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Efficacy of Electronic Cognitive Behavioral Therapy Alone and Combined With Pharmacotherapy for Depression and Anxiety in Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

Electronic cognitive behavioral therapy (e-CBT) is a scalable intervention for anxiety and depressive disorders. While its efficacy against inactive controls is well documented, its comparative effectiveness against first-line pharmacotherapy remains critically underexplored. We conducted a systematic review and meta-analysis (International Prospective Register of Systematic Reviews (PROSPERO): CRD420261413686) of randomized controlled trials (RCTs) comparing e-CBT with waitlist, active psychotherapy, usual care, or medication in adults with anxiety and depression. Effect sizes were pooled using random-effects models with restricted maximum likelihood (REML) and Hartung-Knapp-Sidik-Jonkman (HKSJ) adjustments. Outcomes were assessed using Hedges' g and risk ratios (RR), and evidence certainty was evaluated via the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework. Twenty-two RCTs were included in the analysis. Compared to waitlist/attention controls (k, number of independent contrasts = 11), e-CBT demonstrated a large, statistically significant reduction in depression severity (Hedges' g, standardized mean difference = 0.91; 95% CI: 0.63 to 1.18). However, re-expression onto the Patient Health Questionnaire-9 (PHQ-9) scale yielded an absolute reduction (3.86 points) that fell below the pre-specified minimally important difference (MID) of 5 points. No clear difference was found between e-CBT and active face-to-face or bibliotherapy CBT (k = 3; g = 0.08; 95% CI: -0.59 to 0.75); the wide interval means equivalence could not be established. Adding e-CBT to usual care gave an imprecise, non-significant estimate (k = 3; g = 0.32; 95% CI: -1.41 to 2.05; p = 0.511) that neither confirms nor excludes a benefit. The network geometry revealed zero head-to-head RCTs comparing e-CBT monotherapy directly with antidepressant medication. Nineteen of the 22 trials (86%) were at high overall risk of bias, and funnel-plot asymmetry (Egger's test; p = 0.0056) suggested small-study effects, possibly including publication bias; most GRADE certainty ratings were very low. e-CBT is a scalable option that showed no clear difference from face-to-face CBT in a small number of trials, but its efficacy against inactive controls may be overestimated because of small-study effects and methodological limitations. A critical evidence gap exists regarding its comparative efficacy against pharmacotherapy, necessitating rigorous blinded head-to-head non-inferiority trials.

Categories: Therapeutics, Psychiatry, Pharmacology

Keywords: anxiety disorders, digital therapeutics, electronic cognitive behavioral therapy, internet-based interventions, major depressive disorder, meta-analysis, pharmacotherapy

Introduction And Background

Anxiety and depressive disorders are among the most pervasive and debilitating mental health conditions, representing the leading causes of disability and imposing substantial personal, social, and economic burdens worldwide [1,2]. The World Health Organization (WHO) ranks depression as the single largest contributor to global disability and estimates that hundreds of millions of people live with depressive or anxiety disorders, a large proportion of whom remain untreated [1,3,4].

First-line evidence-based treatments for anxiety and major depressive disorder (MDD) include

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pharmacotherapy (e.g., selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs)) and psychotherapy, with cognitive behavioral therapy (CBT) being considered the gold standard [5-7]. Clinical guidelines and empirical evidence indicate that a combination of pharmacotherapy and CBT yields higher remission rates than antidepressant monotherapy [4]. Furthermore, many patients express a strong preference for psychological therapies over or in combination with medication [4]. However, a treatment gap persists in routine clinical practice. The delivery of traditional in-person CBT is hindered by systemic barriers, including a critical shortage of trained therapists, prohibitive out-of-pocket costs, extended waitlists, geographic isolation, and perceived stigma associated with seeking mental healthcare [1,8,9]. Many patients are prescribed pharmacotherapy alone, highlighting the mismatch between patient treatment preferences, optimal clinical guidelines, and accessible care [4].

Electronic cognitive behavioral therapy (e-CBT), delivered via internet-based platforms, mobile applications, or telehealth, has emerged as a scalable, cost-effective, and highly accessible treatment modality [5,10]. By circumventing geographical and temporal constraints, e-CBT provides patients with time-flexible, private, and standardized care while reducing the requisite hours of therapist time per patient [8,11]. The literature demonstrates that e-CBT, particularly when supported by therapist guidance, can produce clinical improvements in anxiety and depressive symptoms that are comparable to traditional face-to-face CBT [5,7,12].

However, while the clinical efficacy of e-CBT is well documented, significant uncertainty remains regarding its comparative effectiveness when weighed directly against pharmacotherapy or when integrated into combination therapy (e-CBT plus medication) [5,13]. To date, existing systematic reviews and meta-analyses have evaluated e-CBT against inactive controls, waitlists, or treatment-as-usual conditions [7,13]. Direct head-to-head comparisons of e-CBT with established pharmacological treatments and evaluations of combined digital and pharmacological approaches are limited and highly fragmented in the literature [4,5,13].

To address this critical knowledge gap, this systematic review and meta-analysis aimed to evaluate and compare the efficacy of e-CBT, pharmacological treatment, and combination therapy in reducing anxiety and depression symptoms in adults. By quantitatively synthesizing evidence from eligible randomized controlled trials (RCTs), this review determined the relative effectiveness of these interventions in terms of symptom severity, treatment response, and adherence. These findings aim to provide direct comparative evidence to inform clinical decision-making, optimize personalized treatment selection, and guide the future integration of digital therapeutics into mental health services.

Review

Methods

Study Design and Registration

This systematic review and meta-analysis was conducted in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [14]. The review protocol was established a priori, prepared in accordance with the PRISMA Protocols (PRISMA-P) guidelines [15], and prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD420261413686). The eligibility criteria and analytical framework were structured using the Population, Intervention, Comparator, Outcomes, and Study design (PICOS) framework to ensure methodological rigor.

Information Sources and Search Strategy

A systematic literature search was performed across major electronic databases, including the Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase, MEDLINE, PubMed, PsycINFO, Scopus, and Google Scholar. Ongoing and unpublished trials were identified using ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP). The search strategy incorporated a combination of controlled vocabulary (e.g., Medical Subject Headings (MeSH) and Emtree) and free-text terms, utilizing Boolean operators, truncation, and specific field tags. To maximize sensitivity for RCTs, the Cochrane Highly Sensitive Search Strategy was applied [16]. Additionally, backward citation chasing (snowballing) of the included studies and relevant prior reviews was conducted to identify any literature missed by the primary database search [17].

Study Selection

A dual, independent, two-stage screening process (title/abstract followed by a full-text review) was conducted by two investigators. Discrepancies were resolved through adjudication by a third reviewer. The study selection process is documented in a PRISMA 2020 flow diagram. Inter-rater reliability (IRR) was calculated using Cohen's κ [18]. To mitigate the kappa paradox, wherein high exclusion prevalence artificially deflates κ scores, Gwet's AC1 and the prevalence-adjusted bias-adjusted kappa (PABAK) were calculated [19]. IRR estimates were interpreted using the Landis and Koch criteria, with appropriate caveats regarding boundary arbitrariness [20].

Data Extraction and Management

Data extraction was performed independently by two reviewers using a standardized piloted extraction form. When necessary, standard deviations (SDs) were imputed from standard errors (SEs) or 95% confidence intervals (CIs), according to the Cochrane Handbook guidelines [21]. For multi-arm trials sharing a single control group, the sample sizes of the control arm were split, or correlation-adjusted variance structures were utilized to avoid double-counting and unit-of-analysis errors [22].

Risk of Bias and Certainty of Evidence

The risk of bias for all included RCTs was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool [23]. The susceptibility to selective outcome reporting was systematically evaluated using the Outcome Reporting Bias in Trials (ORBIT) framework [24]. The overall certainty of the evidence for each critical outcome was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework [25]. Imprecision was strictly judged against predefined minimally important differences (MIDs) and optimal information size (OIS) thresholds to ensure robustness [26].

Core Meta-Analysis

All statistical analyses were performed in R (version 4.6.0) (R Foundation for Statistical Computing, Vienna, Austria) using the metafor package [27]. Continuous outcomes were primarily synthesized using Hedges' g (standardized mean difference (SMD)) with the J correction applied to adjust for small-sample bias [28]. Mean differences were used as a secondary metric restricted to studies that utilized the Patient Health Questionnaire-9 (PHQ-9) [29]. Dichotomous outcomes (e.g., recovery) were pooled using risk ratios (RR), which were computed when sufficient data were available ($k = 3$ pooled).

Random-effects models were employed given the anticipated clinical and methodological heterogeneity. Continuous data were pooled using the restricted maximum likelihood (REML) estimator [30], while binary data were pooled using the Paule-Mandel estimator [31]. The Hartung-Knapp-Sidik-Jonkman (HKSJ) adjustment was applied to all random-effects models to generate more conservative and robust CIs [32]. To account for dependent effect sizes within individual trials (e.g., multiple time points or psychometric scales), three-level hierarchical models and robust variance estimation (RVE) techniques were employed [33].

Between-study heterogeneity was quantified and tested using Cochran's Q statistic, the I^2 index with corresponding 95% CIs, τ , and τ^2 . To contextualize the expected effect in a future setting, 95% prediction intervals (PI) were calculated for all pooled estimates [34].

Advanced Synthesis and Sensitivity Analyses

To supplement the frequentist approach, Bayesian meta-analyses were conducted using a half-normal (0.5) prior for the heterogeneity variance (τ^2), yielding probabilistic interpretations of the pooled effects [35]. For comparisons with insufficient data for meta-analysis (specifically, medication vs. combination therapy; $k = 1$), a synthesis without meta-analysis (SWiM) approach was employed, utilizing vote counting by direction of effect [36]. A cumulative meta-analysis sorted by publication year was conducted to observe the temporal evolution of the effect size; post hoc power calculations were deliberately avoided in favor of this temporal precision modelling [37].

Publication Bias and Influence Diagnostics

Small-study effects and publication bias were visually assessed using standard and contour-enhanced funnel plots [38]. For outcomes containing ≥ 10 studies, Egger's regression test was applied [39]. Sensitivity to publication bias was further explored using Duval and Tweedie's trim-and-fill procedure [40].

Outlier and influential case diagnostics were assessed. This included leave-one-out analyses, Baujat plots to assess individual study contributions to overall heterogeneity and effect size [41], and a graphical display of study heterogeneity (GOSH) plot [42]. The formal statistical influence was quantified using Viechtbauer and Cheung's diagnostic metrics (e.g., difference in fits (DFFITS), Cook's distance) [43].

Clinical Interpretation and Reporting

To optimize clinical interpretability, the number needed to treat for benefit (NNTB) was calculated alongside Altman's CIs [44]. Absolute paired effects were reported along with relative effects. Additionally, pooled SMDs were re-expressed in PHQ-9 units and mapped against established MIDs for major depression to determine clinical relevance [45]. All visualizations, including forest plots (incorporating study weights, subgroup divisions, summary diamonds, and PIs), contour-enhanced funnel plots, Baujat plots, GOSH plots, leave-one-out forests, and bubble plots for meta-regression, were generated using metafor in R.

Results

Study Selection and Inclusion

A total of 1,758 records were identified through database searches and trial registers. After the removal of 124 duplicates, 1,634 records underwent title and abstract screening, resulting in the exclusion of 1,597 records. Of the 37 reports sought for full-text retrieval, 34 were assessed for their eligibility. Twelve reports were excluded because of deviations from the PICOS criteria (e.g., non-RCT design, lack of appropriate comparator, or non-standardized outcome measures). Twenty-two reports representing 22 independent trials met the inclusion criteria [46–67]. Of these, 16 trials provided extractable continuous data and contributed 18 independent contrasts to the quantitative meta-analysis, while the remaining trials contributed to risk-of-bias assessments, dichotomous outcomes, or narrative synthesis. The study selection process is detailed in the PRISMA 2020 flow diagram (Figure 1).

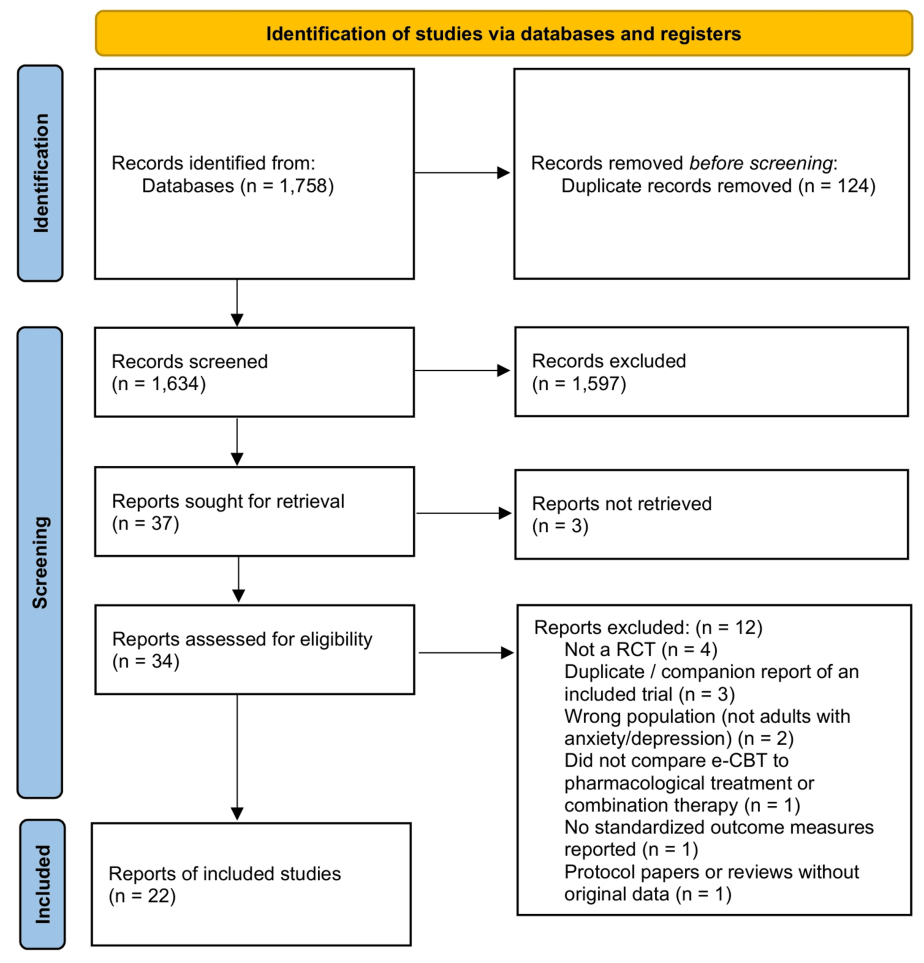


FIGURE 1: PRISMA 2020 flow of records through identification, screening, and inclusion.

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; e-CBT: electronic cognitive behavioral therapy; RCT: randomized controlled trial

Study Characteristics and Risk of Bias

The characteristics of the included study records are summarized in Table 1. The trials encompassed various digital delivery modalities (web-based, stand-alone computer packages, and smartphone applications) with varying degrees of therapeutic guidance (guided, therapist synchronous, minimal, and self-guided). The planned intervention durations ranged from six to 24 weeks.

Trial	Sample size (e-CBT/comparator)	Study population	Intervention	Comparator	Diagnosis	Delivery	Guidance	Duration (wks)	Follow-up (wks)	Overall RoB 2
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Proudfoot et al., 2004 [46]	146/128 (N = 274)	UK primary-care attenders with anxiety and/or depression (CIS-R ≥ 12), 11 general practices	Beating the Blues: 8 sessions of stand-alone multimedia cCBT plus usual GP care	Treatment as usual from the GP	Mixed	Computer	Minimal	8	26	High
Andersson et al., 2005 [47]	36/49 (N = 117)	Community-recruited Swedish adults with mild-to-moderate major depression	Internet self-help CBT (5 modules) with minimal e-mail support plus moderated online discussion group	Moderated online discussion group only (waiting list)	Depression	Web	Guided	9	26	High
Warmerdam et al., 2008 [48]	88/87 (N = 263, 3 arms)	Dutch community adults with self-reported depressive symptoms (CES-D ≥ 16)	Guided internet-based CBT with weekly written therapist feedback	Waiting-list control (trial also included an internet problem-solving arm)	Depression	Web	Guided	8	12	High
Kessler et al., 2009 [49]	113/97 (N = 297)	UK primary-care patients with an ICD-10 depressive episode (BDI ≥ 14); most on antidepressants	Therapist-delivered real-time online CBT (instant messaging, up to 10 sessions) added to usual care	Usual GP care while on a waiting list	Depression	Synchronous	Therapist	10	35	High
Ruwaard et al., 2009 [50]	36/18 (N = 54)	Self-referred Dutch adults with mild-to-moderate depression	Standardized web-based CBT with structured therapist feedback	Waiting-list control	Depression	Web	Guided	11	78	High
Titov et al., 2011 [51]	37/37	Australian adults meeting the criteria for MDD and/or an anxiety disorder	Transdiagnostic clinician-guided iCBT (Wellbeing Program, 8 online lessons + homework)	Waiting-list control	Mixed	Web	Guided	8	12	High
Johansson et al., 2012 [52]	36/39 (N = 121, 3 arms)	Swedish adults with mild-to-moderate depression and comorbid symptoms	Tailored, therapist-guided internet CBT individualized to comorbidity profile	Moderated online discussion group (attention control)	Depression	Web	Guided	10	26	High
Andersson et al., 2013 [53]	33/36 (N = 69)	Swedish adults with diagnosed major depression	Guided internet-delivered CBT	Face-to-face group CBT (non-inferiority design)	Depression	Web	Guided	8	156	High
Newby et al., 2013 [54]	46/53 (N = 99)	Australian adults with comorbid anxiety and depression, recruited from primary care and community	Clinician-guided transdiagnostic iCBT (6 online lessons)	Waiting-list control	Mixed	Web	Guided	10	12	High
Wagner et al., 2014 [55]	32/30 (N = 62)	German-speaking adults with mild-to-moderate depression	Therapist-guided, writing-based internet CBT	Face-to-face individual CBT (non-inferiority design)	Depression	Web	Guided	8	12	High
Gilbody et al., 2015 (BiB) [56]	165/179 (REEACT N = 691, 3 arms)	UK primary-care adults with depression (PHQ-9 ≥ 10), pragmatic multicentre sample	Beating the Blues (commercial cCBT) added to usual GP care, with weekly telephone support	Usual GP care alone	Depression	Computer	Guided	8	104	High
Gilbody et al., 2015 (MoodGYM) [56]	182/179 (REEACT N = 691, 3 arms)	UK primary-care adults with depression (PHQ-9 ≥ 10), pragmatic multicentre sample	MoodGYM (free-to-use cCBT) added to usual GP care, with weekly telephone support	Usual GP care alone	Depression	Computer	Guided	8	104	High
Titov et al., 2015 [57]	27/25 (N = 54)	Australian older adults (≥ 60 years) with symptoms of depression	Therapist-guided iCBT tailored to older adults (Managing Your Mood)	Waiting-list control	Depression	Web	Guided	8	52	High
Richards et al., 2015 [58]	96/92 (N = 188)	Irish community-dwelling adults with symptoms of depression (low-intensity community setting)	Space from Depression: 7-module supported iCBT with trained volunteer supporters	Waiting-list control	Depression	Web	Guided	8	12	High
Rosso et al., 2017 [59]	37/40 (N = 77)	US adults with a primary diagnosis of MDD	Guided internet-based CBT (Sadness Program, 6 lessons) with clinician contact	Monitored attention control (waiting list with weekly monitoring)	Depression	Web	Guided	10	10	Low
Forsell et al., 2017 [60]	22/20 (N = 42)	Pregnant women with antenatal depression attending Swedish maternity care	Guided internet-delivered CBT added to treatment as usual	Treatment as usual alone	Depression	Web	Guided	10	10	High
Smith et al., 2017 (vs waitlist) [61]	54/59 (N = 270, 4 arms)	Australian adults meeting the DSM criteria for MDD	Clinician-guided iCBT for depression (6 lessons)	Waiting-list control	Depression	Web	Guided	12	24	High
Smith et al., 2017 (vs bibliotherapy) [61]	54/74 (N = 270, 4 arms)	Australian adults meeting the DSM criteria for MDD	Clinician-guided iCBT for depression (6 lessons)	Self-help book (CBT bibliotherapy/meditation bibliotherapy arms)	Depression	Web	Guided	12	24	High

Mantani et al., 2017 [62]	81/83 (N = 164)	Japanese adults with MDD refractory to at least one adequate antidepressant trial	Smartphone CBT application (self-guided) added to an antidepressant switch	Antidepressant switch alone (medication monotherapy)	Depression	App	Self-guided	8	17	Low
Rollman et al., 2018 [63]	603/101 (N = 704, 3 arms)	US primary-care patients aged 18-75 referred by their PCP with depression and/or anxiety	Guided cCBT (8 sessions) delivered through a centralized collaborative-care programme, with or without an internet support group	Usual primary-care physician care	Mixed	Computer	Guided	24	52	Some concerns
Johansson et al., 2019 [64]	27/27 (N = 54)	Swedish patients with depression treated in routine outpatient psychiatric services	Guided internet-delivered CBT integrated into routine psychiatric care	Waiting-list/attention control	Depression	Web	Guided	8	52	High
Richards et al., 2020 [65]	241/120 (N = 361)	Adults referred to a UK IAPT Step 2 service with depression and anxiety symptoms	SilverCloud supported iCBT (Space from Depression/Anxiety) within stepped care	Waiting list (usual stepped-care queue)	Mixed	Web	Guided	8	52	High
Adu et al., 2023 [66]	78 total (2 arms)	Canadian adults with treatment-resistant depression referred for rTMS	rTMS sessions plus self-guided internet-delivered CBT	rTMS sessions alone	Depression	Web	Self-guided	6	6	High
Lin et al., 2023 [67]	31/43 (analyzed)	Adults with MDD recruited through a Chinese urban chronic-disease/psychiatric service (Shenzhen)	iCBT delivered via a WeChat mini-programme with general support from non-specialists	Waiting-list control	Depression	App	Guided	8	8	High

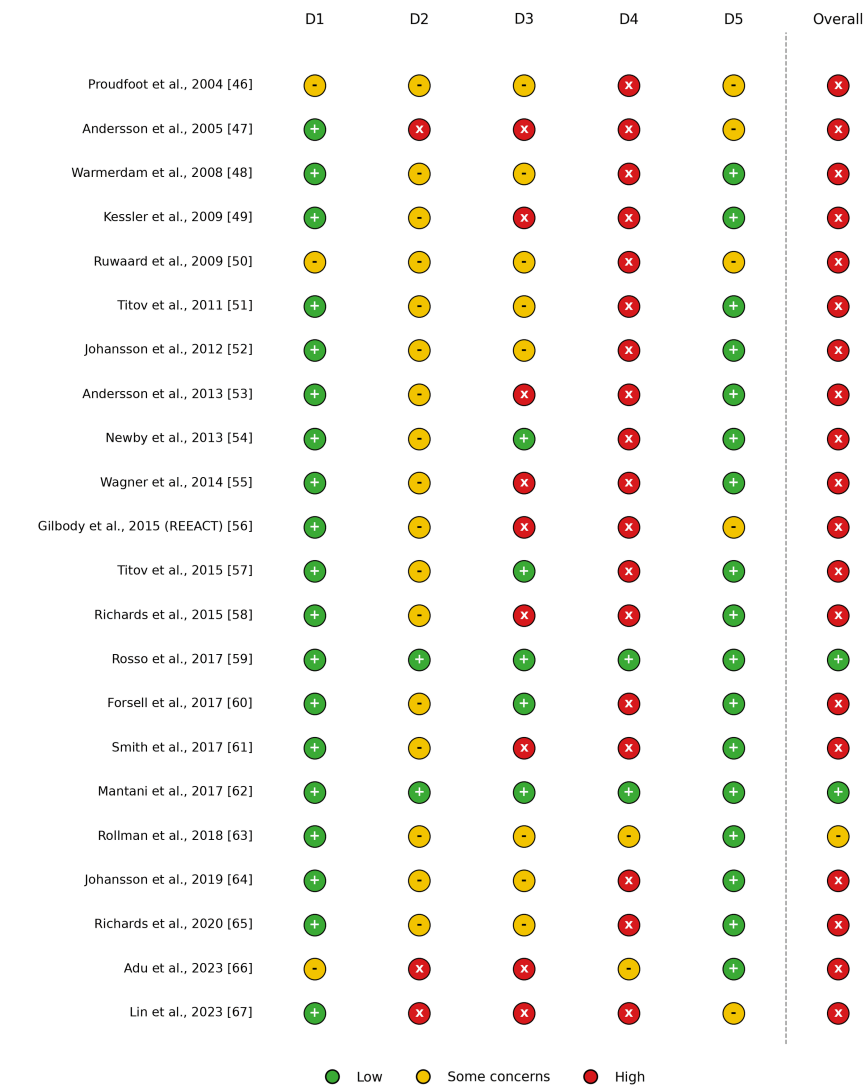
TABLE 1: Characteristics of the included randomized controlled trials (24 independent study-contrast records) entering the review, with overall risk-of-bias judgement.

The 24 study-contrast records refer to the 24 independent comparisons extracted from the 22 included trials. Some trials [56,61] are repeated twice because they contained multiple distinct intervention arms compared against a control group. Gilbody et al. 2015 (BtB) [56] refers to the "Beating the Blues" program arm; Gilbody et al. (MoodGYM) [56] refers to the "MoodGYM" program arm; Smith et al. (vs waitlist) [61] refers to the e-CBT arm compared to a waitlist control; and Smith et al. (vs bibliotherapy) [61] refers to the e-CBT arm compared to a bibliotherapy control.

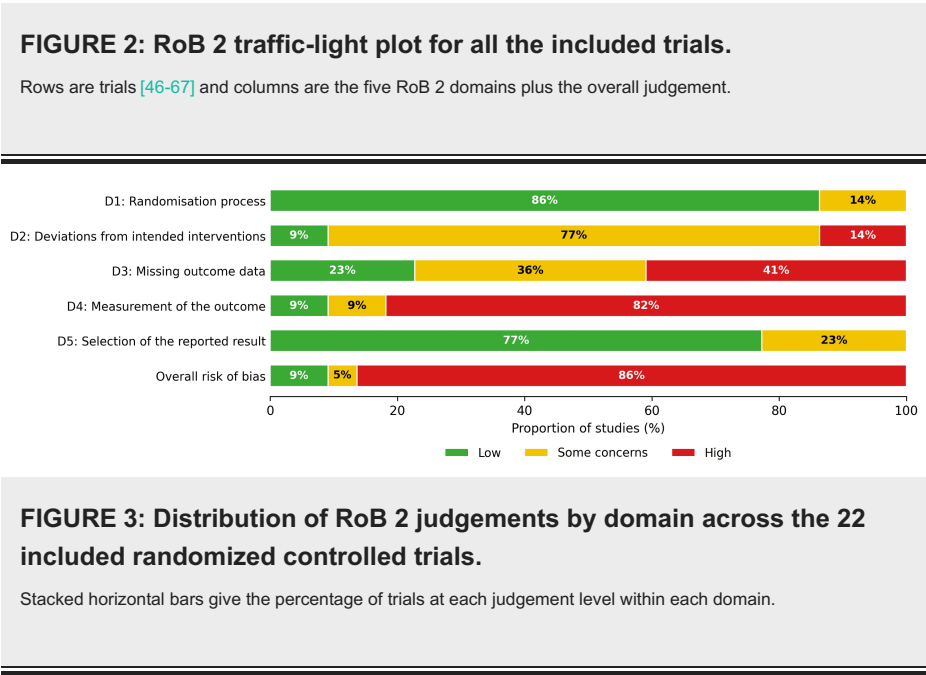
Delivery: Web: internet-delivered programme; Computer: stand-alone computerized package; App: smartphone application; Synchronous: real-time therapist-led online contact. Guidance: Guided: scheduled asynchronous therapist support; Therapist: therapist-delivered synchronous contact; Minimal: brief technical or administrative contact only; Self-guided: no human support. Duration: planned intervention length. Follow-up: longest assessment point reported. Overall RoB 2 represents the least favorable domain judgement.

CIS-R: Clinical Interview Schedule-Revised; CES-D: Center for Epidemiologic Studies Depression Scale; ICD-10: International Classification of Diseases, Tenth Revision; BDI: Beck Depression Inventory; MDD: major depressive disorder; PHQ-9: Patient Health Questionnaire-9; DSM: Diagnostic and Statistical Manual of Mental Disorders; PCP: primary care physician; IAPT: Improving Access to Psychological Therapies; rTMS: repetitive transcranial magnetic stimulation; GP: general practitioner; cCBT: computerized cognitive behavioral therapy; CBT: cognitive behavioral therapy; iCBT: internet-based cognitive behavioral therapy

Risk of bias, evaluated using the RoB 2 tool (Figure 2), was high overall in 19 of the 22 trials (86%); one trial (5%) raised some concerns [63], and two (9%) were at low risk [59,62]. Domain 4 was rated high in 18 trials (82%). The predominant source of high risk was Domain 4 (measurement of the outcome), driven by the ubiquitous reliance on unblinded, self-reported symptom questionnaires in digital intervention research (Figure 3).



D1 Randomisation · D2 Deviations · D3 Missing data · D4 Outcome measurement · D5 Selective reporting



Primary Efficacy: e-CBT vs Waitlist/Attention Control

The primary meta-analysis compared e-CBT with waitlist or attention control conditions ($k = 11$ contrasts; $n = 1,046$ participants). Using a random-effects model with REML and the HKSJ variance correction, e-CBT demonstrated a large, statistically significant reduction in depression symptom severity (Hedges' $g = 0.91$; 95% CI: 0.63 to 1.18; $p < 0.0001$) (Figure 4, Table 2).

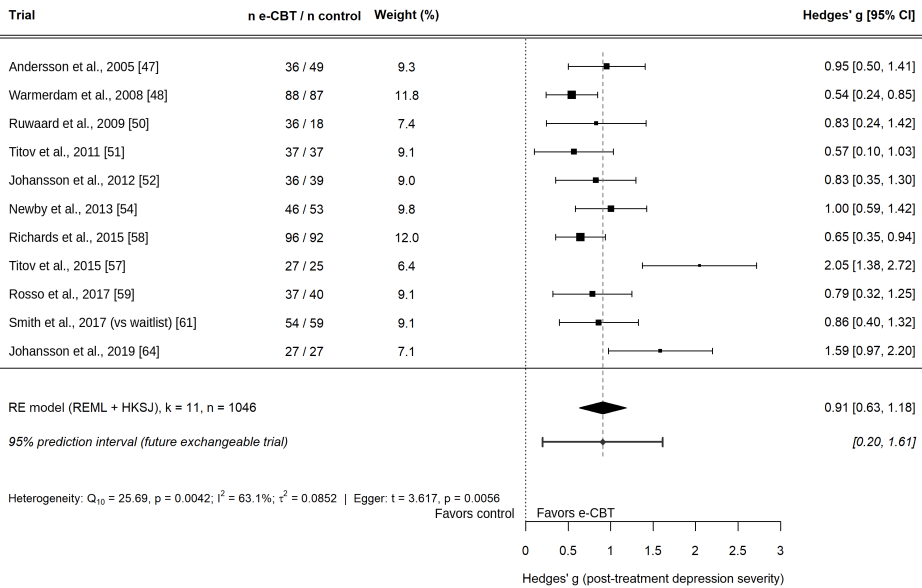


FIGURE 4: Forest plot of the primary comparison: e-CBT versus waitlist or attention control ($k = 11$ independent contrasts).

Random-effects model (REML with HKSJ). The overall pooled estimate (indicated by the overall estimate marker at the bottom) is Hedges' $g = 0.91$ (95% CI: 0.63 to 1.18); the 95% prediction interval (0.20 to 1.61) approaches but does not cross the null. Every one of the 11 contrasts [47,48,50-52,54,57-59,61,64] lies to the right of the null line.

REML: restricted maximum likelihood; HKSJ: Hartung-Knapp-Sidik-Jonkman; e-CBT: electronic cognitive behavioral therapy

Comparison	k	Pooled g	SE	95% CI	95% PI	p	τ²	I² (%)
e-CBT vs waitlist/attention control (PRIMARY)	11 [47,48,50-52,54,57-59,61,64]	0.908	0.124	0.632 to 1.184	0.202 to 1.614	<0.0001	0.0852	63.1
e-CBT added to usual care vs usual care alone	3 [56,60]	0.320	0.403	-1.413 to 2.052	-2.925 to 3.564	0.511	0.4066	92.6
e-CBT vs active psychotherapy or bibliotherapy	3 [53,55,61]	0.081	0.155	-0.587 to 0.750	-0.778 to 0.940	0.654	0.0157	21.3
Combination (e-CBT+med) vs medication	1 [62]	0.332	0.157	0.020 to 0.640	-	-	-	-

TABLE 2: Random-effects pooled estimates for each comparison, with heterogeneity and prediction intervals.

All models fitted with restricted maximum likelihood and the Hartung-Knapp-Sidik-Jonkman variance correction; p-values and confidence limits are therefore based on the t-distribution.

The combination-versus-medication row rests on a single trial [62] and is reported without pooling.

For the comparisons indicating k = 3 but citing two studies[56,60], k represents the number of independent contrasts, not the number of studies. Gilbody et al. [56] contributed two distinct and independent intervention arms (Beating the Blues and MoodGYM) compared to the control group, resulting in three total contrasts from two studies.

k: number of contrasts; SE: standard error; CI: confidence interval; PI: 95% prediction interval for the effect in a new setting; τ²: between-study variance; I²: proportion of total variability attributable to heterogeneity; e-CBT: electronic cognitive behavioral therapy

Moderate-to-severe between-study heterogeneity was observed (I² = 63.1%; Q10 = 25.69; p = 0.0042; τ² = 0.0852). However, the 95% PI (0.20 to 1.61) excluded the null, indicating that the true effect in a future exchangeable trial would reliably favor e-CBT.

When expressed on the PHQ-9 scale for clinical interpretability, the pooled effect equated to a reduction of 3.86 points (95% CI: 2.69 to 5.03). This estimate fell below the pre-specified MID threshold of five PHQ-9 points. A Bayesian random-effects analysis utilizing a weakly informative half-normal (0.5) prior for τ yielded a posterior median effect of 0.895 (95% credible interval: 0.661 to 1.163), confirming the frequentist results (Figure 5). The posterior probability that the true pooled effect exceeded the five-point MID was only 0.024 (2.4%), characterizing the result as reliably positive but likely smaller than the threshold for strict clinical importance.

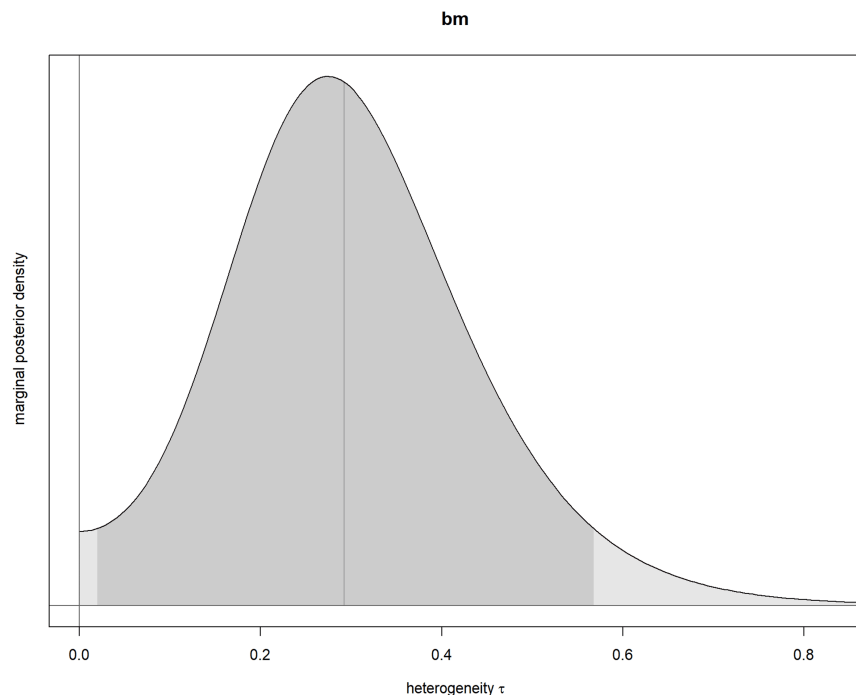


FIGURE 5: Marginal posterior density of the between-study standard deviation τ .

Vertical line at the posterior median ($\tau = 0.292$). The mid-grey region is the 95% shortest credible interval (0.020 to 0.568) and the pale tails fall outside it. The density is right-skewed and its mass is bounded away from zero only weakly, which is consistent with the wide profile-likelihood interval for τ .

The "bm" text at the top of the plot is an artifact indicating the bayesmeta R package used for the analysis.

All 18 contrasts in the quantitative synthesis used depression-severity outcomes. Only two [51,54] enrolled mixed anxiety-depression samples, and anxiety outcomes were reported by too few trials per comparison, on heterogeneous scales, to permit a separate synthesis. Anxiety severity was a registered primary outcome; not pooling it is a deviation from the protocol, and all pooled findings apply to depressive symptoms only.

Efficacy of e-CBT vs Active Psychotherapy

When evaluated against face-to-face CBT or CBT bibliotherapy ($k = 3$ contrasts; $n = 259$), no clear difference in post-treatment depression severity was found ($g = 0.08$; 95% CI: -0.59 to 0.75 ; $p = 0.654$). The interval is wide and includes clinically important benefit and harm, so equivalence or non-inferiority cannot be concluded. The heterogeneity within this comparison was low ($I^2 = 21.3\%$). Face-to-face CBT [53,55] and CBT bibliotherapy [61] were grouped because both deliver CBT content through an established non-digital route, so the comparison asks whether digital delivery loses efficacy relative to standard CBT formats. The two face-to-face trials alone pointed the same way (Andersson et al. [53]: $g = 0.39$; 95% CI: -0.09 to 0.87 ; Wagner et al. [55]: $g = -0.01$; 95% CI: -0.51 to 0.49); with $k = 2$, they were not pooled separately.

Efficacy of Combination Therapy (e-CBT+Medication/Usual Care)

Three contrasts from two trials ($n = 568$) compared e-CBT added to usual care with usual care alone: Forsell et al. [60] (antenatal depression; 22 e-CBT, 20 control) and the two arms of REEACT [56] (Beating the Blues, 165; MoodGYM, 182; shared usual-care arm, 179). Usual care was routine general-practice or maternity care rather than a protocolized medication regimen; antidepressant use at baseline was 5% in Forsell et al. [60] and 88-90% in REEACT [56]. The pooled estimate was non-significant and imprecise ($g = 0.32$; 95% CI: -1.41 to 2.05 ; $p = 0.511$; $I^2 = 92.6\%$), and neither confirms nor excludes a benefit. Recovery was pooled from Kessler et al. [49] and the two REEACT arms [56] ($k = 3$; $n = 736$) and showed no clear difference (RR: 1.05; 95% CI: 0.47 to 2.31). One trial [62] evaluated combination therapy (e-CBT+medication) versus medication alone in an antidepressant-refractory sample. This trial found a small, statistically significant difference favoring the combination ($g = 0.33$; 95% CI: 0.02 to 0.64), equivalent to a mean difference of 1.72 PHQ-9 points (95% CI: 0.25 to 3.19), which is below the five-point MID.

Network Connectivity and the Head-to-Head Evidence Gap

The pre-specified aim of this review was to compare e-CBT with pharmacological treatment. However, network geometry assessment revealed critically disconnected subnetworks in the study. No randomized trial has directly compared e-CBT monotherapy with antidepressant medication monotherapy. Furthermore, the single trial evaluating specific medication [62] did not link to waitlist or psychotherapy nodes, rendering even indirect (network meta-analytic) estimation of the e-CBT versus medication effect impossible.

Influence Diagnostics, Small-Study Effects, and Robustness

Leave-one-out sensitivity analyses confirmed the stability of the primary pooled estimate, which ranged between 0.798 and 0.955, excluding the null, regardless of any single-study omission. However, influence diagnostics (Figure 6), including studentized residuals, DFFITS, Cook's distance, and GOSH plots, identified Titov et al. [57] as a highly influential outlier. Removing this trial reduced I^2 from 63.1% to 22.9%, establishing it as the dominant source of between-study variation (Figure 7).

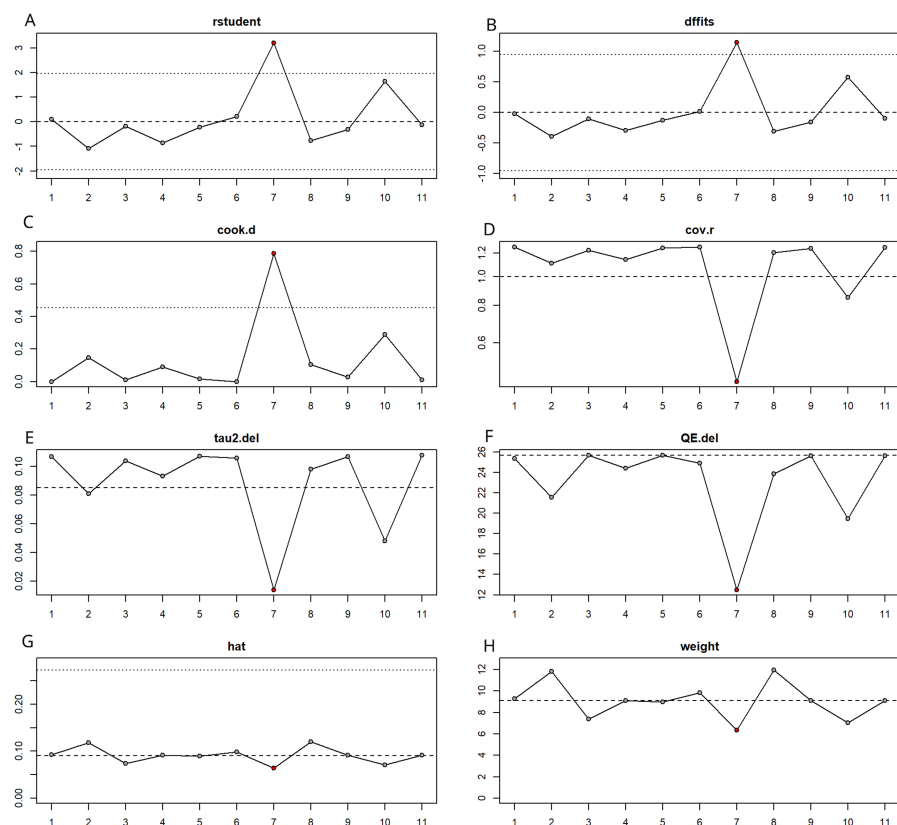


FIGURE 6: Influence diagnostic panels for the primary model comparing e-CBT versus waitlist/attention controls.

Eight stacked panels (A-H) showing influence diagnostics for each of the 11 contrasts. The x-axes on all panels represent the contrast number (1-11), which correspond to the following trials, respectively: 1=[47], 2=[48], 3=[50], 4=[51], 5=[52], 6=[54], 7=[57], 8=[58], 9=[59], 10=[61], and 11=[64]. The y-axes represent the calculated value for each specific diagnostic metric. Panel A: externally studentized residuals; Panel B: DFFITS (difference in fits); Panel C: Cook's distance (measuring the effect of deleting a given observation); Panel D: covariance ratio; Panel E: leave-one-out τ^2 (between-study variance); Panel F: leave-one-out Q statistic (heterogeneity); Panel G: hat value (leverage); Panel H: model weight. Points exceeding the diagnostic cut-offs are highlighted; Titov et al. [57] (contrast 7) is the only study flagged across multiple panels.

e-CBT: electronic cognitive behavioral therapy

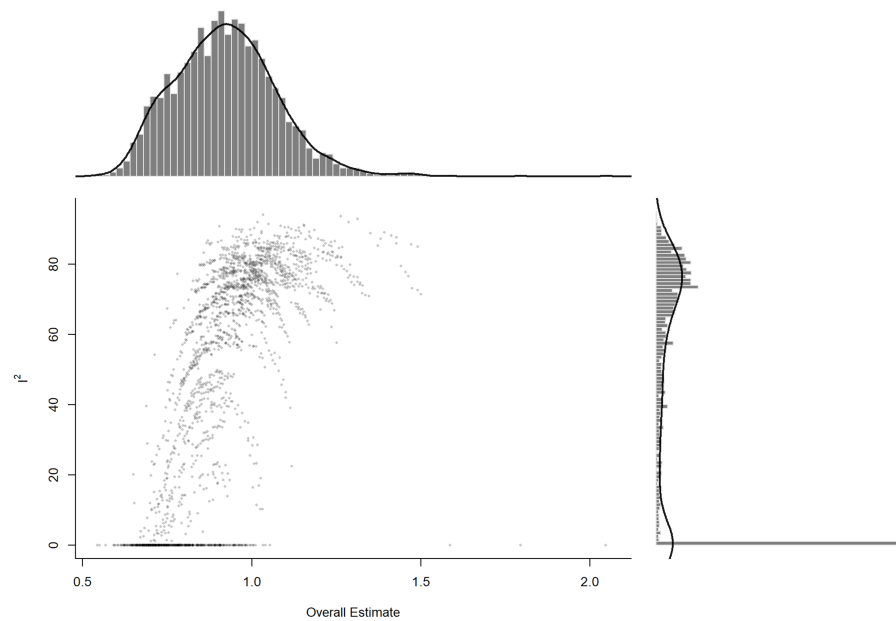


FIGURE 7: GOSH plot: pooled estimate against I^2 across 5,000 random subsets of the primary dataset.

Each point is a meta-analysis of one randomly drawn subset of the 11 contrasts (trials [47,48,50-52,54,57-59,61,64]), plotted by its pooled Hedges' g (horizontal) and I^2 (vertical). A single dense cluster indicates a homogeneous evidence base; distinct clusters indicate subgroups of studies that produce systematically different pooled results. Subsets containing Titov et al. [57] form the higher-effect, higher- I^2 region of the cloud.

GOSH: graphical display of study heterogeneity

Significant funnel plot asymmetry was detected using Egger's regression test ($t = 3.617$; $p = 0.0056$). The contour-enhanced funnel plot (Figure 8) revealed an absence of small trials reporting null or negative results, suggesting that small-study effects, possibly including publication bias, may have inflated the pooled estimate.

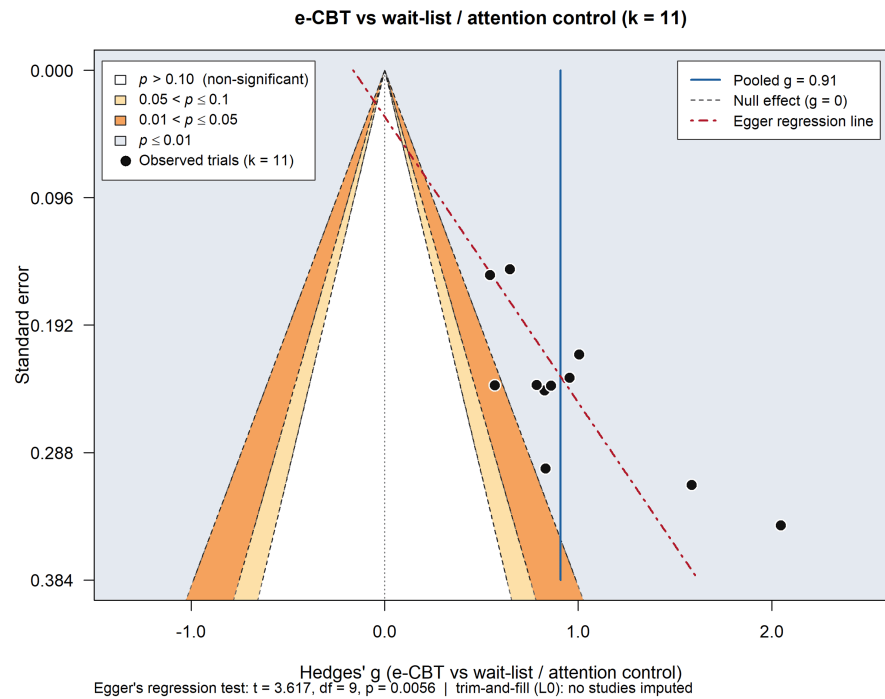


FIGURE 8: Contour-enhanced funnel plot for the primary comparison (k = 11).

Each point is a contrast, plotted by Hedges' g against its standard error, with the reference line at zero. Shaded contours mark the 90%, 95%, and 99% significance regions. The plot is asymmetric: no small trial reporting a null or negative result appears, and all 11 estimates [47,48,50-52,54,57-59,61,64] fall to the right of the null. This pattern is consistent with small-study effects, of which publication bias is one possible cause.

e-CBT: electronic cognitive behavioral therapy

Certainty of Evidence (GRADE)

The certainty of the evidence was assessed using the GRADE framework (Table 3). Evidence certainty was downgraded to very low for almost all critical outcomes, including e-CBT versus waitlist and e-CBT combined with usual care. Downgrades were driven by critical risk of bias, inconsistency (high heterogeneity), and publication bias (funnel asymmetry). The certainty of evidence for combination therapy versus monotherapy was rated as low. There was no evidence available to evaluate head-to-head comparisons of e-CBT versus medication or to pool adverse events or clinical deterioration.

Outcome	Comparison	Studies (k)	Relative effect	Anticipated absolute effect	Certainty	Importance
Depression symptom severity (post-treatment; PHQ-9/BDI-II/MADRS-S/HRSD-17)	e-CBT vs waitlist or attention control	11 [47,48,50-52,54,57-59,61,64]	SMD: 0.91 (0.63 to 1.18)	SMD: 0.91 higher in favor of e-CBT (0.63 to 1.18); ≈3.9 PHQ-9 points (2.7 to 5.0)	Very low	Critical
Depression symptom severity (post-treatment; PHQ-9/MADRS-S)	e-CBT added to usual care vs usual care alone	3 [56,60]	SMD: 0.32 (−1.41 to 2.05)	SMD: 0.32 higher in favor of e-CBT (−1.41 to 2.05)	Very low	Critical
Recovery/response	e-CBT added to usual care vs usual care alone	3 [49,56]	RR: 1.05 (0.47 to 2.31)	449 per 1000 (201 to 989)	Very low	Critical
Depression symptom severity (post-treatment)	e-CBT vs face-to-face or bibliotherapy CBT	3 [53,55,61]	SMD: 0.08 (−0.59 to 0.75)	SMD: 0.08 higher in favor of e-CBT (−0.59 to 0.75)	Very low	Important
Depression symptom severity (PHQ-9 at 9 weeks)	e-CBT plus antidepressant vs antidepressant alone (combination vs medication)	1 [62]	SMD: 0.33 (0.02 to 0.64)	SMD: 0.33 higher in favor of combination (0.02 to 0.64); MD 1.72 PHQ-9 points (0.25 to 3.19)	Low	Critical
Depression symptom severity	e-CBT vs antidepressant medication alone (head-to-head)	0	No estimate	No estimate	No evidence	Critical
Treatment adherence/study retention	e-CBT vs any comparator	22 [46-67]	Not pooled	Retention in e-CBT arms 61-100% (median ≈89%)	Very low	Important
Adverse events/deterioration	e-CBT vs any comparator	0 reporting usable data	Not estimable	Not estimable	No evidence	Critical

TABLE 3: GRADE summary of findings.

Certainty was assessed with GRADE for randomized evidence, starting at high and downgraded for risk of bias, inconsistency, imprecision, and publication bias.

Anticipated absolute effects for continuous outcomes are re-expressed on the PHQ-9 using an assumed pooled standard deviation of 4.25 points.

For the comparisons indicating k = 3 but citing two studies [\[56,60\]](#), k represents the number of independent contrasts, not the number of studies. Gilbody et al. [\[56\]](#) contributed two distinct and independent intervention arms (Beating the Blues and MoodGYM) compared to the control group, resulting in three total contrasts from two studies.

SMD: standardized mean difference; MD: mean difference; RR: risk ratio; CI: confidence interval; GRADE: Grading of Recommendations Assessment, Development, and Evaluation; e-CBT: electronic cognitive behavioral therapy; PHQ-9: Patient Health Questionnaire-9; BDI-II: Beck Depression Inventory-Second Edition; MADRS-S: Montgomery-Åsberg Depression Rating Scale-Self-rated version; HRSD-17: 17-item Hamilton Rating Scale for Depression

Discussion

This systematic review and meta-analysis synthesized data from 22 RCTs to evaluate the efficacy of e-CBT alone and in combination with pharmacotherapy and other control conditions for anxiety and depression. Our findings confirm that e-CBT significantly reduces depressive symptom severity compared to waitlist or attention controls, yielding a large standardized effect size ($g = 0.91$). We found no clear difference between e-CBT and face-to-face or bibliotherapy CBT; however, with only three contrasts and a wide CI (−0.59 to 0.75), this does not show that the two approaches are equally effective.

However, a rigorous critical appraisal tempers these seemingly robust effects. Translating the primary pooled effect into clinical units (PHQ-9) revealed an absolute reduction of 3.86 points, falling short of the pre-specified MID of 5 points required for clinically meaningful improvement. Bayesian re-analysis confirmed that the probability of the true pooled effect exceeding the MID was negligible (2.4%). This review

identified a gap in the literature: despite the ubiquitous prescription of antidepressants [4,5], there are no randomized head-to-head trials comparing e-CBT monotherapy directly to pharmacological monotherapy.

Our finding that e-CBT outperformed inactive controls aligns with previous meta-analyses [12,13]. However, our advanced influence diagnostics and publication bias assessments provide a more nuanced interpretation of these findings. The contour-enhanced funnel plot and Egger's regression tests indicate that the reported efficacy of e-CBT is artificially inflated by small-study effects and publication bias, specifically the conspicuous absence of small trials reporting null or negative results. Furthermore, the pervasive reliance on unblinded, self-reported outcome measures introduces a critical performance and detection bias that reliably overestimates the effects of psychological interventions [11,56]. The GRADE certainty for these outcomes was downgraded to very low certainty.

The evidence regarding combination therapy remains equivocal. The addition of e-CBT to usual care (predominantly antidepressants) did not yield statistically significant improvements in symptom severity or clinical recovery rates. A single low-risk-of-bias trial in antidepressant-refractory depression [62] found a statistically significant difference favoring e-CBT added to an antidepressant switch over the switch alone ($g = 0.33$; mean difference: 1.72 PHQ-9 points; 95% CI: 0.25 to 3.19). Even the upper confidence limit lies below our pre-specified MID of 5 points, so the clinical importance of this difference is uncertain, and as a single trial, it requires replication before it can inform practice.

The most striking finding of our network geometry assessment was the complete disconnection between the e-CBT and pharmacotherapy nodes. Clinical guidelines often position CBT and SSRIs/SNRIs as interchangeable first-line options based on legacy in-person CBT data [6,12]. The digital mental health field has operated under the assumption of transitive equivalence, presuming that because e-CBT is equivalent to in-person CBT, it must also be equivalent to pharmacotherapy. Our data show that this assumption has not been proven in the literature.

This review has several methodological strengths that distinguish it from previous syntheses. We employed highly conservative statistical techniques, including the HKSJ adjustment, which produces wider and more realistic CIs than traditional DerSimonian-Laird estimators [32]. We calculated the 95% PI to estimate the expected effects in future settings and applied a Bayesian framework to test posterior probabilities against strict clinical thresholds (MID). Furthermore, comprehensive influence diagnostics (e.g., GOSH plots, Baujat plots) isolated idiosyncratic trial variance, such as the disproportionate influence of Titov et al. [57].

Nevertheless, this review is constrained by the limitations of primary literature. First, 86% (19/22) of the included trials were assessed as having a high overall risk of bias, largely due to Domain 4 (measurement of outcome). Second, adverse events, negative effects, and clinical deterioration were drastically underreported across the included studies, preventing any quantitative synthesis of the safety of the interventions. Third, high study attrition is common in digital interventions, which complicates the interpretation of intention-to-treat protocols and inflates the risk of missing outcome data (Domain 3).

For clinicians and healthcare systems, e-CBT remains a critical tool for bridging the global mental health treatment gap [1,10]. Within these limits, guided e-CBT (the format used in every trial of the primary comparison) may be a reasonable low-intensity option within stepped-care models, particularly where face-to-face therapy is hard to access. Because most of this evidence is of very low certainty, its role should be confirmed in larger trials with blinded outcome assessment. This approach maximizes resource allocation, allowing scarce in-person psychiatric resources to be reserved for patients with severe, complex, or acute presentations [2,8].

However, policymakers and digital health stakeholders must calibrate their expectations accordingly. The true benefit of e-CBT may be more modest than the pooled estimate suggests, given the funnel asymmetry, the reliance on waitlist controls, and the use of unblinded self-reported outcomes. Furthermore, patients prefer shared decision-making regarding treatment modalities [4,5]. Until definitive comparative data against medications are available, the selection of e-CBT or pharmacotherapy should be driven by patient preference, accessibility, and contraindication profiles rather than presumed superiority.

The findings of this review dictate a clear mandate for future research in psychiatry. First, the field requires large-scale, rigorously designed, non-inferiority RCTs directly comparing e-CBT with first-line pharmacotherapies (e.g., SSRIs/SNRIs). Second, future e-CBT trials must transcend unblinded self-reporting by incorporating blinded clinician-rated outcomes (e.g., 17-item Hamilton Rating Scale for Depression (HRSD-17)), ecological momentary assessment (EMA), or objective digital phenotyping to mitigate detection bias [7,62]. Third, journals and trial registries must enforce mandatory reporting of adverse events and clinical deterioration in digital health interventions to establish a comprehensive safety profile. Finally, future investigations should leverage individual patient data (IPD) meta-analyses to identify prescriptive moderators, enabling clinicians to accurately predict which patients will thrive with e-CBT, which will require pharmacotherapy, and which will necessitate a combination of both.

Conclusions

In adults with depressive symptoms, e-CBT reduced symptom severity compared with waitlist or attention controls, although this effect is probably overestimated and the certainty of evidence is very low. No clear difference was found between e-CBT and face-to-face or bibliotherapy CBT, but the few available trials cannot establish equivalence. No randomized trial has compared e-CBT alone with medication alone; one trial found a small additional effect, of uncertain clinical importance, when e-CBT was added to an antidepressant switch in treatment-resistant depression. Because the pooled outcomes concerned depression, these conclusions should not be extended to anxiety disorders. Head-to-head trials of e-CBT versus pharmacotherapy, with blinded outcome assessment and anxiety outcomes, are needed to define the role of e-CBT alongside medication.

Additional Information

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All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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