2025; Rodrigues et al., 2024; Sareban et al., 2025). Clinical guidance may hinder adoption due to resource limitations, and an insufficient understanding of its specific role and effect presents a significant obstacle to implementation (Berardi et al., 2024). Our findings highlight that fully self-guided DTx remain an essential component of scalable implementation strategies, while clinician guidance should be acknowledged as a potentially crucial factor influencing feasibility in specific contexts. Analyzing the varying effects of clinician guidance according to treatment objectives facilitates more pragmatic planning of hybrid models, workforce distribution, and pricing strategies that align with the necessary clinician engagement level for each application (Baumel et al., 2019; Mohr et al., 2014). Future DTx development and assessment should regard clinician guidance as a dynamic, domain-specific component of the therapeutic design rather than an auxiliary feature. Early-stage planning must identify the requirement and manner of clinician input, contingent upon the intervention's target mechanisms, including symptom reduction, cognitive restructuring, or behavioral exposure. Regulatory and reimbursement pathways would benefit from adopting stratified criteria that consider the functional role of clinician involvement, rather than applying uniform expectations to all digital interventions. Our findings highlight the need for precise implementation strategies that consider psychological factors, user characteristics, and the required guidance levels to inform the design of hybrid models and workforce allocation.

A key strength of this study lies in its meta-analytic synthesis of existing evidence on clinician guidance in digital interventions for panic disorder. The findings emphasize the importance of clinician support as a potentially influential component, highlighting the need for future research to investigate its role with greater granularity across symptom domains and intervention designs.

Our selection of the PDSS, ACQ, and BSQ reflects their established psychometric properties and widespread adoption in digital therapeutics research. While each measure has domain-specific strengths—PDSS for comprehensive severity, ACQ for cognitive distortions, and BSQ for somatic sensitivity—they also have limitations in capturing the full breadth of panic disorder symptomatology. Future research would benefit from incorporating newer DSM-aligned measures such as the Panic Disorder Self-Report (PDSR), though their limited current adoption precludes meaningful meta-analytic synthesis at present.

This study has several limitations to be acknowledged. Initially, our analysis of clinician guidance as a binary moderator (guided vs. self-guided) did not consider qualitative differences in guidance intensity, format (e.g., synchronous vs. asynchronous), or professional expertise level. Future research should examine the required level of professional training and supervision for guidance providers, as this has important implications for cost-effectiveness and workforce scalability in digital therapeutic implementation. Second, the interpretation of outcome-specific effects is another limitation. In this study, PDSS, ACQ, and BSQ were analyzed separately, and therefore no direct statistical comparisons could be made between symptom severity and cognition-related outcomes. Future research should prioritize the simultaneous measurement and reporting of both cognition-related and symptom-related outcomes within the same trials. This data would allow for the direct assessment of whether clinician guidance differentially affects these domains through the use of multivariate meta-analytic techniques. Third, our analysis focused exclusively on panic disorder, and caution should be exercised when generalizing these results to other mental health conditions that may have distinct symptom structures or treatment mechanisms. The dependence on published trials may cause publication bias, mainly due to the inclination to report favorable results for guided interventions. Future research should incorporate individual participant data, real-world implementation outcomes, and experimental manipulation of guidance levels to identify causal mechanisms and refine design strategies for scalable DTx.

## 5. Conclusions

This meta-analysis investigated the role of clinician guidance in DTx for panic disorder, demonstrating that clinician involvement more strongly affects cognition-related outcomes, whereas self-guided interventions can improve symptom severity. These results support a domain-specific and context-sensitive view of guidance, indicating that its necessity depends on the therapeutic targets and implementation settings. These results emphasize the importance of matching DTx design and policy decisions with the specific mechanistic pathways through which therapeutic change is intended to occur.

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## CRediT authorship contribution statement

**Inhye Cho:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Byung-Hoon Kim:** Writing – review & editing. **Hankil Lee:** Writing – review & editing. **Yun-Kyoung Song:** Writing – review & editing. **Min Jung Chang:** Writing – review & editing. **Junhyung Kim:** Writing – review & editing, Validation, Investigation, Funding acquisition. **Euna Han:** Writing – review & editing, Supervision, Methodology, Conceptualization.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.janxdis.2025.103074.

## Data availability

No new data were created or analyzed in this study of the meta-analysis. Data sharing is not applicable to this article.

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