Journal of Affective Disorders 325 (2023) 682–694

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Review Article

CBT-informed psychological interventions for adult patients with anxiety and depression symptoms: A narrative review of digital treatment options

Bruno Biagianti [a], Giuseppe Foti [b], Asia Di Liberto [b], Cinzia Bressi [c,d], Paolo Brambilla [c,d,*]

[a] Department of Psychology, University of Milano-Bicocca, Milan, Italy
[b] University of Milan, Milan, Italy
[c] Department of Neurosciences and Mental Health, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
[d] Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy

ARTICLE INFO

Keywords:
Cognitive Behavioral Therapy
Tele-psychiatry
Affective disorders
Depression
Anxiety disorders

ABSTRACT

Background: Across a range of age, educational and clinical characteristics, adults experiencing depression and anxiety already use digital technology to manage their symptoms. Although several reviews and meta-analyses indicated feasibility and efficacy for adults with depression and anxiety, digital treatments are poorly accessed and disseminated. This review illustrates potentials and limitations of interventions that specifically leveraged unique features of digital technology and were grounded in the principles of Cognitive Behavioral Therapy (CBT).

Methods: This systematic review followed the PRISMA guidelines. An electronic database search was conducted in October 2021. Peer-reviewed, English-language studies were included if i) they reported data from RCTs for adults aged 18+ who engaged with CBT-informed digital interventions targeting primarily depression and anxiety; ii) they used at least PHQ-9 or GAD-7 as standardized and validated assessment self-report measures for depression and anxiety.

Results: Findings from 35 RCTs examining 33 interventions (25 internet-based, 6 mobile-based, a2 mobile/web) are discussed. The quality of the evidence differed widely as many small-scale RCTs reported only short-term feasibility and preliminary efficacy. Effects of CBT-informed digital interventions were substantially larger when compared to waitlist than active control conditions. Greater therapeutic benefits were observed for interventions that offered clinical assistance or were used in combination with other treatments.

Conclusions: CBT-informed digital interventions have accumulated enough scientific evidence to be positioned today as: i) a low-intensity tool for those with subclinical levels of symptoms; ii) a first step in a stepped-care approach to service delivery iii) a low-cost, easily accessible option for targeted preventive programs.

1. Introduction

Incidence and prevalence of depression and anxiety have skyrocketed beyond the possibilities of any mental health system to intervene with in-person individual services (Corruble, 2020). Because depression and anxiety significantly reduce quality of life, wellbeing, and daily functioning, there is an urgent need for treatments that can be delivered rapidly, cost-efficiently and at a large scale. Cognitive Behavioral Therapy (CBT) is considered one of the most established treatments for adults with depression and anxiety, with numerous Randomized Controlled Trials (RCTs) over the last twenty years corroborating its efficacy (Sadler et al., 2018; Nakagawa et al., 2017; Kodal et al., 2018; Norton and Barrera, 2012) However, only 20 % of adults with depression and anxiety seek CBT, and even fewer ultimately receive it (Collins et al., 2004). Certainly, the nature of anxiety and depression contributes to this delay in seeking treatment, as motivation and ease with interpersonal dynamics are required to access and engage with dedicated services (Collins et al., 2004). For those who do seek treatment, access to and engagement with CBT remain outstanding challenges. CBT can place a high scheduling burden and become unsustainable for those with work or family related responsibilities (Taylor et al., 2012). Additionally, CBT may not be available to those living in

* Corresponding author at: Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy; Department of Neurosciences and Mental Health, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan, Italy.
E-mail addresses: bruno.biagianti@unimi.it (B. Biagianti), giuseppe.foti@studenti.unimi.it (G. Foti), cinzia.bressi@unimi.it (C. Bressi), bruno.biagianti@unimib.it (P. Brambilla).

https://doi.org/10.1016/j.jad.2023.01.057
Received 28 June 2022; Received in revised form 3 January 2023; Accepted 13 January 2023
Available online 20 January 2023

rural or under-resourced areas where there are no trained CBT professionals. The time spent reaching the clinic may therefore be another barrier to the implementation of this treatment. Lastly, some individuals with depression and anxiety hesitate to approach traditional mental health treatment settings because of stigma, which interferes with help-seeking behaviors (Angermeyer et al., 2013). These factors all hamper wide and efficient utilization of this intervention.

Remotely delivering CBT through video calls offers advantages, including ready accessibility, time flexibility, and convenience. While research shows that remotely delivering CBT to adults with depression and anxiety via digital platforms is adaptable, feasible, efficient, cost-effective, and equally efficacious (Backhaus et al., 2012; Jenkins-Guarnieri et al., 2015; Fernandez et al., 2021), the rapid expansion of digital health technology has revolutionized the field of treatment development for depression and anxiety, allowing users to engage with CBT-informed digital interventions entirely remotely, anytime, anywhere, on their own schedule. The remote delivery of such treatments decreased scheduling burden, thereby improving adherence to intervention requirements and ultimately increasing cost-effectiveness. Additionally, these digital interventions can be delivered to individuals who are unable or unwilling to come into the clinic. The increasing ubiquity, affordability and ownership of digital technologies allow these CBT-informed interventions to reach underserved vulnerable populations, including members of ethnic minorities, low-income groups, and individuals living in rural and low-resource settings, ultimately addressing the disparities in healthcare provision.

Today, there is increased research interest in using apps for mental health, increased ownership, increased access and use of mental health apps by patients and health care organizations. Evidence indicates that people experiencing depression and anxiety already use, or are interested in using, mobile and web-based technology to manage their conditions, and that these are acceptable across a range of age, sex, educational level and clinical characteristics (Andrews et al., 2018). Several reviews and meta-analyses have been published on digital interventions for adults with depression and anxiety, they show that most interventions have been tested in small studies and reported short-term feasibility and acceptability, largely with positive findings (Lehtimaki et al., 2021; Saramago et al., 2021; Garrido et al., 2019, Lakhtakia and Torous, 2022).

Although the length of intervention does not seem to be relevant to its effectiveness, questions around the performance of these digital interventions over longer durations, in more heterogeneous patient groups, have been raised numerous times (Li et al., 2014; Economides et al., 2019). Additionally, reviews and meta-analyses have often not categorized the interventions based on their guiding psychological principles, grouping together treatments that have very little in common from a therapeutic point of view. Research shows that individual tailoring of computerized treatments is required not only to increase population reach, uptake, and adherence, but also to deliver treatment benefits and improve mental health (Treanor et al., 2021). Another aspect raised by reviews and meta-analyses is that such interventions have lacked rigorous evaluation frameworks, relying on outcome measures that were often non-sufficiently validated in the field (Firth et al., 2017). Taken together, these suggestions indicate that, in terms of scientific evidence on the effectiveness of these various interventions, the data are still scarce. In light of such limitations, this review aims to rigorously scrutinize the literature on CBT-informed digital interventions for depression and anxiety.

2. Methods

2.1. Search strategy

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Page et al., 2021). PRISMA checklist is provided in Supplementary Table 1. Peer-reviewed, English-language research articles were selected for the review; non-human, review and meta-analytic reports were excluded. We identified studies for inclusion through searching the electronic database PubMed. Three sets of keyword search algorithms were used, linked with the Boolean operator AND. The first was related to diagnosis: "anxi*" OR "depr*" OR "affective" OR "mood". The second was related to the intervention and included "interventio*" OR "program*" OR "therap*" OR "treatmen*" OR "app". The third set of search terms was related to the delivery method: "remote" OR "digital" OR "telepsychiatry" OR "online" OR "mobile" OR "app". The following filters were applied: Clinical Trial, Controlled Clinical Trial, Randomized Controlled Trial, Adult: 19+ years.

The search was conducted on October 31th, 2021. Using these criteria, all authors screened the titles and abstracts of search results. During this screening phase, we excluded study protocols that failed to clearly meet inclusion criteria (below). Whenever at least one author raised concerns about study inclusion, the full text was inspected and all authors discussed the study until a consensus was reached. For all search results that passed the first screening, we retrieved and reviewed the full texts. Additionally, at this stage we cross-referenced lists of included studies to gather any papers that the search terms had not identified.

2.2. Eligibility criteria and study selection

We aimed to evaluate the effects of CBT-informed digital interventions on anxiety and depression in adults. Note that "CBT-informed digital intervention" is a broad-based term that can be used to refer to a range of approaches for the amelioration of clinical outcomes. The definition of a CBT-informed digital intervention was narrowed to interventions that specifically leveraged the unique features of digital technology as integral to the design of the intervention. Therefore, studies that simply applied the principles of CBT for tele-therapy, phone calls, on-line forums, SMS-based or email-based therapy were excluded. Studies were excluded if they recruited patients with bipolar or psychotic disorders, as well as if interventions were designed for patients with a primary medical condition (diabetes, HIV, chronic pain, epilepsy) and secondary psychiatric symptoms. This allowed reviewing only interventions targeting primarily depressive and anxiety symptoms. Studies were excluded if they did not use standardized and validated assessment measures of anxiety or depressive symptoms, i.e. PHQ-9 (Kroenke et al., 2001; Gilbody et al., 2007; Löwe et al., 2004) or GAD-7 (Spitzer et al., 2006; Löwe et al., 2008). The choice of restricting the review to studies using PHQ-9 or GAD-7 was made because PHQ-9 is the most validated, short self-report questionnaire designed to be used in primary care for diagnosis and management of depression. Similarly, GAD-7 is useful in primary care and mental health settings as a screening tool and symptom severity measure for the four most common anxiety disorders (Generalized Anxiety Disorder, Panic Disorder, Social Phobia and Post Traumatic Stress Disorder).

Moreover, studies were included if they: 1) were peer-reviewed, English language original articles, 2) recruited and reported data for patients aged 18+, 3) presented findings from Randomized Controlled Trials (RCTs). Studies were excluded if they: 1) only provided data on feasibility, acceptability or engagement, or no data (e.g. published study protocols); 2) were single-case reports or case series; and 3) were secondary analyses of original data previously reported.

For articles that were rated as not eligible by at least one author, we held a discussion meeting where we analyzed any disagreements until a consensus about study inclusion was reached. All articles matching our eligibility criteria were reviewed in full by the authors. From each RCT, we extracted demographics, clinical characteristics (diagnosis, age), and when available, within-group effect sizes of measured clinical and cognitive outcomes. For every mismatch in extracted data, all authors discussed the trial until a consensus was reached. Given the heterogeneity of study designs and samples, we did not code variables related to medication.

Risk of bias assessment was compliant with recent guidelines from the Agency for Healthcare Research and Quality Evidence-based Practice Center (Viswanathan et al., 2012). Constructs used to assess the risk of bias of individual studies included: Poor or inadequate reporting, Selective outcome reporting, Outcome measures, Study design, Fidelity to protocol, Conflict of interest from sponsor bias, and Applicability/external validity. Whenever risk of bias was deemed not low, and/or for every mismatch in extracted data, all authors discussed until a consensus was reached (Viswanathan et al., 2012).

3. Results

This search yielded 1432 total papers. The application of inclusion and exclusion criteria led to the selection of 35 papers, published between 2008 and 2021 (see Fig. 1). Main findings and implications of each study are reported below as well as presented in Table 1. Table 2 describes features and principles for each reviewed intervention. In this table, interventions were classified according to two criteria: i) whether they are self-guided or assisted, and ii) whether they had significant improvements both at post-intervention and at follow-up, or had improvements only at post intervention but not at follow up, or no

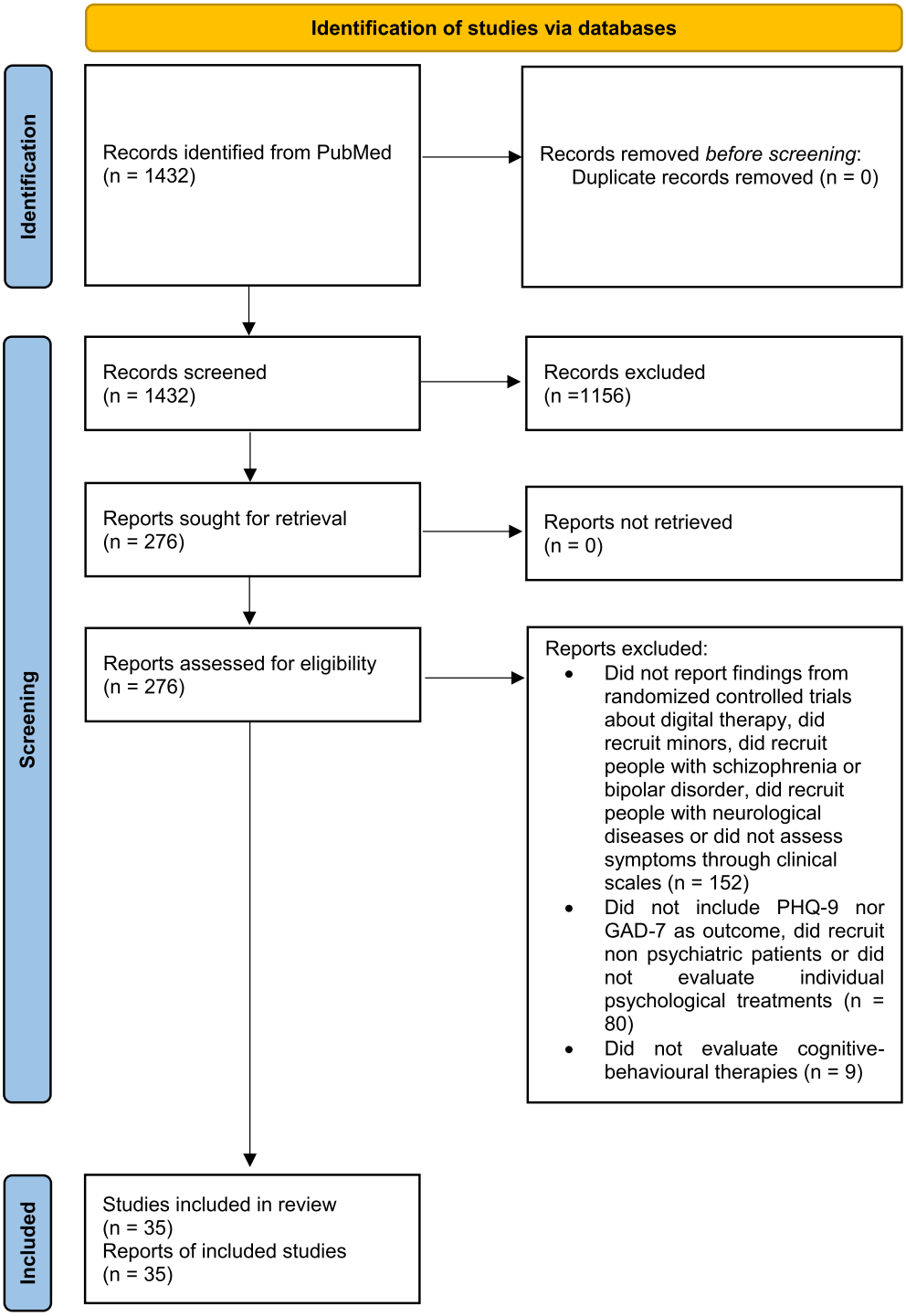

Fig. 1. The PRISMA consort flow diagram showing the process of study selection

Table 1
List of included studies.

Study	Sample	Intervention	Web or app	Method of administration	Patients in the treatment group who completed post-treatment questionnaires	Control condition	Patients in the control group who completed post-treatment questionnaires	Duration (weeks)	Follow-up	Outcome measures
Titov et al., 2008	DSM-IV criteria for social anxiety disorder	Shyness Program	Web	CaCCBT, SgCCBT	CaCCBT 30 SgCCBT 27	WL	34	10	No	SIAS, SPS, PHQ-9, K-10
Robinson et al., 2010	DSM-IV criteria for generalized anxiety disorder	Worry Program	Web	CaCCBT, TaCCBT	CaCCBT 45 TaCCBT 46	WL	47	10	3 months	PHQ-9, GAD-7, PSWQ, K-10
Perini et al., 2009	DSM-IV criteria for major depression	Sadness Program	Web	CaCCBT	18	WL	17	8	No	PHQ-9, BDI-II, K-10
Wims et al., 2010	DSM-IV criteria for panic disorder	Panic Program	Web	CaCCBT	22	WL	22	8	1 month	MIA, ACQ, PHQ-9, PDSS
Titov et al., 2010a	DSM-IV criteria for generalized anxiety disorder, panic disorder and/or social anxiety disorder	Anxiety Program	Web	CaCCBT	36	WL	36	8	3 months	GAD-7, PSWQ, SPSQ, PDSS, PHQ-9, K-10, DASS-21
Titov et al., 2010b	DSM-IV criteria for social anxiety disorder	Shyness Program	Web	SgCCBT	With motivational enhancement strategies 51 Without motivational enhancement strategies 48			11	3 months	SIAS, SPS, PHQ-9, K-10
Titov et al., 2011	DSM-IV criteria for major depression, generalized anxiety disorder, panic disorder and/or social anxiety disorder	Wellbeing Program	Web	CaCCBT	34	WL	35	10	3 months	DASS-21, PHQ-9, PSWQ, PDSS, GAD-7, K-10
Choi et al., 2012	DSM-IV criteria for major depression	Brighten Your Mood Program (a culturally adapted version of the Sadness Program for Chinese Australians)	Web	CaCCBT	23	WL	28	8	3 months	PHQ-9, DASS-21, K-10
Titov et al., 2013	PHQ-9 > 9 and/or GAD-7 > 7 and/or MINI-SPIN >5 and/or ANSQ >1	Wellbeing Course	Web	SgCCBT	With automated emails 84 Without automated emails 92	WL	43	8	3 months	PHQ-9, GAD-7
Watts et al., 2013	DSM-IV criteria for major depression	Sadness Program	App vs web	CaCCBT	App 10 Web 15			8	3 months	PHQ-9, K-10, BDI-II
Roepke et al., 2015	CES-D ≥ 16	SuperBetter	App or web	SgCCBT	CBT-PPT 20 General 18	WL	36	4	6 weeks	CES-D, GAD-7
Engel et al., 2015	CAPS criteria for PTSD	DESTRESS-PC	Web	NaCCBT	31	TAU	33	6	6 weeks	PCL, PHQ-8
Titov et al., 2015	PHQ-9 ≥ 5	Mood Course Wellbeing Course	Web	CaCCBT, SgCCBT	Mood Course Disease Specific 119 Wellbeing Course Trans-Diagnostic 142			8	3 months 12 months 24 months	PHQ-9, GAD-7, MINI-SPIN, PDSS, K-10

(continued on next page)

Table 1 (*continued*)

Study	Sample	Intervention	Web or app	Method of administration	Patients in the treatment group who completed post-treatment questionnaires	Control condition	Patients in the control group who completed post-treatment questionnaires	Duration (weeks)	Follow-up	Outcome measures
Birney et al., 2016	PHQ-9 10–19	MoodHacker	App	SgCCBT	CaCCBT 117 SgCCBT 116 140	Vetted websites on depression	146	6	10 weeks	PHQ-9, BADS, ATQ-R
Milgrom et al., 2016	DSM-IV criteria for post-natal major depressive episode	MomMoodBooster	Web	CaCCBT	19	TAU	21	6	9 weeks 12 weeks	SCID-I, BDI-II, PHQ-9, DASS-21
Deady et al., 2016	DASS-21 $\geq$ 7 AUDIT $\geq$8	DEAL Project	Web	SgCCBT	30	AC	26	4	3 months 6 months	PHQ-9, TOT-AL
Klein et al., 2016	PHQ-9 5–14	Deprexis	Web	SgCCBT if PHQ-9 5–9, CaCCBT if PHQ-9 10–14	395	TAU	399	12	6 months	PHQ-9, HDRS, QIDS
Salisbury et al., 2016	CIS-R criteria for major depression	Healthlines Depression Service	Web	TaCCBT	255	TAU	270	16	8 months 12 months	PHQ-9, GAD-7
Zwerenz et al., 2017	BDI-II $\geq$ 13 and ICD-10 criteria for major depression	Deprexis	Web	SgCCBT	109	AC	110	12	No	BDI-II, PHQ-9, GAD-7
Kuhn et al., 2017	PCL-C $\geq$ 35	PTSD Coach	App	SgCCBT	51	WL	52	12	3 months	PCL-C, PHQ-8
Rosso et al., 2017	DSM-IV-TR criteria for major depression	Sadness Program	Web	TaCCBT	30	AC	30	10	No	HDRS, PHQ-9, K-10
Gilbody et al., 2017	PHQ-9 $\geq$ 10	MoodGYM	Web	SgCCBT, CaCCBT	SgCCBT 128 CaCCBT 141			16	1 year	PHQ-9, GAD-7
Tomasino et al., 2017	PHQ-8 $\geq$ 8 GDS-15 $\geq$ 7	MoodTech	Web	CaCCBT	Individual 9 Peer-support 19	WL	12	8	No	PHQ-9, GAD-7, SPS
Forsell et al., 2017	DSM-IV criteria for major depression	Stockholm Internet Psychiatry Clinic	Web	CaCCBT	20	TAU	17	10	No	MADRS-S, EPDS, GAD-7, ISI, AUDIT, DUDIT
Mantani et al., 2017	DSM-5 criteria for treatment-resistant major depression (BDI-II $\geq$ 10 despite antidepressant drug at adequate dosage for at least 4 weeks)	Kokoro-App	App	CaCCBT	81	TAU	83	8	No	PHQ-9, BDI-II
Newby et al., 2018	DSM-5 criteria for illness anxiety disorder or somatic symptom disorder	Health Anxiety Program	Web	CaCCBT	37	PE	32	12	No	SHAI, GAD-7, K-10, CABAH
Hadjistavropoulos et al., 2017	PHQ-9 $\geq$ 5 GAD-7 $\geq$ 5	Wellbeing Course	Web	CaCCBT	Standard weekly therapist support 76 Optional weekly therapist support 71			8	No	PHQ-9, GAD-7, K-10, PDSS, SIAS, SPS
		Beating the Blues	Web	CaCCBT		TAU	94	24		

(*continued on next page*)

Table 1 (*continued*)

Study	Sample	Intervention	Web or app	Method of administration	Patients in the treatment group who completed post-treatment questionnaires	Control condition	Patients in the control group who completed post-treatment questionnaires	Duration (weeks)	Follow-up	Outcome measures
Rollman et al., 2018	PHQ-9 ≥ 10 GAD-7 ≥ 10				With internet support group 260 Without internet support group 258				12 months	GAD-7, PHQ-9
Loughnan et al., 2019	PHQ-9 ≥ 9 GAD-7 ≥ 9	MUMentum Pregnancy	Web	SgCCBT	23	TAU	36	9	4 months	PHQ-9, GAD-7, K-10, EPDS, BDI-II
Reins et al., 2019	DSM-IV criteria for major depression	GET.ON Mood Enhancer	Web	CaCCBT	54	PE	55	6	12 weeks	HRDS, QIDS, PHQ-9, HADS
Stiles-Shields et al., 2019	PHQ-9 ≥ 10 QIDS ≥11	Thought Challenger Boost Me	App	CaCCBT BA	7	WL	10	6	No	PHQ-9, QIDS
Moberg et al., 2019	PHQ-9 5–14 GAD-7 5–14	Pacifica	App	SgCCBT	79	WL	101	4	No	DASS-21, PHQ-8, GAD-7
Segal et al., 2020	PHQ-9 5–9	Mindful Mood Balance	Web	SgMBCT	164	TAU	198	12	1 year	PHQ-9, GAD-7
Fletcher et al., 2021	PHQ-2 ≥ 2	myCompass online program (SgCCBT) This Way Up program (CaCCBT) [Nurse-led collaborative care]	Web	SgCCBT CaCCBT	451 + 80 [+79] = 531 [+79] = 610	TAU	673	12	1 year	PHQ-9, GAD-7
Raevuori et al., 2021	ICD-10 criteria for major depression	Meru Health Program	App	CaCCBT	44	TAU	48	8	3 months 6 months	PHQ-9, GAD-7, ISI, PSS

Note. Abbreviations: ACQ = Agoraphobic Cognitions Questionnaire; ATQ-R = Automatic Thoughts Questionnaire-Revised; AUDIT = Alcohol Use Disorders Identification Test; BADS = Behavioral Activation for Depression Scale; BDI = Beck Depression Inventory; CABAH = Cognitions About Body And Health Questionnaire; CES-D = Center for Epidemiologic Studies Depression; DASS-21 = Depression Anxiety Stress Scales; DUDIT = Drug Use Disorders Identification Test; EPDS = Edinburgh Postnatal Depression Scale; GAD-7 = Generalized Anxiety Disorder 7-Item Scale; HADS = Hospital Anxiety and Depression Scale; HDRS = Hamilton Depression Rating Scale; ISI = Insomnia Severity Index; K-10 = Kessler 10; MADRS-S = Montgomery-Åsberg Depression Rating Scale-Self Report; MIA = Mobility Inventory for Agoraphobia; MINI-SPIN = Mini-Social Phobia Inventory; PCL = PTSD Checklist; PDSS = Panic Disorder Severity Scale; PHQ-8 = Patient Health Questionnaire 8-Item Scale; PHQ-9 = Patient Health Questionnaire 9-Item Scale; PSS = Perceived Stress Scale; PSWQ = Penn State Worry Questionnaire; QIDS = Quick Inventory of Depressive Symptomatology; SHAI = Short Health Anxiety Inventory; SIAS = Social Interaction Anxiety Scale; SPS = Social Phobia Scale; SPSQ = Social Phobia Screening Questionnaire; TOT-AL = total alcohol past week; AC = attention control; BA = behavioral activation; CaCCBT = Clinician-Assisted Computerized CBT; CBT = Cognitive Behavioral Therapy; NaCCBT = Nurse-Assisted Computerized CBT; PE = psychoeducation; SgCCBT = Self-Guided Computerized CBT; TaCCBT = Technician-Assisted Computerized CBT; TAU = treatment as usual; WL = waiting list.

significant improvements at post-intervention.

Titov et al. (2008) conducted in 2008 the first RCT of guided versus self-guided internet-based CBT (iCBT) for Social Phobia. A program consisting of 6 sessions to be completed within 10 weeks was offered using two delivery methods: clinician-assisted iCBT (completed by 30 patients), and self-guided iCBT (completed by 27 patients). Additionally, 34 patients were randomized to the treatment as usual (TAU) arm. Trial findings showed greater efficacy on anxiety for clinician-assisted iCBT compared to self-guided iCBT and TAU, while no significant differences emerged on depression ratings. The potential benefits of clinical assistance for iCBT were further investigated by Robinson et al. (2010), who compared clinician vs. technician assisted iCBT in patients with generalized anxiety disorder. In this three-arm RCT, patients were randomized to clinician-assisted (completed by 45 patients), technician-assisted CBT (completed by 46 patients), and waiting list (WL, completed by 47 participants). Here too, the iCBT program consisted of 6 sessions to be completed within 10 weeks. Compared to WL, the assisted iCBT programs induced similar reductions of anxiety and depression, with effect sizes comparable to those observed in face-to-face CBT.

Building upon this line of research, Titov et al. (2010a, 2010b) studied the augmentation effect of motivational enhancement strategies (ME) on self-guided iCBT. In this two-arm RCT, patients were randomized to 11 weeks of iCBT (48 completers) vs iCBT + ME (51 completers). ME did not significantly augment the efficacy of iCBT on anxiety and depression. Titov et al. (2010a, 2010b) conducted a RCT where patients with various anxiety disorders (Generalized Anxiety Disorder, Panic Disorder, Social Phobia) were randomized to 8 weeks of clinician-assisted iCBT (36 completers) vs WL (36 completers), with significant reductions in the experimental arm for anxiety and depression. The following year, the same research group (Titov et al., 2011) used a similar design to study the transdiagnostic efficacy of clinician assisted iCBT. Patients with various anxiety disorders were randomized to 10 weeks of clinician assisted iCBT (34 completers) vs WL (35 completers),

Table 2
Categorization of studies based on presence/absence of clinical assistance and Significant improvement at post-intervention.

	Significant improvement at post-intervention and at follow-up	Significant improvement at post-intervention (no follow-up data)	No significant improvement at post-intervention	Total
Self-guided	a 12 interventions	b 2 interventions	c 1 interventions	15
Assisted	d 16 interventions	e 8 interventions	f 1 interventions	25
Total	28	10	2	40

Category a. Shyness program (Titov et al., 2010a, 2010b): A computerized CBT consisting of six online lessons, homework assignments and participation in an online discussion forum. Part of the content of each lesson was presented in the form of an illustrated story about a young man with social phobia who, with the help of a clinical psychologist, successfully gains mastery over his symptoms;
Wellbeing course, Self-guided version (Titov et al., 2013; Titov et al., 2015): A five lesson transdiagnostic online intervention based on models of cognitive behavioral and interpersonal therapies. Participants are strongly encouraged to learn about and practice the psychological skills taught in the course, and to adopt these into their everyday lives. The course systematically teaches core psychological skills that aim to increase the frequency of cognitions and behaviors that promote emotional health, and reduce those that maintain distressing symptoms; SuperBetter (Roepke et al., 2015): A computer- and smartphone-based self-help program based on cognitive-behavioral therapy and positive psychotherapy strategies to target depression. The general version of SuperBetter focused on self-esteem and acceptance; Mood course, Self-guided version (Titov et al., 2015): It includes 5 lessons delivered online over 8 weeks, lesson summaries and homework assignments for each lesson. Each lesson is presented in a slide format combining text and images; MoodHacker (Birney et al., 2016): A 6-week CBT-based depression self-management mobile app. It's designed to educate users about depression and the benefits of CBT-based strategies to improve mood self-management and to activate (1) daily mood and activity monitoring, (2) increased engagement in positive behavioral activities, (3) decreased negative thinking and increased positive thinking, (4) increased practice of gratitude, mindfulness, and strength-based cognitions and behaviors, and (5) daily practice of these skills to improve depression symptoms and increase resilience to future mood disturbances; DEAL Project (Deady et al., 2016): An automated Web-based self-help intervention that consists of four 1-hour modules to be completed over a 4-week period (homework is provided at the conclusion of each module and reviewed at the beginning of the subsequent module). The program is based on the SHADE program, which consists of evidence-based CBT and motivational interviewing; Deprexis, Self-guided version (Klein et al., 2016): An online self-help intervention including an eclectic program that uses techniques from different psychotherapeutic orientations like CBT, positive psychology, emotion-focused therapy, and dream work; PTSD Coach (Kuhn et al., 2017): A skills-based, nontrauma-focused intervention that includes four major sections: Learn, Self Assessment, Manage Symptoms, and Find Support. In the Manage Symptoms section, users can practice Cognitive Behavioral Therapy (CBT)– based tools for PTSD-related symptoms; MoodGYM, Self-guided version (Gilbody et al., 2017): A free-to-use, internet-based, interactive CBT program for depression. It consists of five interactive modules released sequentially and lasting approximately 30–45 min and a sixth session that is predominantly consolidation and revision. The program provides patients with CBT techniques to overcome patterns of unhelpful thinking using cartoon characters to represent habits of thought; MUMentum Pregnancy (Loughnan et al., 2019): A brief unguided iCBT intervention tailored specifically to women experiencing generalized anxiety and depressive symptoms in the antenatal period; Mindful Mood Balance (Segal et al., 2020): A web-based application that delivers an 8-session mindfulness-based cognitive therapy through a self-administered platform; myCompass online program (Fletcher et al., 2021): An interactive, self-help Internet resource consisting of information, accounts of others' experiences, CBT-based treatment modules with home tasks, and mood tracking functions.
Category b. Deprexis, Self-guided version (Zwerenz et al., 2017): An online self-help intervention including an eclectic program that uses techniques from different psychotherapeutic orientations like CBT, positive psychology, emotion-focused therapy, and dream work. vs. an active control group of weekly online information on depression. It was a blended care approach, including online intervention combined with inpatient face-to-face psychotherapy; Pacifica (Moberg et al., 2019): A self-help app for the self-management of mild-to-moderate stress, anxiety, and depression. The tools implemented in the intervention are based on the integration of CBT, mindfulness, and mood and health tracking.
Category c. Shyness program (Titov et al., 2008): A computerized CBT consisting of six online lessons, homework assignments and participation in an online discussion forum. Part of the content of each lesson was presented in the form of an illustrated story about a young man with social phobia who, with the help of a clinical psychologist, successfully gains mastery over his symptoms.
Category d. Worry program (Robinson et al., 2010): An internet-based CBT program with demonstrated efficacy at reducing symptoms of GAD that consists of six online lessons, printable summary and homework assignments, automatic emails, and additional resource documents; Panic program (Wims et al., 2010): It consists of six CBT-based online lessons, homework assignments, participation in an online discussion forum and regular email contact with a mental health clinician; Anxiety program (Titov et al., 2010a, 2010b): A clinician assisted CBT administered via the internet lasting 8 weeks. It contains materials from existing disorder-specific iCBT programs for GAD, social phobia, and panic disorder. It comprises six online lessons, a summary/homework assignment for each lesson, an online discussion forum for each lesson, regular automatic reminder and notification emails and instant messaging to allow secure email; Wellbeing program (Titov et al., 2011): It is based on evidence-based principles of CBT and comprises materials derived from existing disorder-specific iCBT programs for depression, GAD, social phobia, and panic disorder. It included a weekly email or telephone contact from a clinical psychologist, and an access to a moderated online discussion forum. The clinician spent a mean time of 84.76 min (SD = 50.37) per person over the program; Brighten Your Mood Program (Choi et al., 2012): A culturally attuned version of the Sadness iCBT Program for Chinese Australians. It consisted of 6 lessons conducted over an 8 week period. The lessons read like a comic book and participants follow the story of Jess, a comic character that has depression, and through her story learn how she comes to manage her symptoms, and participants can then apply these principles to their own life. It included a weekly telephone support with Mandarin/Cantonese-speaking support personnel; Sadness program (Watts et al., 2013): It consisted of 6 lessons conducted over an 8 week period. The lessons read like a comic book and participants follow the story of Jess, a comic character that has depression, and through her story learn how she comes to manage her symptoms, and participants can then apply these principles to their own life; DESTRESS-PC (Engel et al., 2015): It utilizes a variant of CBT-based and stress inoculation training approaches in a nurse-guided online patient self-management paradigm for PTSD; Mood course, Assisted version (Titov et al., 2015): It includes 5 lessons delivered online over 8 weeks, lesson summaries and homework assignments for each lesson. Each lesson is presented in a slide format combining text and images; Wellbeing course, Assisted version (Titov et al., 2015): A five lesson transdiagnostic online intervention based on models of cognitive behavioral and interpersonal therapies for the treatment of major depression and symptoms present in comorbidities. Participants are strongly encouraged to learn about and practice the psychological skills taught in the course, and to adopt these into their everyday lives. The course systematically teaches core psychological skills that aim to increase the frequency of cognitions and behaviors that promote emotional health, and reduce those that maintain distressing symptoms; MomMoodBooster (Milgrom et al., 2016): A CBT intervention for postnatal depression that is highly interactive, includes a partner website, and is supported by low-intensity telephone coaching; Deprexis, Assisted version (Klein et al., 2016): An online self-help intervention including an eclectic program that uses techniques from different psychotherapeutic orientations like CBT, positive psychology, emotion-focused therapy, and dream work; Healthlines Depression Service (Salisbury et al., 2016): A guided self-help treatment where reading material, assessments, homework and work-sheets delivered via a secure online platform + a CBT-trained, and regularly supervised, therapist providing regular feedback, encouragements and support in written messages mirroring the interventions; MoodGYM, Assisted version (Gilbody et al., 2017): A free-to-use, internet-based, interactive CBT program for depression. It consists of five interactive modules released sequentially and lasting approximately 30–45 min and a sixth session that is predominantly consolidation and revision. The program provides patients with CBT techniques to overcome patterns of unhelpful thinking using cartoon characters to represent habits of thought: Beating the Blues (Rollman et al., 2018): It consists of a 10-minute introductory

video followed by eight 50-minute interactive sessions. Each session used easily understood text, audiovisual clips, and "homework" assignments to impart basic CBT techniques; GET.ON Mood Enhancer (Reins et al., 2019): A guided self-help iCBT intervention that consists of six interactive sessions. Each session lasts about 30 min; This Way Up program (Fletcher et al., 2021): It comprises six structured online lessons using CBT principles and includes lessons in the form of an illustrated story about someone with depression, printable summaries, and homework assignments, and symptom monitoring at the beginning of each session.

Category e. Shyness program, Assisted version (Titov et al., 2008): A computerized CBT consisting of six online lessons, homework assignments and participation in an online discussion forum. Part of the content of each lesson was presented in the form of an illustrated story about a young man with social phobia who, with the help of a clinical psychologist, successfully gains mastery over his symptoms; Sadness program (Perini et al., 2009; Rosso et al., 2017): It consisted of 6 lessons conducted over an 8 week period. The lessons read like a comic book and participants follow the story of Jess, a comic character that has depression, and through her story learn how she comes to manage her symptoms, and participants can then apply these principles to their own life; MoodTech (Tomasino et al., 2017): An online intervention for depression based on CBT principles developed for adults aged 65 years and older. One group included Peer support and coaches primarily interacted with participants through group moderation. Moderation involved daily review of the feed to monitor safety, identify unanswered questions, and reinforce use; Stockholm Internet Psychiatry Clinic (Forsell et al., 2017): An adapted version of the iCBT for depression currently (2017) in use in regular care at the Internet Psychiatry Clinic in Stockholm since 2007. The treatment was a guided self-help treatment where reading material, assessments, homework and work-sheets were delivered via a secure online platform. Patients also had a CBT-trained, and regularly supervised, therapist providing regular feedback, encouragements and support in written messages mirroring the interventions; Kokoro-App (Mantani et al., 2017): A self-help smartphone app consisting of eight sessions, including one welcome session, two sessions on self-monitoring, two sessions on behavioral activation, two sessions on cognitive restructuring, and an epilog focusing on relapse prevention. In each session, explanation of the principles and skills of CBT is provided in the format of instant messenger exchanges among cartoon characters; Health Anxiety Program (Newby et al., 2018): A 6-lesson illustrated comic-style clinician-guided iCBT program for health anxiety; Wellbeing course, Assisted version (Hadjistavropoulos et al., 2017): A five lesson transdiagnostic online intervention based on models of cognitive behavioral and interpersonal therapies. Participants are strongly encouraged to learn about and practice the psychological skills taught in the course, and to adopt these into their everyday lives. The course systematically teaches core psychological skills that aim to increase the frequency of cognitions and behaviors that promote emotional health, and reduce those that maintain distressing symptoms; Thought Challenger (Stiles-Shields et al., 2019): An Android app based upon thought restructuring (the core strategy in Cognitive Therapy, that involves identifying and appraising maladaptive thoughts and creating adaptive counter thoughts).

Category f. Meru Health Program (Raevuori et al., 2021): A therapist-guided, 8-week intervention for depression delivered via a smartphone app. Consists of 8 modules, with content derived from Mindfulness-Based Stress Reduction, Mindfulness-Based Cognitive Therapy, CBT and Behavioral Activation Therapy. The content includes text, videos, audio-guided mindfulness exercises, infographics illustrating CBT principles, and journal prompts. Daily content and practice time range between 10 and 45 min. It includes anonymous peer support via moderated group discussion board, and asynchronous support by a remote therapist, who review participant engagement and provide one-to-one support via chat messaging and, infrequently, by phone calls.

with significant reductions in the experimental arm for anxiety and depression. Titov et al. (2013) conducted an adequately powered three-arm RCT, where patients with anxiety and depression were randomized to self-guided iCBT (92 completers), self-guided iCBT with email-based engagement reminders (84 completers), and WL (43 completers). While iCBT expectedly improved anxiety and depression compared to WL, automatic emails were proven efficacious in increasing completion rates of iCBT, and in inducing greater clinical improvements in patients who had more severe symptoms at baseline. The line of research on the value of transdiagnostic applications of iCBT culminated in a publication by Titov et al. (2015), who conducted a large 4-arm RCT, where 290 patients with PHQ-9 > 5 and comorbid anxiety were randomized based on two criteria: a disease-specific, 8-week iCBT program vs a transdiagnostic 8-week iCBT program, and self-guided iCBT vs clinician-assisted iCBT. Once again, while similarly efficacious on multiple anxiety and depression outcomes, no significant differences emerged based on disease specific vs transdiagnostic approaches, or on self-guided vs clinician-assisted modality. Research on the type of clinical assistance required to ensure the efficacy of iCBT continued with an interesting publication by the same group (Hadjistavropoulos et al., 2017), who conducted a two-arm RCT where patients seeking iCBT for depression and/or anxiety received two forms of web-based, 8 week clinician-assisted iCBT, one where weekly therapist support was provided regularly (76 completers), and one where it was made available upon patient request (61 completers). Here too, while generally efficacious for anxiety and depression, these two approaches did not reveal significant between-group differences.

The first RCT on the effects of iCBT for Major Depression Disorder (MDD) was published in 2009. Perini et al. (2009) compared an 8-week iCBT program (18 patients) vs WL (17 patients). While results from this underpowered study indicated a significant reduction of depressive symptoms, the small sample size and the absence of an active control condition greatly limit the generalizability of the findings. The same limitations apply to the first study that examined the efficacy of iCBT on panic disorder (PD). Wims et al. (2010) conducted a two-arm RCT where PD patients with or without agoraphobia were randomized to an 8-week clinician-assisted iCBT program (22 completers) vs WL (22 completers). Here too, clinician-assisted ICBT showed significant reductions of panic and depressive symptoms. Choi et al. (2012) ran a 2-arm RCT where patients with MDD were randomized to 8-weeks of a iCBT program culturally attuned to Chinese Australians (23 completers) vs WL (28 completers). Results from this study showed a reduction of depressive symptoms in iCBT vs WL.

2013 marks the advent of mobile technology into the field of digital health research. Researchers began to investigate the comparative efficacy of mobile phone vs. computer-based interventions. Watts et al. (2013) conducted a small, pilot RCT where MDD patients were randomized to smartphone-based, clinician-assisted CBT (mCBT, 10 completers) vs clinician-assisted iCBT (15 completers). Albeit underpowered, the study indicated similar efficacy between the two delivery methods.

Two years later, Roepke et al. (2015) reported on a three-arm RCT that studied the effects of two forms of self-guided CBT for depression. The first version consisted of CBT with positive psychology strategies (CBT-PP), the later version focused CBT on self-esteem and acceptance. These two interventions could be accessed via app or web, and required the engagement of at least 10 min/day for a month. Patients were randomized to CBT-PP (20 completers), general CBT (18 completers), or WL (36 completers). While both versions of CBT improved depressive symptoms compared to WL, no significant differences emerged between the two.

Research on the efficacy of iCBT expanded its investigations to the study of clinical subpopulations, comorbidities with substance use disorders, and blended treatment approaches. The first RCT on the effects of iCBT for PTSD was published in 2015. Engel et al. (2015) randomize patients with PTSD to nurse-assisted, internet-based, 6-week iCBT program (31 completers) vs treatment as usual (TAU, 33 completers). Interestingly, 6 weeks were sufficient for iCBT to induce significant improvements in PTSD symptoms, but not in depressive symptoms. Kuhn et al. (2017) conducted a similar study where PTSD patients were randomized to a 3-month, mCBT program (51 completers) vs WL (52 completers). The experimental arm induced significantly larger improvements in PTSD and depressive symptoms, suggesting that a longer intervention may be required to target depression.

Given that pregnancy and postpartum are known to be vulnerable time windows for the emergence of depressive symptoms, several studies investigated the efficacy of iCBT in this patient group. Forsell et al. (2017) conducted a two-arm RCT where women with antenatal

depression were randomized to a 10-week clinician-assisted iCBT program focused on antenatal depressive symptoms (39 completers) vs TAU (17 completers). Women in the experimental arm showed greater improvements in depression and anxiety compared to TAU.

Loughnan et al. (2019) explored the efficacy of self-guided iCBT for antenatal depression and anxiety. In this two-arm RCT, women were randomized to a 9-week iCBT program (23 completers) vs TAU (36 completers). Compared to TAU, women in the experimental arm showed moderate to large reductions of anxiety and psychological distress, but not for depressive symptoms. Finally, in their two-arm RCT, Milgrom et al. (2016) randomized women with postnatal depression to 6 disease-specific, weekly clinician-assisted iCBT sessions (19 completers) vs TAU (21 completers). iCBT showed preliminary efficacy, with greater reduction in depressive symptoms and a significantly higher percentage of clinical remission compared to TAU.

The impact of iCBT was also investigated in other vulnerable periods of life: youth and senility. Deady et al. (2016) studied the effects of iCBT-based Intervention for co-occurring depression and problematic alcohol use in youth aged 18–25. Participants were randomized to a 4-week, self-guided, iCBT program (30 completers) or a web-based attention-control condition (26 completers). Compared to the control condition, youth randomized to iCBT showed larger improvements in depression and reduced alcohol abuse. Finally, in their small three-arm RCT, Tomasino et al. (2017) investigated the effects of a 8-week iCBT program, delivered in an unguided fashion (9 completers) or harnessing peer support (19 completers), vs WL (12 completers). While the study is certainly underpowered to draw any conclusions, findings from previous studies are replicated here, with general efficacy on anxiety and depression, but lack of augmentation with peer support.

From 2016 onwards, several research groups studied the possible integration of iCBT into complex intervention packages. Salisbury et al. (2016) conducted a two-arm RCT where patients with MDD were randomized to TAU (270 completers) vs a multifaceted intervention (255 completers) that included a 4-month iCBT program focusing supplemented by regular phone calls from trained counselors who 1) followed standardized scripts generated by an interactive software; 2) guided patients in using the online platform 3) promoted engagement and 4) encouraged a healthy lifestyle. The experimental intervention induced greater reductions of anxiety and depression compared to TAU. Zwerenz et al. (2017) were the first to study unguided iCBT as an add-on to inpatient psychodynamic psychotherapy. In this two-arm RCT, MDD patients undergoing psychotherapy were randomized to 12-week of iCBT (81 completers) vs 12 weeks of computerized depression-related information (82 completers). compared to the active control condition, the iCBT program induced greater reductions in anxiety and depression. iCBT as an adjunct to evidence-based treatments was also studied by Mantani et al. (2017), who conducted a two-arm RCT where patients with refractory depression were randomized to medication switch + 8 weeks of clinician-assisted mCBT (71 completers) vs medication switch alone (83 completers). mCBT was proven to be efficacious at reducing depressive symptoms as an adjunct.

With few exceptions, one of the most problematic limitations of RCTs of iCBT is the choice of appropriate control conditions. WL and TAU are often used, although this does not allow to examine the comparative efficacy of CBT with respect to other evidence-based treatments. Only five studies conducted direct head-to-head comparisons. Birney et al. (2016) conducted an RCT where people with mild-to-moderate depression were randomized to 6 weeks of self-guided mCBT (140 completers) or to vetted websites on depression (146 completers). There was a significant reduction in depressive symptoms in the experimental arm. Rosso et al. (2017) recruited MDD patients, who were randomly assigned to 10 weeks of technician-assisted iCBT (30 completers) vs a monitored attention-control intervention (30 completers). Albeit underpowered, this study showed that iCBT was more efficacious at improving depressive symptoms. Newby et al. (2018) randomized patients with illness anxiety disorder or somatic symptom disorder with health anxiety to either a 6-lesson clinician-assisted iCBT program for health anxiety (37 completers) or anxiety psychoeducation, clinical support, and monitoring (32 completers) over a 12-week period. Compared to psychoeducation, patients randomized to iCBT showed greater improvements on health anxiety, depression, and generalized anxiety. Reins et al. (2019) studied in MDD patients the efficacy of iCBT (54 completers) vs unguided online psychoeducation (55 completers). Both groups showed significant improvements upon exposure to treatment, although greater improvements for depressive symptoms were observed in iCBT. A fifth RCT conducted by Stiles-Shields et al. (2019) randomly assigned depressed patients to 6 weeks of clinician-assisted mCBT (7 completers) vs clinician-assisted behavioral activation (10 completers) vs WL (10 completers). Due to the small sample size, the two experimental arms did not show significant between-group differences.

Another line of research dealt with the integration of psychological principles from other treatment models into CBT packages. Moberg et al. (2019) studied the effects of a mobile app integrating CBT with mindfulness techniques. Patients with mild-to-moderate stress, anxiety, and depression were randomized to WL (101 completers) vs 4 weeks of naturalistic app usage, without requirements in terms of frequency or intensity (79 completers). Participants in the experimental arms showed greater reductions in stress, anxiety and depression that, interestingly enough, were independent of usage patterns. Segal et al. (2020) randomized patients with residual depressive symptoms to three months of a web-based application that delivers mindfulness-based CBT + usual depression care, which included treatment with antidepressants, individual/group psychotherapy, or both vs. usual depression care only. In the experimental arm, participants had: significantly greater reductions in residual depressive symptoms; a greater proportion achieved remission; and significantly rates of depressive relapse. Recently, another app integrating CBT, mindfulness and behavioral activation was studied by Raevuori et al. (2021) as a treatment for MDD in young adults. Patients were randomized to 8 weeks of the app (44 completers) vs TAU (48 completers). No significant between-group differences emerged on depression, anxiety and insomnia, indicating questionable efficacy of the app.

The literature reviewed until here relied on samples that were often small, thereby reducing the generalization potential of study findings. Large scale RCTs for iCBT were inaugurated by a large study conducted by Klein et al. (2016). In this two-arm RCT, patients with variable severity of depressive symptoms were randomized to 12 weeks of iCBT (395 completers) vs TAU (399 completers). If depression symptoms were mild, iCBT was delivered in an unguided fashion; if they were moderate, iCBT leveraged clinician assistance. Compared to TAU, patients in the experimental arm showed a significant reduction of depressive symptoms. While this study did not examine the differences between these two delivery methods for iCBT, Gilbody et al. (2017) conducted a two-arm RCT where MDD patients were randomized to 4 months of telephone-supported, clinician-assisted iCBT (141 completers) vs self-guided iCBT (128 completers). Telephone support was shown to increase treatment engagement, which led to greater improvements in depression for clinician-assisted iCBT compared to self-guided iCBT, while no between-group differences were found for anxiety and somatic symptoms. A third, large scale RCT was conducted in patients with mood and anxiety disorders recruited from primary care settings. Rollman et al. (2018) randomized patients to 8 weeks of transdiagnostic clinician-assisted iCBT (258 completers) vs iCBT + internet-based support groups (260 completers) vs TAU (94 completers). While no additional effect was brought by support groups, a general reduction of anxiety and depression was observed compared to TAU. An interesting study conducted by Fletcher et al. (2021) recently attempted to match depression management to severity prognosis in primary care. In this completed RCT, patients were randomized to TAU (673 completers) vs a stepped-care iCBT treatment for depression (610 completers). If patients had mild to minimal prognosis, they were assigned to self-guided iCBT; if they had moderate prognosis, they received iCBT

with clinical assistance; if prognosis was severe, they were engaged in a collaborative care program, where qualified nurse practitioners in collaboration with primary care physicians delivered up to 8 sessions, via phone or in-person. Compared to TAU, patients in the experimental arm showed greater reductions in anxiety and depression.

4. Discussion

4.1. Main findings

Our systematic search identified 35 RCTs, examining 33 mental health interventions, of which 25 were iCBT, 6 were mCBT, and 2 were both available via mobile or web. A total of 4021 and 2744 participants were randomized to the experimental and control arms, respectively. However, the quality of the evidence in the selected studies differed widely and included a number of small-scale RCTs.

The scarce number of adequately powered and rigorously controlled RCTs indicates that numerous digital CBT-informed approaches are feasible and efficacious at reducing self-reported depressive and anxiety symptoms when measured with gold-standard self-report questionnaires. Moreover, studies reporting follow-up data show maintenance of such effects at 1.5–12 months, supporting the use of iCBT and mCBT for depression. However, effects of CBT-informed digital interventions were substantially larger when compared to inactive than active control conditions. This finding is consistent with the broader psychotherapy literature showing an overall pattern of weakening evidence and diminishing effect sizes as the control condition becomes more rigorous, raising the question of absolute vs. relative efficacy (Wampold, 2015). This highlights the importance of the comparison condition when designing and interpreting the results of RCTs. While offering overall good-quality evidence, when looking at the between-group effect sizes of the interventions reviewed here, effect sizes were medium when compared with waitlist, small when compared with active controls - a finding that is in line with recent meta-analysis (Lecomte et al., 2020) showing larger effect when smartphone-based interventions were compared with inactive controls ($g = 0.56$) than when compared with active controls ($g = 0.21$; Königbauer et al., 2017).

A second implication pertains to the difference between internet-based and mobile-based interventions. The growing evidence for digital interventions delivered through the internet as an effective means to treat affective disorders cannot be directly translated to digital interventions delivered as standalone mobile apps (Goldberg et al., 2022). While recent meta-analyses on internet-based interventions targeting depression found a mean standardized effect size of 0.90, a recent meta-analysis of 22 smartphone-based apps for depression among 18 RCTs and 3414 participants found an effect size of 0.38 for depressive symptoms (Firth et al., 2017). Unlike established internet interventions, where manuals for in-person psychotherapy can be directly translated, for app-based interventions greater attention should be directed to the process of creating from those same manuals a new treatment model that is shaped by the technological features and user interface characteristics.

Observationally and in line with a recent publication (Linardon et al., 2019), effect sizes in the medium range were found by iCBT/mCBT studies that reminded participants to engage in the intervention, that offered professional guidance, and that were used with an ongoing treatment, compared to small effects for stand-alone interventions. However, the quality of evidence remains better for stand-alone apps (Lecomte et al., 2020). Our results confirm that the therapeutic benefits of CBT-informed digital interventions are seen especially in their application in combination with other treatment methods and for mild-to-moderate levels of depression. With respect to clinicians' support and role, previous research has shown that health care professionals play a vital role when it comes to the application of new and effective therapeutic approaches (Sekhon et al., 2017). They are the primary advisors to patients and directly influence their attitude formation towards a treatment method. A combined therapeutic approach may not only be more effective for patients in improving adherence and outcomes, but also more acceptable to practitioners and therefore easier to implement in clinical practice.

Finally, although all studies that showed post-treatment improvements proved maintenance of these effects at follow-up assessments, there were large differences in follow-up times, and drop-outs were dealt with inconsistently across studies. Unlike the psychotherapy literature in which treatments are often time-limited and meta-analyses can cleanly examine effects at post-treatment versus follow-up (Cuijpers et al., 2007), digital interventions - particularly those without guidance - can be easily accessed ongoingly thus making demarcation of "post-treatment" more ambiguous. As a result, although the sustainability of improvements, possible presence of sleeper effects and long-term adherence all need to be confirmed in studies over a longer period of time, this endeavor could unfortunately become rather problematic (Mohr et al., 2017). A rush to implementation has proven detrimental to the longer-term adoption of mobile interventions, which would greatly improve if the design looked less like Internet-based manualized treatments, and more in line with ways in which people today use smartphones. How to reconcile this with the need to conduct rigorous research? Traditional study designs such as RCTs that are typical of the pharmaceutical development and FDA-approval model can take up to fifteen years to move an intervention from initial conceptualization to implementation. Conversely, digital technologies are continuously evolving to address changes in the technological ecosystem, thus requiring rapid evaluation to prevent obsolescence. As a consequence, trials evaluating their efficacy should not lock down intervention elements, but allow for the integration of continuous quality improvement methods and principles of iterative design.

4.2. Limitations

Our preliminary findings should be interpreted carefully as they are affected by several limitations that are inherent to the specific research field.

First, the observed effects on depressive symptoms could arise from using the device itself, rather than the psychotherapeutic components of the intervention. In other words, we cannot exclude for all reviewed interventions a "digital-placebo" effect related to the use of the device itself or from the expectations' effect rather than from possible active components (Torous and Firth, 2016).

A second shortcoming relates to our inclusion and exclusion criteria. We chose to exclusively review studies that used at least GAD-7 for anxiety symptoms, and at least PHQ-9 for depressive symptoms. While PHQ-9 is the most validated, short self-report questionnaire for diagnosis and management of depressive disorders, anxiety disorders have specific symptomatology beyond general anxiety. As a matter of fact, GAD-7 may not be the best screening tool and symptom severity measure for panic disorder, social phobia and post-traumatic stress disorder. In limiting our search to studies that used GAD-7, we may have missed interventions targeting specific aspects of anxiety and assessing efficacy through disease-specific measures.

Another limitation in this field is the significant heterogeneity found across the studies. This could be due to two sets of factors: i) because digital interventions for affective disorders are a new research topic (the majority of RCTs were published in the last five years) the current evidence is limited even if this area of research is gaining significant momentum and is growing exponentially; ii) CBT has experienced alterations and divisions into smaller treatment sections (e.g., mindfulness-based therapy as a component of CBT). These alterations lead to an imprecise use of the definition of CBT. Heterogeneity was substantial in most analyses, as was risk of bias. In this review, heterogeneity was not explored in a content-focused manner, nor did we investigate the effects of different features and components on efficacy or engagement.

A third limitation deals with risk of bias associated with the widespread reliance on self-report measures as outcome measures within this literature. In our review, only 19 studies out of 35 (54,29 %) recruited the sample from a clinical setting with an actual clinician-administered diagnosis. The remaining studies recruited from the general population and partly used self-assessment tools for inclusion. 16 studies out of 35 (45,71 %) were conducted with nonclinical populations, who presented with symptoms in absence of a diagnosed disorder. This is typical for digital interventions that tend to recruit from large pools of individuals, sometimes the entire internet. A previous meta-analysis demonstrated that clinician-rated instruments yield significantly larger effect sizes in psychotherapy trials than self-reported measures (Cuijpers et al., 2010). Coupled with the lack of blinding of personnel and participants and the difficulty inherent in blinding participants to psychological interventions all diminish the confidence in study results, and limit their generalizability for clinical populations. The quality of this field of literature would greatly be improved through the use of objective measures (to reduce bias due to self-reports or unblinded outcome assessors), use of intention-to-treat analyses (to reduce bias due to incomplete outcome data), and preregistration of outcomes (to reduce selective reporting bias). Furthermore, research is needed to establish the ways in which user engagement, expectancy effects, and individual patient characteristics influence intervention outcomes.

4.3. Final considerations and future directions

Several CBT-informed digital interventions for adult patients with affective disorders have shown feasibility and efficacy. If so, why are these interventions poorly disseminated, implemented, and accessed? Based on our review, we have identified two reasons. First, awareness of existing CBT-informed digital interventions seems to be quite low. Professionals lack knowledge and experience related to use in the treatment of affective disorders. The provision of information on the potential benefits of such interventions as well as the training of professionals in the application of new technologies may increase mental health care professionals' awareness and knowledge about CBT-informed interventions for the treatment of affective disorders. Second, although digital technologies hold the potential to reduce disparities in mental health care, evolving technologies may, in fact, widen gaps between those who can access digital care and those who cannot. One of many reasons for this might be the fact that validated and reliable interventions are often not freely available because they were designed for study purposes, and have not been integrated into standard health care provision. Despite these limitations, CBT-informed digital interventions have accumulated enough scientific evidence to be positioned today as: i) a possible low-intensity intervention tool for those with subclinical or less severe levels of symptoms; ii) a first step in a stepped-care approach to service delivery (van Straten et al., 2015), with more intensive resources reserved for those who fail to respond; iii) a low-cost, easily accessible, and user-friendly option for selective or indicated preventive programs (Steinhubl et al., 2013) that can reduce the global burden of disease associated with affective disorders.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2023.01.057.

CRediT authorship contribution statement

Conceptualization Bruno Biagianti, Giuseppe Foti, Asia Di Liberto, Cinzia Bressi, Paolo Brambilla
Investigation, Bruno Biagianti, Giuseppe Foti, Asia Di Liberto, Cinzia Bressi, Paolo Brambilla
Methodology, Bruno Biagianti, Giuseppe Foti, Asia Di Liberto, Cinzia Bressi, Paolo Brambilla
Writing - Original draft Bruno Biagianti, Giuseppe Foti, Asia Di Liberto, Cinzia Bressi, Paolo Brambilla
Formal Analysis; Bruno Biagianti, Giuseppe Foti, Asia Di Liberto, Cinzia Bressi, Paolo Brambilla
Writing - Review & editing Bruno Biagianti, Giuseppe Foti, Asia Di Liberto, Cinzia Bressi, Paolo Brambilla
Role of the Funding source Bruno Biagianti, Giuseppe Foti, Asia Di Liberto, Cinzia Bressi, Paolo Brambilla.

This study was supported by the 2020-1366 Regione Lombardia, Cariplo e Fondazione Umberto Veronesi (PB). Additionally, this work has been supported by Fondazione Regionale per la Ricerca Biomedica (Regione Lombardia), project ID 2681424-Call MSCA Seal of Excellence.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding agencies.

Conflict of interest

PB is a co-investigator for a research project that is testing the efficacy of neuroplasticity-based cognitive training in patents with psychotic disorders. The other authors report no conflict of interest.

Acknowledgments

None.

References

Andrews, G., Basu, A., Cuijpers, P., Craske, M.G., McEvoy, P., English, C.L., Newby, J.M., 2018. Computer therapy for the anxiety and depression disorders is effective, acceptable and practical health care: an updated meta-analysis. J. Anxiety Disord. 55, 70–78. https://doi.org/10.1016/j.janxdis.2018.01.001. Epub 2018 Feb 1 PMID: 29422409.

Angermeyer, M.C., Matschinger, H., Schomerus, G., 2013. Attitudes towards psychiatric treatment and people with mental illness: changes over two decades. Br. J. Psychiatry J. Ment. Sci. 203, 146–151.

Backhaus, A., Agha, Z., Maglione, M.L., Repp, A., Ross, B., Zuest, D., Thorp, S.R., 2012. Videoconferencing psychotherapy: a systematic review. Psychol. Serv. 9, 111–131.

Birney, A., Gunn, R., Russell, J., Ary, D., 2016. MoodHacker mobile web app with email for adults to self-manage mild-to-moderate depression: randomized controlled trial. JMIR Mhealth Uhealth 4 (1), e8. https://doi.org/10.2196/mhealth.4231.

Choi, I., Zou, J., Titov, N., Dear, B.F., Li, S., Johnston, L., Andrews, G., Hunt, C., 2012. Culturally attuned internet treatment for depression amongst Chinese Australians: a randomised controlled trial. J. Affect. Disord. 136 (3), 459–468. https://doi.org/10.1016/j.jad.2011.11.003. Feb.

Collins, K.A., Westra, H.A., Dozois, D.J., Burns, D.D., 2004. Gaps in accessing treatment for anxiety and depression: challenges for the delivery of care. Clin. Psychol. Rev. 24 (5), 583–616. https://doi.org/10.1016/j.cpr.2004.06.001.

Corruble, E., 2020. A viewpoint from Paris on the COVID-19 pandemic: a necessary turn to telepsychiatry. The Journal of Clinical Psychiatry 81 (3), 1721.

Cuijpers, P., van Straten, A., Warmerdam, L., 2007. Behavioral activation treatments of depression: a meta-analysis. Clin. Psychol. Rev. 27 (3), 318–326. Pmid:17184887.

Cuijpers, P., Li, J., Hofmann, S.G., et al., 2010. Self-reported versus clinician-rated symptoms of depression as outcome measures in psychotherapy research on depression: a meta-analysis. Clin. Psychol. Rev. 30, 768–778.

Deady, M., Mills, K.L., Teesson, M., Kay-Lambkin, F., 2016. An online intervention for co-occurring depression and problematic alcohol use in young people: primary outcomes from a randomized controlled trial. J. Med. Internet Res. 18 (3), e71 https://doi.org/10.2196/jmir.5178. Mar 23.

Economides, M., Ranta, K., Nazander, A., Hilgert, O., Goldin, P.R., Raevuori, A., Forman-Hoffman, V., 2019. Long-term outcomes of a therapist-supported, smartphone-based intervention for elevated symptoms of depression and anxiety: quasiexperimental, pre-postintervention study. JMIR mHealthuHealth 7 (8), e14284.

Engel, C.C., Litz, B., Magruder, K.M., Harper, E., Gore, K., Stein, N., Yeager, D., Liu, X., Coe, T.R., 2015. Delivery of self training and education for stressful situations (DESTRESS-PC): a randomized trial of nurse assisted online self-management for PTSD in primary care. Gen. Hosp. Psychiatry 37 (4), 323–328. https://doi.org/10.1016/j.genhosppsych.2015.04.007. Jul-Aug.

Fernandez, E., Woldgabreal, Y., Day, A., Pham, T., Gleich, B., Aboujaoude, E., 2021. Live psychotherapy by video versus in-person: a meta-analysis of efficacy and its relationship to types and targets of treatment. Clin. Psychol. Psychother. 28 (6), 1535–1549. https://doi.org/10.1002/cpp.2594. Nov.

Firth, J., Torous, J., Nicholas, J., Carney, R., Pratap, A., Rosenbaum, S., 2017. Sarris, 697 J. 2017. The efficacy of smartphone-based mental health interventions for 698 depressive symptoms: a meta-analysis of randomized controlled trials. World Psychiatry 16 (3), 287–298.

Fletcher, S., Chondros, P., Densley, K., Murray, E., Dowrick, C., Coe, A., Hegarty, K., Davidson, S., Wachtler, C., Mihalopoulos, C., Lee, Y.Y., Chatterton, M.L., Palmer, V. J., Gunn, J., 2021. Matching depression management to severity prognosis in

primary care: results of the target-D randomised controlled trial. Br. J. Gen. Pract. 71 (703), e85–e94. https://doi.org/10.3399/BJGP.2020.0783. Jan 28.
Forsell, E., Bendix, M., Holländare, F., Szymanska von Schultz, B., Nasiell, J., Blomdahl-Wetterholm, M., Eriksson, C., Kvarned, S., Lindau van der Linden, J., Söderberg, E., Jokinen, J., Wide, K., Kaldo, V., 2017. Internet delivered cognitive behavior therapy for antenatal depression: a randomised controlled trial. J. Affect. Disord. 221, 56–64. https://doi.org/10.1016/j.jad.2017.06.013. Oct 15.
Garrido, S., Millington, C., Cheers, D., Boydell, K., Schubert, E., Meade, T., Nguyen, Q.V., 2019. What works and what doesn't work? A systematic review of digital mental health interventions for depression and anxiety in young people. Front.Psychiatry 10, 759.
Gilbody, S., Brabyn, S., Lovell, K., Kessler, D., Devlin, T., Smith, L., Araya, R., Barkham, M., Bower, P., Cooper, C., Knowles, S., Littlewood, E., Richards, D.A., Tallon, D., White, D., Worthy, G., REEACT collaborative, 2017. Telephone-supported computerised cognitive-behavioural therapy: REEACT-2 large-scale pragmatic randomised controlled trial. Br. J. Psychiatry 210 (5), 362–367. https://doi.org/10.1192/bjp.bp.116.192435. May.
Gilbody, S., Richards, D., Brealey, S., Hewitt, C., 2007. Screening for depression in medical settings with the Patient Health Questionnaire (PHQ): a diagnostic meta-analysis. J. Gen. Intern. Med. 22 (11), 1596–1602. https://doi.org/10.1007/s11606-007-0333-y. Nov.
Goldberg, S.B., Lam, S.U., Simonsson, O., Torous, J., Sun, S., 2022. Mobile phone-based interventions for mental health: a systematic meta-review of 14 meta-analyses of randomized controlled trials. PLOS Digit.Health 1 (1), e0000002.
Hadjistavropoulos, H.D., Schneider, L.H., Edmonds, M., Karin, E., Nugent, M.N., Dirkse, D., Dear, B.F., Titov, N., 2017. Randomized controlled trial of internet-delivered cognitive behaviour therapy comparing standard weekly versus optional weekly therapist support. J. Anxiety Disord. 52, 15–24. https://doi.org/10.1016/j.janxdis.2017.09.006. Dec.
Jenkins-Guarnieri, M., Pruitt, L.D., Luxton, D.D., Johnson, K., 2015. Patient perceptions of telemental health: systematic review of direct comparisons to in-person psychotherapeutic treatments. Telemedicine and e-Health 21 (8), 652–660.
Klein, J.P., Berger, T., Schröder, J., Späth, C., Meyer, B., Caspar, F., Lutz, W., Arndt, A., Greiner, W., Gräfe, V., Hautzinger, M., Fuhr, K., Rose, M., Nolte, S., Löwe, B., Anderssoni, G., Vettorazzi, E., Moritz, S., Hohagen, F., 2016. Effects of a psychological internet intervention in the treatment of mild to moderate depressive symptoms: results of the EVIDENT study, a randomized controlled trial. Psychother. Psychosom. 85 (4), 218–228. https://doi.org/10.1159/000445355.
Kodal, A., Fjermestad, K., Bjelland, I., Gjestad, R., Öst, L.G., Bjaastad, J.F., Haugland, B., Havik, O.E., Heiervang, E., Wergeland, G.J., 2018. Long-term effectiveness of cognitive behavioral therapy for youth with anxiety disorders. J.Anxiety Disord. 53, 58–67. https://doi.org/10.1016/j.janxdis.2017.11.003.
Königbauer, J., Letsch, J., Doebler, P., Ebert, D., Baumeister, H., 2017. Internet- and mobile-based depression interventions for people with diagnosed depression: a systematic review and meta-analysis. J. Affect. Disord. 223, 28–40.
Kroenke, K., Spitzer, R.L., Williams, J.B.W., 2001. The PHQ-9. Validity of a brief depression severity measure. J. Gen. Intern. Med. 16, 606613.
Kuhn, E., Kanuri, N., Hoffman, J.E., Garvert, D.W., Ruzek, J.I., Taylor, C.B., 2017. A randomized controlled trial of a smartphone app for posttraumatic stress disorder symptoms. J. Consult. Clin. Psychol. 85 (3), 267–273. https://doi.org/10.1037/ccp0000163. Mar.
Lakhtakia, T., Torous, J., 2022. Current directions in digital interventions for mood and anxiety disorders. Curr.Opin.Psychiatry 35 (2), 130–135.
Lecomte, T., Potvin, S., Corbière, M., Guay, S., Samson, C., Cloutier, B., Francoeur, A., Pennou, A., Khazaal, Y., 2020. Mobile apps for mental health issues: meta-review of meta-analyses. JMIR Mhealth Uhealth 8 (5), e17458. https://doi.org/10.2196/17458.
Lehtimaki, S., Martic, J., Wahl, B., Foster, K.T., Schwalbe, N., 2021. Evidence on digital mental health interventions for adolescents and young people: systematic overview. JMIR Ment.Health 8 (4), e25847.
Li, J., Theng, Y.L., Foo, S., 2014. Game-based digital interventions for depression therapy: a systematic review and meta-analysis. Cyberpsychol. Behav. Soc. Netw. 17 (8), 519–527.
Linardon, J., Cuijpers, P., Carlbring, P., Messer, M., Fuller-Tyszkiewicz, M., 2019. The efficacy of app-supported smartphone interventions for mental health problems: a meta-analysis of randomized controlled trials. World Psychiatry 18 (3), 325–336.
Löwe, B., Decker, O., Müller, S., Brähler, E., Schellberg, D., Herzog, W., Herzberg, P.Y., 2008. Validation and standardization of the generalized anxiety disorder screener (GAD-7) in the general population. Med. Care 46 (3), 266–274. https://doi.org/10.1097/MLR.0b013e318160d093. Mar.
Löwe, B., Unützer, J., Callahan, C.M., Perkins, A.J., Kroenke, K., 2004. Monitoring depression treatment outcomes with the patient health questionnaire-9. Med. Care 42 (12), 1194–1201. https://doi.org/10.1097/00005650-200412000-00006. Dec.
Loughnan, S.A., Sie, A., Hobbs, M.J., Joubert, A.E., Smith, J., Haskelberg, H., Mahoney, A.E.J., Kladnitski, N., Holt, C.J., Milgrom, J., Austin, M.P., Andrews, G., Newby, J.M., 2019. A randomized controlled trial of 'MUMentum Pregnancy': internet-delivered cognitive behavioral therapy program for antenatal anxiety and depression. J. Affect. Disord. 243, 381–390. https://doi.org/10.1016/j.jad.2018.09.057. Jan 15.
Mantani, A., Kato, T., Furukawa, T.A., Horikoshi, M., Imai, H., Hiroe, T., Chino, B., Funayama, T., Yonemoto, N., Zhou, Q., Kawanishi, N., 2017. Smartphone cognitive behavioral therapy as an adjunct to pharmacotherapy for refractory depression: randomized controlled trial. J. Med. Internet Res. 19 (11), e373 https://doi.org/10.2196/jmir.8602. Nov 3.
Milgrom, J., Danaher, B.G., Gemmill, A.W., Holt, C., Holt, C.J., Seeley, J.R., Tyler, M.S., Ross, J., Ericksen, J., 2016. Internet cognitive behavioral therapy for women with postnatal depression: a randomized controlled trial of MumMoodBooster. J. Med. Internet Res. 18 (3), e54 https://doi.org/10.2196/jmir.4993. Mar 7.
Moberg, C., Niles, A., Beermann, D., 2019. Guided self-help works: randomized waitlist controlled trial of Pacifica, a mobile app integrating cognitive behavioral therapy and mindfulness for stress, anxiety, and depression. J. Med. Internet Res. 21 (6), e12556 https://doi.org/10.2196/12556. Jun 8.
Mohr, D.C., Tomasino, K.N., Lattie, E.G., Palac, H.L., Kwasny, M.J., Weingardt, K., Karr, C.J., Kaiser, S.M., Rossom, R.C., Bardsley, L.R., Caccamo, L., Stiles-Shields, C., Schueller, S.M., 2017. IntelliCare: an eclectic, skills-based app suite for the treatment of depression and anxiety, 20 J. Med. Internet Res. 19 (1), e10. https://doi.org/10.2196/ jmir.6645.
Nakagawa, A., Mitsuda, D., Sado, M., Abe, T., Fujisawa, D., Kikuchi, T., Iwashita, S., Mimura, M., Ono, Y., 2017. Effectiveness of supplementary cognitive-behavioral therapy for pharmacotherapy-resistant depression: a randomized controlled trial. J. Clin.Psychiatry 78 (8), 1126–1135. https://doi.org/10.4088/JCP.15m10511.
Newby, J.M., Smith, J., Uppal, S., Mason, E., Mahoney, A.E.J., Andrews, G., 2018. Internet-based cognitive behavioral therapy versus psychoeducation control for illness anxiety disorder and somatic symptom disorder: a randomized controlled trial. J. Consult. Clin. Psychol. 86 (1), 89–98. https://doi.org/10.1037/ccp0000248. Jan.
Norton, P.J., Barrera, T.L., 2012. Transdiagnostic versus diagnosis-specific cbt for anxiety disorders: a preliminary randomized controlled noninferiority trial. Depress.Anxiety 29 (10), 874–882. https://doi.org/10.1002/da.21974.
Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., et al., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372, n71. https://doi.org/10.1136/bmj.n71.
Perini, S., Titov, N., Andrews, G., 2009. Clinician-assisted internet-based treatment is effective for depression: randomized controlled trial. Aust. N. Z. J. Psychiatry 43 (6), 571–578. https://doi.org/10.1080/00048670902873722. Jun.
Raevuori, A., Vahlberg, T., Korhonen, T., Hilgert, O., Aittakumpu-Hyden, R., Forman-Hoffman, V., 2021. A therapist-guided smartphone app for major depression in young adults: a randomized clinical trial. J. Affect. Disord. 286, 228–238. https://doi.org/10.1016/j.jad.2021.02.007. May 1.
Reins, J.A., Boß, L., Lehr, D., Berking, M., Ebert, D.D., 2019. The more I got, the less I need? Efficacy of internet-based guided self-help compared to online psychoeducation for major depressive disorder. J. Affect. Disord. 246, 695–705. https://doi.org/10.1016/j.jad.2018.12.065. Mar 1.
Robinson, E., Titov, N., Andrews, G., McIntyre, K., Schwencke, G., Solley, K., 2010. Internet treatment for generalized anxiety disorder: a randomized controlled trial comparing clinician vs. technician assistance. PLoS One 5 (6), e10942. https://doi.org/10.1371/journal.pone.0010942. Jun 3.
Roepke, A.M., Jaffee, S.R., Riffle, O.M., McGonigal, J., Broome, R., Maxwell, B., 2015. Randomized controlled trial of SuperBetter, a smartphone-based/internet-based self-help tool to reduce depressive symptoms. Games Health J. 4 (3), 235–246. https://doi.org/10.1089/g4h.2014.0046. Jun.
Rollman, B.L., Herbeck Belnap, B., Abebe, K.Z., Spring, M.B., Rotondi, A.J., Rothenberger, S.D., Karp, J.F., 2018. Effectiveness of online collaborative care for treating mood and anxiety disorders in primary care: a randomized clinical trial. JAMA Psychiatry 75 (1), 56–64. https://doi.org/10.1001/jamapsychiatry.2017.3379. Jan 1.
Rosso, I.M., Killgore, W.D., Olson, E.A., Webb, C.A., Fukunaga, R., Auerbach, R.P., Gogel, H., Buchholz, J.L., Rauch, S.L., 2017. Internet-based cognitive behavior therapy for major depressive disorder: a randomized controlled trial. Depress. Anxiety 34 (3), 236–245. https://doi.org/10.1002/da.22590. Mar.
Sadler, P., McLaren, S., Klein, B., Harvey, J., Jenkins, M., 2018. Cognitive behavior therapy for older adults with insomnia and depression: a randomized controlled trial in community mental health services. Sleep 41 (8). https://doi.org/10.1093/sleep/zsy104.
Salisbury, C., O'Cathain, A., Edwards, L., Thomas, C., Gaunt, D., Hollinghurst, S., Nicholl, J., Large, S., Yardley, L., Lewis, G., Foster, A., Garner, K., Horspool, K., Man, M.S., Rogers, A., Pope, C., Dixon, P., Montgomery, A.A., 2016. Effectiveness of an integrated telehealth service for patients with depression: a pragmatic randomised controlled trial of a complex intervention. Lancet Psychiatry 3 (6), 515–525. https://doi.org/10.1016/S2215-0366(16)00083-3. Jun.
Saramago, P., Gega, L., Marshall, D., Nikolaidis, G.F., Jankovic, D., Melton, H., Bojke, L., 2021. Digital interventions for generalized anxiety disorder (GAD):systematic review and network meta-analysis. Front. Psychiatry 12.
Segal, Z.V., Dimidjian, S., Beck, A., Boggs, J.M., Vanderkruik, R., Metcalf, C.A., Gallop, R., Felder, J.N., Levy, J., 2020. Outcomes of online mindfulness-based cognitive therapy for patients with residual depressive symptoms: a randomized clinical trial. JAMA Psychiatry 77 (6), 563–573. https://doi.org/10.1001/jamapsychiatry.2019.4693. Jun 1.
Sekhon, M., Cartwright, M., Francis, J.J., 2017. Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework. BMC Health Serv. Res. 17 (1), 88. https://doi.org/10.1186/s12913-017-2031-8.
Spitzer, R.L., Kroenke, K., Williams, J.B.W., Löwe, B., 2006. A brief measure for assessing generalized anxiety disorder the GAD-7. Arch. Intern. Med. 166, 1092–1097.
Steinhubl, S.R., Muse, E.D., Topol, E.J., 2013. Can mobile health technologies transform health care? published online October 24 JAMA 310 (22), 2395–2396. https://doi.org/10.1001/jama.2013.281078.
Stiles-Shields, C., Montague, E., Kwasny, M.J., Mohr, D.C., 2019. Behavioral and cognitive intervention strategies delivered via coached apps for depression: pilot trial. Psychol. Serv. 16 (2), 233–238. https://doi.org/10.1037/ser0000261. May.
Taylor, S., Abramowitz, J.S., McKay, D., 2012. Non-adherence and non-response in the treatment of anxiety disorders. J.Anxiety Disord. 26 (5), 583–589.

Titov, N., Andrews, G., Choi, I., Schwencke, G., Mahoney, A., 2008. Shyness 3: randomized controlled trial of guided versus unguided internet-based CBT for social phobia. Aust. N. Z. J. Psychiatry 42 (12), 1030–1040. https://doi.org/10.1080/00048670802512107. Dec.

Titov, N., Andrews, G., Johnston, L., Robinson, E., Spence, J., 2010. Transdiagnostic internet treatment for anxiety disorders: a randomized controlled trial. Behav. Res. Ther. 48 (9), 890–899. https://doi.org/10.1016/j.brat.2010.05.014. Sep.

Titov, N., Andrews, G., Schwencke, G., Robinson, E., Peters, L., Spence, J., 2010. Randomized controlled trial of internet cognitive behavioural treatment for social phobia with and without motivational enhancement strategies. Aust. N. Z. J. Psychiatry 44 (10), 938–945. https://doi.org/10.3109/00048674.2010.493859. Oct.

Titov, N., Dear, B.F., Schwencke, G., Andrews, G., Johnston, L., Craske, M.G., McEvoy, P., 2011. Transdiagnostic internet treatment for anxiety and depression: a randomised controlled trial. Behav. Res. Ther. 49 (8), 441–452. https://doi.org/10.1016/j.brat.2011.03.007. Aug.

Titov, N., Dear, B.F., Johnston, L., Lorian, C., Zou, J., Wootton, B., Spence, J., McEvoy, P. M., Rapee, R.M., 2013. Improving adherence and clinical outcomes in self-guided internet treatment for anxiety and depression: randomised controlled trial. PLoS One 8 (7), e62873. https://doi.org/10.1371/journal.pone.0062873. Jul 3.

Titov, N., Dear, B.F., Staples, L.G., Terides, M.D., Karin, E., Sheehan, J., Johnston, L., Gandy, M., Fogliati, V.J., Wootton, B.M., McEvoy, P.M., 2015. Disorder-specific versus transdiagnostic and clinician-guided versus self-guided treatment for major depressive disorder and comorbid anxiety disorders: a randomized controlled trial. J. Anxiety Disord. 35, 88–102. https://doi.org/10.1016/j.janxdis.2015.08.002. Oct.

Tomasino, K.N., Lattie, E.G., Ho, J., Palac, H.L., Kaiser, S.M., Mohr, D.C., 2017. Harnessing peer support in an online intervention for older adults with depression. Am. J. Geriatr. Psychiatry 25 (10), 1109–1119. https://doi.org/10.1016/j.jagp.2017.04.015. Oct.

Torous, J., Firth, J., 2016. The digital placebo effect: mobile mental health meets clinical psychiatry. Lancet Psychiatry 3 (2), 100–102.

Treanor, C.J., Kouvonen, A., Lallukka, T., Donnelly, M., 2021. Acceptability of computerized cognitive behavioral therapy for adults: umbrella review. JMIR Ment. Health 8 (7), e23091. https://doi.org/10.2196/23091. PMID: 34255714; PMCID: PMC8292944.

van Straten, A., Hill, J., Richards, D., et al., 2015. Stepped care treatment delivery for depression: a systematic review and meta-analysis. Psychol. Med. 45, 231–246.

Viswanathan, M., Ansari, M.T., Berkman, N.D.N., Chang, S., Hartling, L., McPheeters, M., Santaguida, P.L., Shamliyan, T., Singh, K., Tsertsvadze, A., Treadwell, J.R., MT, A., Berkman, N.D.N., Chang, S., Hartling, L., McPheeters, M., et al., 2012. Assessing the risk of bias of individual studies in systematic reviews of health care interventions - methods guide – chapter | AHRQ effective health care program. In: Methods Guid. Eff. Comp. Eff. Rev.

Wampold, B.E., 2015. How important are the common factors in psychotherapy?An update. World Psychiatry 14 (3), 270–277. https://doi.org/10.1002/wps.20238.

Watts, S., Mackenzie, A., Thomas, C., Griskaitis, A., Mewton, L., Williams, A., Andrews, G., 2013. CBT for depression: a pilot RCT comparing mobile phone vs. computer. BMC Psychiatry 13, 49. https://doi.org/10.1186/1471-244X-13-49. Feb 7.

Wims, E., Titov, N., Andrews, G., Choi, I., 2010. Clinician-assisted internet-based treatment is effective for panic: a randomized controlled trial. Aust. N. Z. J. Psychiatry 44 (7), 599–607. https://doi.org/10.3109/00048671003614171. Jul.

Zwerenz, R., Becker, J., Knickenberg, R.J., Siepmann, M., Hagen, K., Beutel, M.E., 2017. Online self-help as an add-on to inpatient psychotherapy: efficacy of a new blended treatment approach. Psychother. Psychosom. 86 (6), 341–350. https://doi.org/10.1159/000481177.