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Computerized Cognitive Behavioral Therapy for Adults with Depressive or Anxiety Disorders

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PREFACE

Quality Enhancement Research Initiative's (QUERI's) Evidence-based Synthesis Program (ESP) was established to provide timely and accurate syntheses of targeted healthcare topics of particular importance to Veterans Affairs (VA) managers and policymakers, as they work to improve the health and healthcare of Veterans. The ESP disseminates these reports throughout VA.

QUERI provides funding for four ESP Centers and each Center has an active VA affiliation. The ESP Centers generate evidence syntheses on important clinical practice topics, and these reports help:

- develop clinical policies informed by evidence,
- guide the implementation of effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures, and
- set the direction for future research to address gaps in clinical knowledge.

In 2009, the ESP Coordinating Center was created to expand the capacity of QUERI Central Office and the four ESP sites by developing and maintaining program processes. In addition, the Center established a Steering Committee comprised of QUERI field-based investigators, VA Patient Care Services, Office of Quality and Performance, and Veterans Integrated Service Networks (VISN) Clinical Management Officers. The Steering Committee provides program oversight, guides strategic planning, coordinates dissemination activities, and develops collaborations with VA leadership to identify new ESP topics of importance to Veterans and the VA healthcare system.

Comments on this evidence report are welcome and can be sent to Nicole Floyd, ESP Coordinating Center Program Manager, at nicole.floyd@va.gov.

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BACKGROUND

Given the high rates of mental illness among Veterans returning from Iraq and Afghanistan, it is not surprising that the demand for mental health services in Veterans Health Administration (VHA) has increased 132 percent since 2006. The most commonly diagnosed and treated disorders among Veterans receiving care at VHA include (1) PTSD, (2) depressive disorders, (3) episodic mood disorders, (4) anxiety disorders, and (5) substance use disorders. Unfortunately, shortages in trained mental health providers and logistical barriers limit Veterans' access to evidence-based therapies.

To address the growing need and barriers to accessing mental health services, the VA/Department of Defense (DoD) developed the Integrated Mental Health Strategy (IMHS), which includes the development of a series of Web-based self-help programs. Because web-based programs can be accessed anonymously, anytime, anywhere, and by multiple Veterans simultaneously, these services have the potential to surmount stigma and geographical and financial barriers to accessing mental health treatment.

Cognitive behavioral therapy (CBT), using group or individual face-to-face therapy, is effective in treating mild to severe mental health symptoms. Computer-based self-help programs grounded in CBT (computerized CBT [cCBT]) have generally been shown to produce significant reductions in depressive and anxiety symptoms, but treatment effects vary across studies. The availability of support via email, instant messaging, or phone contact with a therapist may mitigate attrition and improve treatment outcomes. Still, it is unclear how support-related factors influence treatment response to cCBT programs. To support the development of cCBT self-help programs, the VA commissioned the Evidence-based Synthesis Program to conduct a systematic review of the literature.

The key research questions for this systematic review were developed after a topic refinement process that included a preliminary review of published, peer-reviewed literature; consultation with internal partners and investigators; and consultation with content experts and key VA stakeholders. During the topic refinement process, the scope of this review was narrowed to focus on depressive and anxiety disorders, with plans to complete a subsequent review on alcohol and substance abuse disorders. The Key Questions (KQs) for this systematic review are:

KQ 1: For adults with depressive disorder, posttraumatic stress disorder, panic disorder, or generalized anxiety disorder, what are the effects of computerized CBT (cCBT) interventions compared with inactive controls?

KQ 2: For cCBT interventions, what level, type, and modality of user support is provided (e.g., daily telephone calls, weekly email correspondence); who provides this support (e.g., therapist, graduate student, peer); what is the clinical context (primary intervention, adjunct); and how is this support related to patient outcomes?

KQ 3: For adults with depressive disorder, posttraumatic stress disorder, panic disorder, or generalized anxiety disorder, what are the effects of cCBT interventions compared with face-to-face therapy?

METHODS

This review was commissioned by the VA's Evidence-based Synthesis Program. We followed a standard protocol for this review; certain methods map to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist. The topic was nominated after a process that included a preliminary review of published peer-reviewed literature and consultation with investigators, VA and non-VA experts, and key stakeholders (Mental Health Web Services, Mental Health Services, and Mental Health QUERI).

SEARCH STRATEGY AND STUDY SELECTION

In consultation with a master librarian, we searched MEDLINE® (via PubMed®), Cochrane Central Register of Controlled Trials, Embase®, CINAHL®, and PsycINFO® from January 1, 1990, to August 30, 2013, for peer-reviewed publications of trials that compared cCBT with usual care or face-to-face therapy in adults with depressive symptoms or disorders, and selected anxiety disorders. We limited the search to RCTs published in the English language.

Using prespecified inclusion and exclusion criteria, two reviewers assessed titles and abstracts for relevance to the KQs. Full-text articles identified by either reviewer as potentially relevant were retrieved and examined by two reviewers against the eligibility criteria. In addition, trials with three or more arms were examined for appropriateness of all arms for inclusion. Data elements to be abstracted from articles after full text review included descriptors to assess applicability, quality elements, intervention/exposure details, and outcomes. Key characteristics abstracted included patient descriptors, setting, features and dose of the cCBT intervention, and features of the comparator. Key features relevant to applicability include the match between the sample and target populations and the training and experience of the clinician. Data from published reports were then abstracted into the final abstraction form by a trained reviewer, and confirmed by a second reviewer.

DATA SYNTHESIS

When meta-analysis was feasible, we computed summary estimates of effect, stratified by condition (e.g., major depressive disorder, panic disorder), for both end-of-treatment and longest followup point ≥6 months. Because the primary outcome—symptom severity—was measured across the trials using different instruments, the measurements of symptom severity were combined using standardized mean differences (SMDs) in a random-effects model.

In addition, symptom severity for a single trial was often reported using more than one instrument (e.g., Beck Depression Inventory and Hamilton Depression Rating Scale). When multiple instruments were used, we calculated the mean effect from all instruments measuring symptoms directly related to the eligible illness, so that each study provided only one effect size for each treatment comparison.

We used subgroup analyses to explore potential sources of heterogeneity, including the category of support given with the intervention and the type of control group. We classified interventions into the following four mutually exclusive categories: (1) "no support" except technical (cCBT-NS);

(2) "supported" but via delayed communication modes such as email (cCBT-S); (3) "live support" featuring immediate bidirectional communication such as over the phone (cCBT-LS); and (4) "adjunct to therapy," where the cCBT program was used to augment face-to-face therapy (cCBT-AT). We classified control groups into three categories: waitlist, treatment as usual, and attention/information control. Because subgroup analyses involve indirect comparisons (across studies) and are susceptible to confounding, we considered these analyses to be hypothesis-generating. Publication bias was assessed using findings from a ClinicalTrials.gov search or funnel plots.

Where quantitative synthesis was not feasible (as for patient satisfaction and adherence outcomes), we analyzed the data qualitatively. The qualitative syntheses focused on documenting and identifying patterns in efficacy and safety of the intervention across conditions and outcome categories.

RISK OF BIAS (QUALITY) AND STRENGTH OF EVIDENCE ASSESSMENT

We used the key quality criteria described in the Agency for Healthcare Research and Quality's (AHRQ's) "Methods Guide for Effectiveness and Comparative Effectiveness Reviews," adapted to this specific topic and customized to RCTs. For RCTs, these criteria are adequacy of randomization and allocation concealment, the comparability of groups at baseline, blinding, the completeness of followup and differential loss to followup, whether incomplete data were addressed appropriately, the validity of outcome measures, and conflict of interest. We assigned a summary risk of bias score (low, moderate, or high) to individual studies.

In addition to rating the quality of individual studies, we evaluated the overall strength of evidence for each KQ using the approach recommended by AHRQ. In brief, this approach requires assessment of four domains: risk of bias, consistency, directness, and precision. An additional domain considered was publication bias. These domains were considered qualitatively, and a summary rating of high, moderate, low, or insufficient strength of evidence was assigned after discussion by two reviewers.

PEER REVIEW

A draft of the report was reviewed by technical experts and clinical leadership. A transcript of their comments and our responses is available in the appendix.

RESULTS

We identified 1552 unique citations from our combined search of 5 databases. Manual searching of key bibliographies and review articles identified 13 additional citations for a total of 1565 citations. After title and abstract screening and full text review, we included 54 articles (representing 47 unique trials involving 7270 patients plus 7 companion articles) for data abstraction. Because some RCTs contained multiple treatment arms, there were 64 relevant comparisons: 53 compared cCBT with control (KQ 1), 4 compared cCBT with different levels of therapist support (KQ 2), and 7 compared cCBT with face-to-face therapy (KQ 3).

The majority of the 47 included trials were conducted outside of the United States; only one was conducted in U.S. military personnel or Veterans. Overall risk of bias was assessed as high in 5 studies, moderate in 27 studies, and low in 15 studies. All but one trial reported one or more measures of symptom severity, and 25 reported health-related quality of life (HRQOL) at the end of treatment; 22 trials also reported symptom severity at a later followup.

The 47 included trials targeted the following patient groups:

- Depressive symptoms (15 trials)
- Major depressive disorder (11 trials)
- Depression, anxiety, or mixed anxiety/depression (3 trials)
- Panic disorder (10 trials)
- Generalized anxiety disorder (4 trials)
- PTSD (2 trials)
- Anxiety symptoms (2 trials)

Participants in the trials were often in the middle-aged adult range (median 39.8 years of age; range 20.7 to 58.0 years of age); no studies focused on older adults. Most trials specifically excluded patients currently engaged in traditional CBT and patients with suicidal ideation or concurrent substance abuse. Many studies excluded patients with severe symptoms. Psychotropic medications, usually with a restriction for a stable dose, were allowed in approximately 70 percent of the studies.

KQ 1: For adults with depressive disorder, posttraumatic stress disorder, panic disorder, or generalized anxiety disorder, what are the effects of cCBT interventions compared with inactive controls?

Key Points

- Computerized CBT was delivered primarily through the internet, and most trials (79%) utilized some form of therapist support.
- Treatment adherence was reported in 62 percent of comparisons and varied substantially across studies (median proportion completing all cCBT sessions was 49.5%, range 11% to 100%). Adherence rates were lower for patients with depressive symptoms than for other conditions.
- For patients with depressive disorders or symptoms:
    - Compared with control groups, trials of patients diagnosed with major depressive disorder who received cCBT generally reported large treatment effects at end of treatment (standardized mean difference [SMD] -0.82), with relatively little variability between studies, though more distal followup effects were more modest.
    - Trials of patients identified with depressive symptoms from self-report questionnaires, with no confirmed depression diagnosis, found only modest effects at end of treatment and followup (SMD -0.40), and treatment effects varied importantly across trials. Heterogeneity in treatment effects was explained in part by the category of cCBT support but not by the type of control group.

  - In trials of major depressive disorder and depressive symptoms, cCBT resulted in small to moderate improvements in HRQOL relative to control groups (SMD 0.37 and 0.26 respectively).

- For patients with anxiety disorders and symptoms:
  - Treatment effects were large and consistent across trials of patients with generalized anxiety disorder (SMD -.94). Trials of panic disorder also had large treatment effects (SMD -1.08), but they were inconsistent across interventions. Heterogeneity in treatment effects was explained in part by the category of cCBT support.
  - Few trials evaluated the long-term treatment effects of cCBT interventions. The available evidence suggests that treatment effects are small at 6 months or longer.
  - In trials of generalized anxiety disorder and panic disorder, cCBT resulted in moderate improvements in HRQOL relative to control groups (SMD 0.57 and 0.49 respectively).
  - The evidence was insufficient to determine the effect of cCBT in patients with PTSD or in patients with anxiety symptoms who were not diagnosed with a specific disorder.
- Data are lacking on cCBT safety and adverse events and only 47 percent of trials reported effects on HRQOL.

We found at least moderate strength of evidence (SOE) that cCBT interventions improved symptoms to a greater degree than control conditions (usual care, waitlist, or attention controls) for depressive symptoms, major depressive disorder, generalized anxiety disorder, and panic disorder (Table 1). For the latter three conditions, the effects measured at end of treatment were large. For PTSD and anxiety symptoms, however, there were few trials, and our confidence in the estimate of treatment effect was low. Patterns were similar for effects on HRQOL. For the subset of trials in our systematic review that evaluated outcomes at 6 months or longer, treatment effects were smaller, but remained statistically significant.

The rate of adherence was low when compared with general estimates of treatment completion for major depressive disorder and generalized anxiety disorder. The limited adherence rates in clinical trials, where patients are often more adherent than in typical practice, are a concern for effective implementation of cCBT.

Table 1. Summary of the strength of evidence for KQ 1: cCBT compared with control at end of treatment by disorder

Outcome	Strength of Evidence Domains				Effect Estimate (95% CI)[a]	SOE
	Number of Studies (Patients)	Study Design/ Risk of Bias	Consistency Directness	Precision Publication Bias		
Adults with depressive symptoms						
Symptom severity	13 (3010)	RCT/Moderate	Inconsistent Direct	Precise None detected	SMD = -0.40 (-0.49 to -0.31)	Moderate
HRQOL	4 (1269)	RCT/Moderate	Consistent Direct	Precise None detected	SMD = 0.26 (0.11 to 0.41)	Moderate
Adults with major depressive disorder or dysthymia						
Symptom severity	11 (931)	RCT/Moderate	Consistent Direct	Precise None detected	SMD = -0.82 (-.98 to -0.67)	High
HRQOL	8 (941)	RCT/Moderate	Consistent Direct	Precise None detected	SMD = 0.37 (0.22 to 0.52)	High
Adults with generalized anxiety disorder						
Symptom severity	4 (321)	RCT/Low	Consistent Direct	Imprecise None detected	SMD = -0.94 (-1.34 to -0.54)	Moderate
HRQOL	3 (176)	RCT/Moderate	Consistent Direct	Imprecise None detected	SMD = 0.57 (0.27 to 0.87)	Low
Adults with panic disorder						
Symptom severity	7 (333)	RCT/Moderate	Consistent Direct	Imprecise None detected	SMD = -1.08 (-1.45 to -0.72)	Moderate
HRQOL	6 (250)	RCT/Moderate	Consistent Direct	Imprecise None detected	SMD = 0.49 (0.23 to 0.75)	Moderate
Adults with PTSD						
Symptom severity	2 (71)	RCT/Moderate	Consistent Direct	Imprecise None detected	No summary estimate. SMD range from -0.42 to -0.46	Low
HRQOL	1 (40)	RCT/Moderate	NA Direct	Imprecise None detected	No summary estimate. SMD = 0.60 (-0.04 to 1.23) from one study	Insufficient
Adults with anxiety symptoms						
Symptom severity	2 (132)	RCT/High	Consistent Direct	Imprecise None detected	No summary estimate. SMD range from -0.28 to -0.42	Low
HRQOL	0 (0)	NA	NA NA	NA NA	NA	Insufficient

a For symptom severity, a negative effect estimate favors cCBT; for health-related quality of life, a positive effect estimate favors cCBT.

Abbreviations: CI=confidence interval; HRQOL=health-related quality of life; NA=not applicable; PTSD=posttraumatic stress disorder; RCT=randomized controlled trial; SMD=standardized mean difference; SOE=strength of evidence

KQ 2: For cCBT interventions, what level, type, and modality of user support is provided (e.g., daily telephone calls, weekly email correspondence); who provides this support (e.g., therapist, graduate student, peer); what is the clinical context (primary intervention, adjunct); and how is this support related to patient outcomes?

Key Points

- Of the 57 cCBT intervention arms examined, 15 (26.3%) were classified as not supported, 26 (45.6%) were supported, 14 (24.6%) were supported with live features, and 2 (3.5%) were used as adjuncts to therapy.
- All but three studies allowed patients to access the program from a nonclinical location (e.g., home, library, or community facility), and an advertisement on the internet was the most common means of recruitment (53%).
- Most trials used email in some form (74%), while phone support by clinical staff (35%) and peer support via discussion board or chat room (25%) and were used less often. Instant messaging was used in a single study.
- The intervention components of studies classified as supported and supported with live features were highly variable, making firm conclusions difficult to draw.
- Exploratory subgroup analysis, using indirect comparisons, showed an association between higher levels of support and greater treatment effects. Two small studies directly compared different levels of therapist support and did not find a differential treatment effect.

Most of the cCBT interventions were accessed via the internet from nonclinical locations and were supported by a therapist. Approximately one-third included a peer support discussion board. The level of therapist support varied widely, ranging from minimal feedback on homework assignments via email to a full therapy session via instant messaging or a chat room format. In two studies, cCBT was used as an adjunct to face-to-face therapy, but for most interventions, cCBT was a standalone treatment. Exploratory subgroup analysis, using indirect comparisons, showed an association between higher levels of support and greater treatment effects. Two small studies directly compared different levels of therapist support and did not find a differential treatment effect.

KQ 3: For adults with depressive disorder, posttraumatic stress disorder, panic disorder, or generalized anxiety disorder, what are the effects of cCBT interventions compared with face-to-face therapy?

Key Points

- Only seven trials directly compared cCBT interventions with standard face-to-face therapy. Five trials used an internet-based platform, while two trials incorporated a computerized complement to face-to-face therapy.
- For patients with anxiety disorders or symptoms, only panic disorder had enough trials to provide a summary effect size. Evidence suggests that there is minimal difference between cCBT and face-to-face therapy for panic disorder (SMD -0.07; 95% CI, -0.34 to 0.21).
- For patients with depressive disorders or symptoms, more data are needed to evaluate the differential effect between cCBT and face-to-face therapy.
- No trials of this type were conducted in patients with PTSD.

Seven studies directly compared cCBT with face-to-face therapy (Table 2). Panic disorder was the only condition with more than two studies making this comparison, and these trials showed no difference in effects on symptom severity or HRQOL (moderate SOE). Two studies, a relatively large, high-quality trial and a smaller, fair-quality trial, found no difference in treatment effects for participants with depressive symptoms (low SOE). The sample size in the single pilot study on major depressive disorder was too small to determine SOE. Therefore, we conclude the current literature is generally insufficient for making a determination about whether the efficacy of cCBT is comparable to traditional, face-to-face therapy.

Table 2. Summary of the strength of evidence for KQ 3

Outcome	Strength of Evidence Domains				Effect Estimate (95% CI)[a]	SOE
	Number of Studies (Patients)	Study Design/ Risk of Bias	Consistency Directness	Precision Publication Bias		
Adults with depressive symptoms						
Symptom severity	2 (254)	RCT/Low	Consistent Direct	Imprecise None detected	No summary estimate. SMD range (0.01 to 0.06)	Low
HRQOL	0 (0)	NA	NA NA	NA NA	No studies	Insufficient
Adults with major depression or dysthymia						
Symptom severity	1 (26)	RCT/Moderate	NA Direct	Imprecise None detected	No summary estimate. SMD = -0.20 (-0.98 to 0.57) from one study	Insufficient
HRQOL	0 (0)	NA	NA NA	NA NA	No studies	Insufficient
Adults with panic disorder						
Symptom severity	4 (319)	RCT/Low	Consistent Direct	Imprecise None detected	SMD = -0.07 (-0.34 to 0.21)	Moderate
HRQOL	3 (239)	RCT/Low	Consistent Direct	Imprecise None detected	SMD = -0.07 (-0.34 to 0.21)	Moderate

a For symptom severity, a negative effect estimate favors cCBT; for health-related quality of life, a positive effect estimate favors cCBT.

Abbreviations: HRQOL=health related quality of life; NA=not applicable; RCT=randomized controlled trial; SMD=standardized mean difference; SOE=strength of evidence

CLINICAL AND POLICY IMPLICATIONS

The VHA will need to determine whether to offer commercially available cCBT programs to patients or develop its own programs. New programs could be tailored to a Veteran sample and could incorporate recent developments in treatment as well as be adapted for increasingly prevalent technologies such as smartphones. VHA should not underestimate the challenge of introducing different approaches to care delivery. Offering choice and meeting patient preferences is a patient-centered approach that has the potential to improve adherence and clinical outcomes. Alternatively, facilities might consider using cCBT in a stepped-care model that offers cCBT as a first-line psychotherapy for patients with mild to moderate illness. In this

model, patients who do not report benefit from cCBT could then be referred for face-to-face therapy. Effective implementation could be informed by research on these competing options.

Another implementation issue to address is the question of when, and for whom, should cCBT be offered. Our review suggests greater effects for patients meeting criteria for full disorders and mild to moderate symptom severity. Requiring a diagnosis and clinician referral to the program could ensure more careful diagnostic evaluations and closer followup. However, this approach could partially negate some of the advantages of the cCBT format, such as anonymity and overcoming time constraints and travel barriers.

Another consideration is how much therapist support to provide with cCBT treatments. Psychotherapy models identify the therapeutic alliance between patient and therapists as an important mechanism of achieving improved psychiatric symptoms. Based on indirect comparisons, we found a relatively consistent gradient showing greater treatment effects with greater support. However, very few studies evaluated more intensive human support for some conditions, and we were unable to isolate the specific features or degree of support associated with treatment benefit. Based on current evidence, we conclude that health systems implementing cCBT should include therapist support via email or brief telephone sessions, or both.

Finally, facilities implementing cCBT also need to consider the staffing needs for these interventions. The studies we reviewed did not provide reliable estimates of the panel size that a single therapist could support, but based on the median of approximately 13 to 15 minutes devoted to each patient weekly, a therapist supporting cCBT could provide care to a substantially larger cohort than those utilizing face-to-face therapy.

RECOMMENDATIONS FOR FUTURE RESEARCH

We used the framework recommended by Robinson et al. to identify gaps in evidence and classify why these gaps exist (Table 3). This approach considers PICOTS (population, intervention, comparator, outcomes, timing, and setting) to identify gaps and classifies them as due to (1) insufficient or imprecise information, (2) biased information, (3) inconsistency or unknown consistency, and (4) not the right information. Using this structure, we have identified gaps in evidence and propose study designs to address these gaps.VA and other healthcare systems should consider their clinical and policy needs when deciding whether to invest in research to address gaps in evidence.

Table 3. Evidence gaps and future research needs

Evidence Gap	Reason	Type of Studies to Consider
Patients		
Effects in patients with PTSD or anxiety symptoms	Insufficient information	Randomized controlled trials
Effects on access to care	Insufficient information	Observational studies to evaluate if cCBT users differ from users of traditional mental health services and changes in proportion of veterans with mental illness receiving evidence-based therapies
Identifying factors (such as severity, educational level) that predict successful treatment with cCBT	Insufficient information	Large trials, observational studies, or patient level meta-analysis
Interventions		
Optimal level of therapist support	Insufficient information Exploratory analysis suggest possible differential effect	RCTs or quasi-experimental studies of limited versus more robust therapist support
Optimal mode of support delivery, i.e., phone vs. email vs. chat-room, etc.	Insufficient information	Head-to-head comparisons of mode, duration and intensity of therapist support.
Amount of therapist support. i.e., frequency and duration of contact independent of mode	Insufficient information	Head-to-head comparisons of mode, duration and intensity of therapist support.
Optimal case-load for a therapist supporting cCBT interventions	Insufficient information	Time-in-motion or related study designs
Optimal mode of implementation, e.g., patient choice vs. stepped-care	Insufficient information	RCTs or quasi-experimental studies of patient choice versus cCBT first, then face-to-face therapy for nonresponders
Optimal platform (e.g., Web or mobile device) and interface design	Insufficient information: few studies of mobile devices; no detailed analysis of Web design features	RCTs, quasi-experimental, and single case experimental designs to test novel technology. Studies should contain multiple platform comparisons including web-only, web + mobile, web on mobile, and mobile-only. Also include various mobile features such as text messaging, video messaging, and mobile applications.
Comparator		
Effectiveness compared to in person treatment	Insufficient information	Trials with end or treatment and 6 to 12 month outcome assessments
Outcomes		
Effects on adherence rates	Insufficient information	Trials with 6- to 12-month outcome assessments
Durability of treatment effects beyond the end of treatment	Insufficient information	Trials with 6- to 12-month outcome assessments
Uncertain effects on adverse events and patient safety	Insufficient information	Multisite observational studies; patient registries

Abbreviation: cCBT=computerized cognitive behavioral therapy; PTSD=posttraumatic stress disorder; RCT=randomized controlled trial

CONCLUSION

We found moderate to strong evidence that cCBT is effective in improving short-term symptoms for mid-life patients with mild to moderate major depressive disorder, generalized anxiety disorder, and panic disorder. Treatment effects were smaller for patients with depressive symptoms. We found evidence suggesting that the level of therapist support was related to the magnitude of benefit, but additional head-to-head trials are needed to address this issue definitively. VA/DoD should consider this body of evidence when updating their clinical guidelines for depression and anxiety disorders.

ABBREVIATIONS TABLE

AHRQ	Agency for Healthcare Research and Quality
cCBT	computerized (or Web-based) cognitive behavioral therapy
cCBT-AT	cCBT-adjunct to therapy
cCBT-LS	cCBT-live support
cCBT-NS	cCBT-no support
cCBT-S	cCBT-supported
CI	confidence interval
DoD	Department of Defense
HRQOL	health-related quality of life
IMHS	Integrated Mental Health Strategy
KQ	Key Question
NA	not applicable
PRISMA	Preferred Reporting Items for Systematic Reviews
PTSD	posttraumatic stress disorder
QUERI	Quality Enhancement Research Initiative
RCT	randomized controlled trial
RD	risk difference
SMD	standardized mean difference
SOE	strength of evidence
VA	Department of Veterans Affairs
VHA	Veterans Health Administration

EVIDENCE REPORT

INTRODUCTION

Mental health disorders negatively affect an individual's ability to perform basic daily activities, are associated with increased risk of morbidity and mortality, and impose a substantial economic burden on the U.S. healthcare system.[1-3] Of the 5.2 million Veterans who received healthcare from Veterans Health Administration (VHA) in 2010, approximately 1.2 million received care for mental health needs.[4] Consistent with these Veteran-specific data, national epidemiological studies have shown that mental health disorders are highly prevalent among adults in the United States, with the 12-month prevalence rates of mood disorders and anxiety disorders estimated to be 9.5 percent and 18.1 percent, respectively.[5] Given the high rates of mental illness among Veterans returning from Iraq and Afghanistan, it is not surprising that the demand for mental health services in VHA has increased 132 percent since 2006.[4] The most commonly diagnosed and treated disorders among Veterans receiving care at VHA include (1) adjustment reactions (e.g., posttraumatic stress disorder [PTSD]), (2) depressive disorders, (3) episodic mood disorders, (4) anxiety disorders (e.g., panic disorder, generalized anxiety disorder, phobias), and (5) substance abuse disorders. Unfortunately, a variety of logistical barriers prevent Veterans from accessing VHA mental healthcare, including distance and transportation challenges that hinder travel to and from appointments, challenges in arranging child care and spousal support, time constraints, and difficulty scheduling appointments.[4]

To address the growing need for mental health services and barriers to accessing these services, the Department of Defense and VHA launched the Integrated Mental Health Strategy (IMHS) in 2010. The IMHS consists of a series of 28 strategic actions designed to help both agencies better meet the unique mental health needs of military service members, Veterans, and their families. One strategic action involves creating a series of web-based self-help programs. Programs under this initiative leverage technology to enhance and expand the capacity of mental health treatment providers to deliver interventions through the use of health information technology and applications available for use on computer operating systems (e.g., desktop, laptop) and mobile operating systems (e.g., smartphones, tablets, personal digital assistant, portable media devices). Given that these services can be accessed anonymously, anytime, anywhere, and by multiple Veterans simultaneously, computer- and web-based services have the potential to surmount stigma along with geographical and financial barriers to accessing mental health treatment. In November 2012, "Moving Forward," based on problem-solving therapy, was the first in this series to be released. Programs focusing on parenting and anger management are planned to be released in 2013, and additional programs for selected mental health disorders are under review.

Important considerations for interventions developed through the IMHS initiative include evaluation of the empirical evidence for an intervention, understanding the elements that make an intervention successful, and for whom and under what circumstances is an intervention effective. One approach about which a great deal is known is cognitive behavioral therapy (CBT). CBT is a structured, time-limited, present-focused approach to psychotherapy that helps patients learn and apply specific strategies to modify maladaptive thoughts and behaviors that contribute to distress. Originally developed for the treatment of depression,[6,7] CBT has since been adapted

for the treatment of anxiety disorders,[8] substance use disorders,[9] personality disorders,[10] eating disorders,[11] and severe mental illnesses, including bipolar disorder[12] and schizophrenia.[13] CBT is effective in treating mild, moderate, and severe mental health symptoms.[14,15] Further, CBT is equally as effective as psychotropic medications in the short term and, for some conditions, is more effective than psychotropic medications in the long term.[16]

COMPUTERIZED COGNITIVE BEHAVIORAL THERAPY

Although computer-based self-help programs grounded in CBT—which we refer to as computerized CBT (cCBT)—have generally been shown to produce significant reductions in depressive and anxiety symptoms, there is variation across studies in the implementation and effects of these interventions.[17-19] Also, participation in such programs typically declines after the initial engagement, with reports of attrition higher than 50 percent in some studies.[20-22] The availability of support via email, instant messaging, or phone contact with a therapist, coach, or peer specialist may mitigate attrition and improve treatment outcomes.[19,23] However, it remains unclear how support-related factors (e.g., frequency of contact between patient and support provider, method and frequency of communication, optimal level of support provider training) influence treatment response to cCBT programs.

To support the development of cCBT self-help programs, the VA commissioned the Evidence-based Synthesis Program (ESP) to conduct a systematic review of the literature. Thus, our objectives in summarizing the results of randomized controlled trials (RCTs) that tested cCBT interventions were threefold. The first aim was to compare the effectiveness of cCBT with inactive controls. The second was to examine the influence of support-related factors on treatment outcomes including satisfaction, response, and completion. The third was to compare the effectiveness of cCBT with face-to-face CBT. Additional analyses and qualitative descriptions sought to explain critical components of effective cCBT interventions, identify gaps in the treatment literature, and generate hypotheses and ideas for future research studies.

METHODS

TOPIC DEVELOPMENT

We followed a standard protocol for this review; certain methods map to PRISMA (i.e., Preferred Reporting Items for Systematic Reviews and Meta-Analyses).[24] The topic was nominated after a process that included a preliminary review of published peer-reviewed literature and consultation with investigators, VA and non-VA experts, and key stakeholders (Mental Health Web Services, Mental Health Services, and Mental Health QUERI).

The Key Questions (KQs) are:

KQ 1: For adults with depressive disorder, posttraumatic stress disorder, panic disorder, or generalized anxiety disorder, what are the effects of computerized CBT (cCBT) interventions compared with inactive controls?

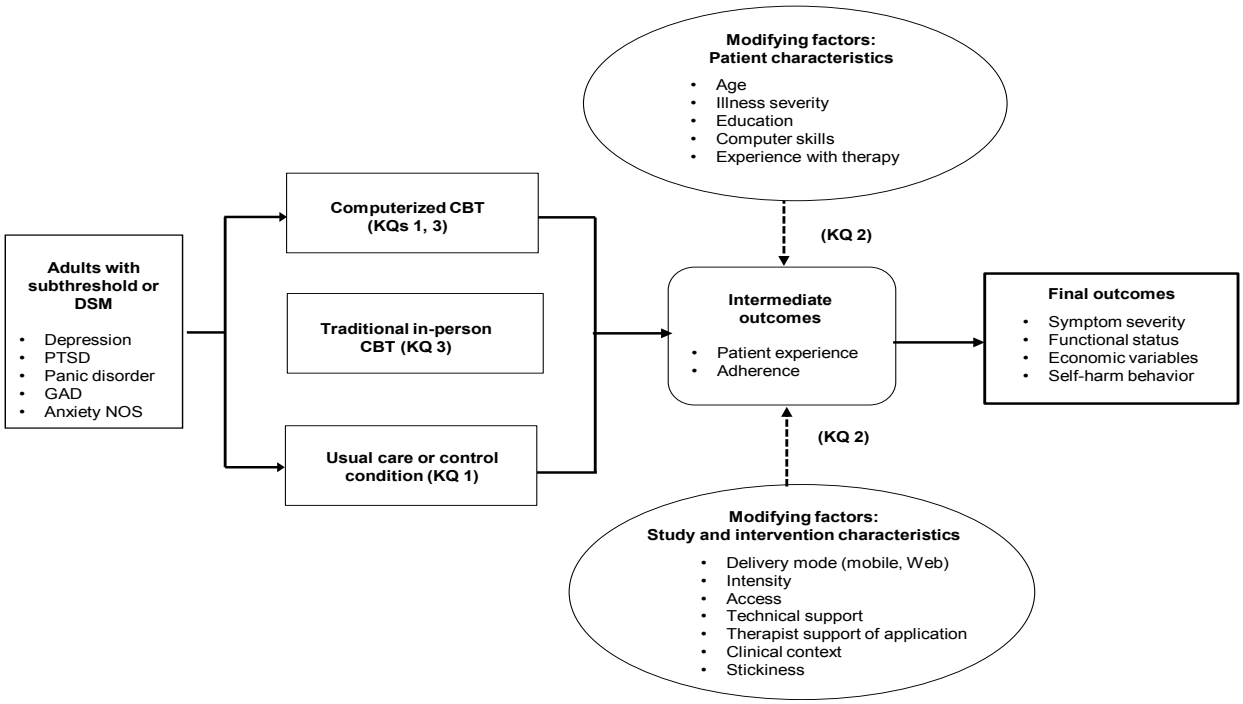
KQ 2: For cCBT interventions, what level, type, and modality of user support is provided (e.g., daily telephone calls, weekly email correspondence); who provides this support (e.g., therapist, graduate student, peer); what is the clinical context (primary intervention, adjunct); and how is this support related to patient outcomes?

KQ 3: For adults with depressive disorder, posttraumatic stress disorder, panic disorder, or generalized anxiety disorder, what are the effects of cCBT interventions compared with face-to-face therapy?

ANALYTIC FRAMEWORK

Our approach was guided by the analytic framework shown in Figure 1.

Figure 1. Analytic framework for evaluating computerized CBT interventions



Abbreviations: CBT=cognitive behavioral therapy; DSM=Diagnostic and Statistical Manual of Mental Disorders; GAD=generalized anxiety disorder; KQ=Key Question; NOS=not otherwise specified; PTSD=posttraumatic stress disorder

SEARCH STRATEGY

We conducted a primary review of the literature by systematically searching, reviewing, and analyzing the scientific evidence as it pertains to the KQs. To identify relevant articles, in consultation with a master librarian, we searched MEDLINE® (via PubMed®), Cochrane Central Register of Controlled Trials, Embase®, CINAHL®, and PsycINFO® from January 1, 1990, to August 30, 2013, for peer-reviewed publications of trials that compared cCBT with usual care or face-to-face therapy in adults with depressive symptoms or disorders, selected anxiety disorders (i.e., panic disorder or generalized anxiety disorder), and PTSD.

We used Medical Subject Heading (MeSH) terms and selected free-text terms for the conditions of interest; cognitive behavioral therapy and closely related therapies; and the electronic delivery mode, including computer-assisted, internet, and terms for mobile devices (Appendix A). We added validated search terms for RCTs. We limited the search to RCTs published in the English language. We further searched the bibliographies of exemplar trials and applicable systematic reviews for missed publications.[17,18,23,25-33] To assess for publication bias, we searched www.clinicaltrials.gov to identify completed but unpublished studies meeting our eligibility criteria, an indicator of possible publication bias.

All citations were imported into two electronic databases (for referencing, EndNote® Version X5, Thomson Reuters, Philadelphia, PA; for data abstraction, DistillerSR; Evidence Partners Inc., Manotick, ON, Canada).

STUDY SELECTION

Using prespecified inclusion and exclusion criteria, two reviewers assessed titles and abstracts for relevance to the KQs. Full-text articles identified by either reviewer as potentially relevant were retrieved for further review and examined by two reviewers against the eligibility criteria. Disagreements on inclusion, exclusion, or the major reason for exclusion were resolved by discussion or by a third reviewer. The criteria to screen articles for inclusion or exclusion at both the title-and-abstract and full-text screening stages are detailed in Table 4. In addition, trials with three or more arms were examined for appropriateness of all arms for inclusion. For example, any active arm that did not include cCBT (such as a telephone-only intervention) was not abstracted for inclusion in the analysis.

Table 4. Summary of inclusion and exclusion criteria

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Population	Adults (≥18 years of age) with one or more of the following conditions: • Unipolar depressive disorder (major depressive disorder, dysthymia, minor depression, adjustment disorder with depressed mood, or mixed anxiety/depression) as defined by DSM criteria • Posttraumatic stress disorder as defined by DSM criteria • Generalized anxiety disorder, panic disorder, and anxiety disorder not otherwise specified as defined by DSM criteria • Patients scoring above the threshold for significant depressive or anxiety symptoms using a validated questionnaire as a condition of eligibility • Comorbid psychiatric disorders as long as the primary disorder is a condition of interest • In studies that include mixed samples of children and adults, at least 80% must be ≥18 years old (or the mean age minus 1.5 SD ≥18 years old) • In studies that include patients with a large number of conditions, at least 80% must have one of the conditions of interest	Patients with test anxiety Phobias and social anxiety disorder

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Intervention	Intervention must be a therapy based on cognitive behavioral therapy (CBT) and delivered primarily by a computerized (i.e., electronic) mechanism. Interventions may be designed for self-guided treatment or with the support of a clinician, but the computerized program must be the key intervention that differs from the control group. • **Delivery mode:** Internet, mobile platform (e.g., smartphone), computer in clinic • **Treatment model:** Therapy is CBT or derived from cognitive or behavioral therapies. CBT interventions adhere to the premise that changing maladaptive thinking leads to change in affect and in behavior. CBT includes six phases: 1 Assessment 2 Reconceptualization 3 Skills acquisition 4 Skills consolidation and application training 5 Generalization and maintenance 6 Posttreatment assessment followup Therapies that are closely related to CBT and included in this review are exposure therapy, stress inoculation training, cognitive processing therapy, cognitive therapy, dialectical behavior therapy, problem solving therapy, and acceptance and commitment therapy. • **Treatment phase:** Intervention is designed for acute-phase treatment, not relapse prevention or the prevention of mental illness.	Psychodynamic therapy and interpersonal therapy Interventions designed to prevent onset or relapse of mental illness Interventions that are primarily telemedicine-based (e.g., therapy via video chat or telephone interactions, including those by interactive voice response) Interventions using virtual reality as the primary therapeutic mode Therapies that do not use the key components of CBT Disease management interventions where CBT is only one component of a more comprehensive intervention Therapies that are delivered primarily in face-to-face encounters but supplemented by text messages or online materials that do not meet the definition of a CBT or CBT-related intervention
Comparator	KQ 1, KQ 2: Usual care not involving psychotherapy; waitlist control; attention/information control KQ 2: cCBT with a different level of therapist support KQ 3: Face-to-face CBT	Any comparator where the effect of the cCBT intervention cannot be isolated
Outcome	Patient experience (e.g., satisfaction measure) Adherence to the intervention (e.g., number of planned sessions completed, proportion completing the planned intervention) Validated, self-report symptom measures (e.g., BDI, HDRS) Validated, functional status measures of global or mental health functioning (e.g., SF-36, Sheehan Disability Scale) Safety outcomes such as emergency department visits or hospital admissions related to the disorder being treated; self-harm behaviors	None
Timing	Outcomes reported ≥2 months from randomization and initiation of intervention	Outcomes reported <2 months

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Setting	Patients may be identified from primary care, medical specialty, mental health, or community populations Patients do not have to be engaged in treatment with a clinician and may be identified through self-assessments without a definitive clinical diagnosis	Inpatient settings
Study design	Randomized controlled trials with n >20. The sample size requirement is designed to exclude small pilot studies that typically are underpowered and have more methodological problems than larger trials. Studies with small samples sizes and no treatment effect are also less likely to be published than those finding a treatment effect, increasing the risk of publication bias.	Any study design other than RCT
Publications	English-language only Published from 1990 to present[a] Peer-reviewed, full publication Study conducted in North America, Western Europe, Australia/New Zealand[b]	Non-English language Published before 1990 Abstract only

[a] Rationale is that CBT was developed in the 1970s, personal computers in the early 1980s, and the internet in the 1990s. Based on our assessment of studies included in existing systematic reviews, the earliest relevant publication was in 1990.
[b] Rationale is to include economically developed countries with sufficient similarities in healthcare system and culture to be applicable to U.S. medical care.
Abbreviations: BDI=Beck Depression Inventory scale; CBT=cognitive behavioral therapy; cCBT=computerized cognitive behavioral therapy; HDRS=Hamilton Depression Rating Scale; KQ=Key Question; RCT=randomized controlled trial

DATA ABSTRACTION

Before general use, the abstraction form templates, designed specifically for this report, were piloted on a sample of included articles and revised to ensure that all relevant data elements were captured and that there was consistency and reproducibility between abstractors. Data elements include descriptors to assess applicability, quality elements, intervention/exposure details, and outcomes. Key characteristics abstracted include patient descriptors (including education, computer skills, experience with therapy), setting, features and dose of the cCBT intervention, features of the comparator, and outcomes as described previously. Key features relevant to applicability include the match between the sample and target populations (e.g., comorbidity, age, education level) and the training and experience of the clinician. Data from published reports were then abstracted into the final abstraction form by a trained reviewer. All data abstractions were confirmed by a second reviewer. Disagreements were resolved by consensus or by obtaining a third reviewer's opinion.

We abstracted the following key information for each included study:

- Study characteristics
  - Study design
  - Location (country) and recruitment setting (clinic, etc.) of study
  - Types of comparison groups
  - Inclusion and exclusion criteria (eligible diagnoses, etc.)
  - Number of participants eligible for, randomized, or enrolled in and completed study

- Population characteristics
  - Sex, race, and age of sample
  - Inclusion of active duty or Veteran participants
  - Psychiatric diagnoses
  - Baseline severity of symptoms
- Description of the intervention
  - "Brand" name of intervention
  - Components of intervention
  - Therapist credentials
  - Number of treatment modules, time allowed for completion
  - Level of therapist support, including homework feedback, email communication, live communication (e.g., telephone)
  - Technical support offered
  - Presence of peer support (discussion board, chat-room, etc.)
- Outcomes
  - Time points measured
  - Treatment adherence: mean sessions completed or proportion completing all sessions
  - Patient satisfaction
  - Symptom severity
  - Health-related quality of life (HRQOL)
  - Safety: emergency department visits or hospital admissions related to the disorder; self-harm behaviors

RISK OF BIAS (QUALITY) ASSESSMENT

We abstracted data necessary to assess the risk of bias of included trials. Across all included trials, quality criteria were applied for each RCT by two independent reviewers (Appendix B). Disagreements were resolved between the two reviewers or, when needed, by arbitration from a third reviewer. We used the key risk of bias criteria described in the Agency for Healthcare Research and Quality's (AHRQ's) "Methods Guide for Effectiveness and Comparative Effectiveness Reviews"[34] adapted to this specific topic and customized to RCTs. These criteria are adequacy of randomization and allocation concealment, the comparability of groups at baseline, blinding, the completeness of followup and differential loss to followup, whether incomplete data were addressed appropriately, the validity of outcome measures, and conflict of interest. We assigned a summary risk of bias score (low, moderate, or high) to individual studies.

DATA SYNTHESIS

While synthesizing relevant abstracted data, we developed a summary table describing the key outcomes used to test cCBT interventions in included RCTs. We then determined the feasibility of completing a quantitative synthesis (i.e., meta-analysis) to estimate summary effects. Feasibility depends on the volume of relevant literature, conceptual homogeneity of the trials, and completeness of results reporting.

When meta-analysis was feasible, we computed summary estimates of effect, stratified by condition (e.g., major depressive disorder, panic disorder), for both end-of-treatment and longest followup point ≥6 months. Because the primary outcome—symptom severity—was measured across the trials using different instruments, the measurements of symptom severity were combined using standardized mean differences (SMDs) in a random-effects model.[35,36] At each time point, the SMD was calculated by subtracting the average score of the treatment group from the average score of the control group and dividing the result by the pooled standard deviations of the two groups. SMDs of 0.2 can be considered small treatment effects; 0.5, moderate effects; and ≥0.8, large effects.[37]

In addition, symptom severity for a single trial was often reported using more than one instrument (e.g., Beck Depression Inventory and Hamilton Depression Rating Scale). When multiple instruments were used, we calculated the mean effect from all instruments measuring symptoms directly related to the eligible illness, so that each study provided only one effect size for each treatment comparison. When trials included more than one relevant intervention compared with a single control, we allocated one-half the control sample to each comparison to avoid false precision. We evaluated for statistical heterogeneity using Cochrane's Q and I^2 statistics. An I^2 of 0 percent indicates no observed heterogeneity, and larger values suggest increasing heterogeneity: 25 percent is interpreted as low, 50 percent as moderate, and ≥75 percent as high heterogeneity.[38]

Levels of cCBT Support

We used subgroup analyses to explore potential sources of heterogeneity, including the level of support given with the intervention and the type of control group. We classified interventions into the following four mutually exclusive categories:

1. *No support* (cCBT-NS) interventions were designed to be standalone cCBT interventions. The participant was encouraged to go to a website and work through the cCBT program modules at an approximate rate of one per week. After beginning the intervention, no significant human support, feedback, or engagement was provided. However, participants may have received technical support for problems accessing or utilizing the program but not to explain material.

2. *Supported* (cCBT-S) interventions used a form of interaction involving a technician (nonlicensed staff) or clinician (licensed professional) regarding the content of the cCBT modules. Such support included feedback on the participant's previous interactions with the program, and psychoeducation. This type of support was bidirectional but not in real time; that is, receipt of a communication from either party was delayed (not synchronous).

3. *Live support* (cCBT-LS) interventions involved real-time interactions with study technicians or clinicians, including phone sessions, a scheduled chat on internet forums, or instant messaging.

4. *Adjunct to therapy* (cCBT-AT) interventions employed a traditional, face-to-face therapy protocol as the primary intervention, with components of cCBT as part of the intervention but not the focus; the cCBT program was used to augment or reinforce the face-to-face session.

Types of Control Groups

We classified control groups into three categories:

1. *Waitlist* control groups typically completed assessments with no study-related treatment provided while the cCBT arm was receiving treatment. The control group would then receive the intervention.
2. *Treatment as usual* control groups typically received a referral or had primary care physicians who received information on treating the symptoms or disorder that was the focus of the trial.
3. *Attention/information* control groups typically received supportive treatment or psychoeducation regarding the symptoms or disorder being targeted.

Because subgroup analyses involve indirect comparisons (across studies) and are susceptible to confounding, we considered these analyses to be hypothesis-generating. We used meta-regression analyses to test whether there was a significant relation between the proportion of patients completing all treatment modules and the treatment effect. We used Comprehensive Meta-Analysis (version 2.2.064) to calculate the summary SMD, and conduct meta-regression and subgroup analyses. Publication bias was assessed using findings from a ClinicalTrials.gov search. We included funnel plots when at least 10 studies were included in the analysis.

Where quantitative synthesis was not feasible (as for patient satisfaction and adherence outcomes), we analyzed the data qualitatively. We gave more weight to the evidence from higher quality studies with more precise estimates of effect. The qualitative syntheses focused on documenting and identifying patterns in efficacy and safety of the intervention across conditions and outcome categories. We also analyzed potential reasons for inconsistency in treatment effects across studies by evaluating differences in the study population, intervention, comparator, and outcome definitions.

STRENGTH OF THE BODY OF EVIDENCE

In addition to rating the quality of individual studies, we evaluated the overall strength of evidence (SOE) for each KQ as described in the "Methods Guide."[34] In brief, this approach requires assessment of four domains: risk of bias, consistency, directness, and precision. These domains along with evidence for publication bias were considered qualitatively, and a summary rating of high, moderate, low, or insufficient SOE was assigned after discussion by two reviewers. The four-level rating scale consists of the following definitions:

- **High**—We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate**—We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low**—Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

- **Insufficient**—Evidence on an outcome is absent or too weak, sparse, or inconsistent to estimate an effect.

When a rating of high, moderate, or low was not possible or was imprudent to make, a rating of insufficient was assigned.

PEER REVIEW

A draft of the report was reviewed by technical experts and clinical leadership. A transcript of their comments and our responses is available in Appendix C.

RESULTS

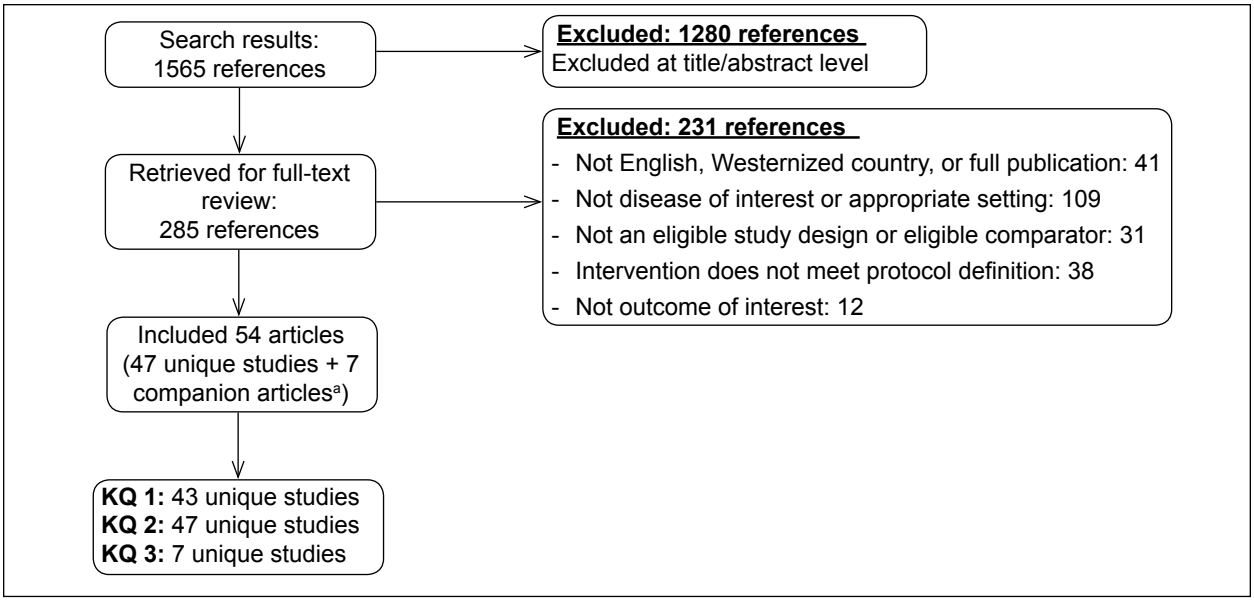
LITERATURE SEARCH

The flow of articles through the literature search and screening process is illustrated in Figure 2. We identified 1552 unique citations from a combined search of MEDLINE (via PubMed, n=483), CINAHL (n=356), Embase (n=232), PsycINFO (n=168), and Cochrane (n=313) conducted from 1990 through January 4, 2013, and updated on August 30, 2013. Manual searching of included study bibliographies and review articles identified 13 additional citations for a total of 1565 citations. After applying inclusion and exclusion criteria at the title-and-abstract level, 285 full-text articles were retrieved and screened. Of these, 231 were excluded at the full-text screening stage, leaving 54 articles (representing 47 unique trials and 7 companion articles) for data abstraction.

Our search of www.clinicaltrials.gov on August 2, 2013, identified one relevant article missed by our literature search.[39] All other articles identified were captured by the update to the literature search performed on August 30, 2013.

It was necessary to contact 24 authors for clarification of abstracted elements during the course of the data abstraction process. Twelve authors responded with the requested information.

Figure 2. Literature flow diagram



[a] Refer to Glossary for a definition of companion articles.

DESCRIPTION OF INCLUDED STUDIES

We identified 47 unique RCTs involving 7270 patients that met our inclusion criteria.[39-85] Because some trials contained multiple treatment arms, there were 64 comparisons relevant to this review: 53 compared cCBT with control (KQ 1), 4 compared cCBT with different levels of therapist support (KQ 2), and 7 compared cCBT with face-to-face therapy (KQ 3).

The 47 trials targeted the following patient groups:

- Depressive symptoms (15 trials)[42,44,48,49,56,58,60,62,71,72,78,79,82-84]
- Major depressive disorder (11 trials)[39,43,45,52,54,55,57,64,67,80,81]
- Depression, anxiety, or mixed anxiety/depression (3 trials)[68,70,85]
- Panic disorder (10 trials)[41,50,51,59,63,65,66,69,74,75]
- Generalized anxiety disorder (4 trials)[40,46,53,73]
- PTSD (2 trials)[47,61]
- Anxiety symptoms (2 trials) [76,77]

Participants in the trials were often in the middle-aged adult range (median 39.8 years of age; range 20.7 to 58.0 years of age). Most trials specifically excluded patients currently engaged in traditional CBT and patients with suicidal ideation or concurrent substance abuse. Many studies excluded patients with severe symptoms. Psychotropic medications, usually with a restriction for a stable dose, were allowed in approximately 70 percent of the studies. cCBT interventions were almost always provided by remote web-based access and only rarely in office settings. When delivered by remote access, most studies used some degree of therapist support.

The majority of the 47 included trials were conducted outside of the United States; only one[61] was conducted with U.S. military personnel or Veterans. Overall risk of bias was assessed as high in 5 studies, moderate in 27 studies, and low in 15 studies. Common methodological concerns included outcome assessment by personnel with knowledge of treatment assignment and unclear or inadequate randomization or allocation concealment procedures. All but one trial[72] reported one or more measures of symptom severity, and 25 reported HRQOL at the end of treatment; 22 trials also reported symptom severity at a later followup. Outcomes were assessed between 7 and 14 weeks for end of treatment in most studies (83%) and ≥24weeks for later followup.

Detailed study characteristics for the 47 trials are in Table D-1 in Appendix D. Next, we give further details and analysis of the included studies organized by KQ.

KEY QUESTION 1. For adults with depressive disorder, posttraumatic stress disorder, panic disorder, or generalized anxiety disorder, what are the effects of cCBT interventions compared with inactive controls?

Key Points

- Computerized CBT was delivered primarily through the internet, and most trials (79%) utilized some form of therapist support.
- Only 47 percent of trials reported effects on HRQOL.

- Data are lacking on cCBT safety and adverse events.
- Treatment adherence was reported in 62 percent of comparisons and varied substantially across studies (median proportion completing all cCBT sessions was 49.5%, range 11% to 100%. Adherence rates were lower for patients with depressive symptoms than for other conditions.
- For patients with depressive disorders or symptoms:
    - Compared with control groups, trials of patients diagnosed with major depressive disorder who received cCBT generally reported large treatment effects at end of treatment (standardized mean difference [SMD] -0.82), with relatively little variability between studies, though more distal followup effects were more modest.
    - Trials of patients identified with depressive symptoms from self-report questionnaires, with no confirmed depression diagnosis, found only modest effects at end of treatment and followup (SMD -0.40), and treatment effects varied importantly across trials. Heterogeneity in treatment effects was explained in part by the category of cCBT support but not by the type of control group.
    - In trials of major depressive disorder and depressive symptoms, cCBT resulted in small to moderate improvements in HRQOL relative to control groups (SMD 0.37 and 0.26 respectively).
    - The type of control group did not explain variability in treatment effects.
- For patients with anxiety disorders or symptoms:
    - Treatment effects were large and consistent across trials of patients with generalized anxiety disorder (SMD -.94). Trials of panic disorder also had large treatment effects (SMD -1.08), but they were inconsistent across interventions. Heterogeneity in treatment effects was explained in part by the category of cCBT support.
    - Few trials evaluated the long-term treatment effects of cCBT interventions. The available evidence suggests that treatment effects are small at 6 months or longer.
    - In trials of generalized anxiety disorder and panic disorder, cCBT resulted in moderate improvements in HRQOL relative to control groups (SMD 0.57 and 0.49 respectively).
    - The evidence was insufficient to determine the effect of cCBT in patients with PTSD or in patients with anxiety symptoms who were not diagnosed with a specific disorder.

Study Characteristics

We identified 43 trials involving 6960 patients and 53 comparisons that met inclusion criteria for evaluating KQ 1.[39-49,51-58,60-65,67-78,80-85] Of these 43 trials, 11 (15 comparisons) evaluated the effects of cCBT versus control on treatment of major depressive disorder, and 14 (18 comparisons) enrolled participants who exceeded a threshold for significant depressive symptoms on a self-report questionnaire. For anxiety disorders, 4 trials (5 comparisons) targeted generalized anxiety disorder, 7 (8 comparisons) targeted panic disorder, 2 (2 comparisons) targeted PTSD, and 2 (2 comparisons) enrolled participants on the basis of exceeding a threshold of significant anxiety symptoms. Last, 3 trials (3 comparisons) targeted psychiatric disorder symptoms in a mixed group of patients with depressive and anxiety disorders.

Table 5 summarizes the patient and study characteristics of the 43 trials, including the 53 comparisons between cCBT and control. Racial background of participants was reported in only 8 trials, with the majority of participants being white, although one trial[82] reported the percentage of participants who spoke English at home. We report the effects of treatment by target disorder and outcome: (1) symptom severity and HRQOL at end of treatment and (2) symptom severity at later followup. These summary estimates of treatment effect are presented as SMDs. For symptom severity, we explore heterogeneity in end-of-treatment effects, categorizing studies by the level of cCBT support and type of comparator. Other outcomes (e.g., patient satisfaction, treatment adherence) are summarized qualitatively across all studies.

Table 5. Study characteristics of cCBT interventions

Study characteristics	
N trials (N patients)	43 trials (6960 patients)
Trial location: N (%)	
United States	4 (9.3%)
Western Europe	22 (51.2%)
Australia/New Zealand	17 (39.5%)
Disorders: N (%)	
Major depressive disorder	11 (25.6%)
Significant depressive symptoms	14 (32.6%)
Generalized anxiety disorder	4 (9.3%)
Panic disorder	7 (16.3%)
Mixed disorders	3 (7%)
Posttraumatic stress disorder	2 (4.7%)
Significant anxiety symptoms	2 (4.7%)
Studies reporting ≥6 months of followup for treatment and control: N (%)	
Followup data reported	19 (44.5%)
Followup data not reported	24 (56.5%)
Studies reporting treatment adherence at end of treatment: N (%)	
Adherence reported	27 (63%)
Adherence not reported	16 (47%)
Patient characteristics	
Age: median (range)	41.5 (20.7 to 57.9)[a]
Sex: N patients (%)	
Female	4055 (59.7%)
Male	2805 (40.3%)
Time of end-of-treatment outcomes assessment: N (%)[b]	
6 weeks or less	5 (11.6%)
7–9 weeks	19 44.2%)
10–17 weeks	19 (44.2%)
Intervention characteristics (53 total cCBT comparisons)	
Level of therapist support: N (%)	
No support	15 (28.3%)
Support	25 (47.2%)
Live support	11 (20.7%)
Adjunct to therapy	2 (3.8%)
Control group type: N (%)	
Waitlist	28 (65.1%)
Treatment as usual	7 (16.3%)
Attention/information control	8 (18.6%)

[a] Age represents 42 of the 43 studies because one study reported age as a range.
[b] One study[74] reported end-of-treatment outcomes ranging from 6 to 14 weeks after baseline assessment, but this study was categorized as 7 to 9 weeks followup for this table.

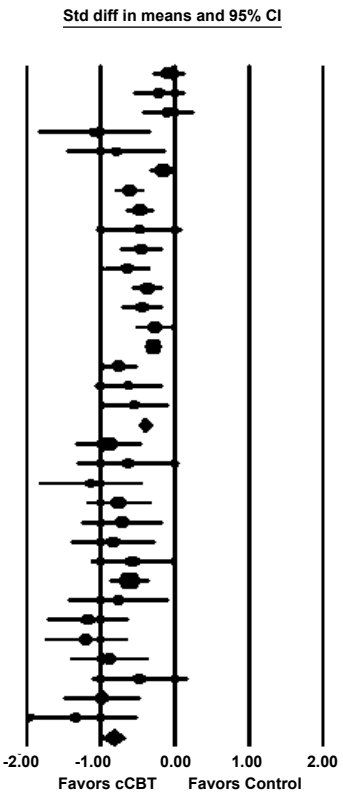
Effects of cCBT Interventions in Patients with Depressive Disorders and Symptom Thresholds

End-of-Treatment Outcomes

Figure 3 shows a forest plot of SMDs for all studies conducted in patients with depression. Of the 43 treatment-versus-control comparisons used in the quantitative meta-analysis, 14 trials (18 comparisons) examining patients with depressive symptoms provided end-of-treatment outcome data. In these comparisons, cCBT was associated with a small to moderate difference in depression severity (SMD -0.40; 95% CI, -0.49 to -0.31) with evidence of heterogeneity in effect sizes (Q=42.38; p=0.001; I^2=60%).

Figure 3. Forest plot of cCBT versus control in patients with major depressive disorder or depressive symptoms

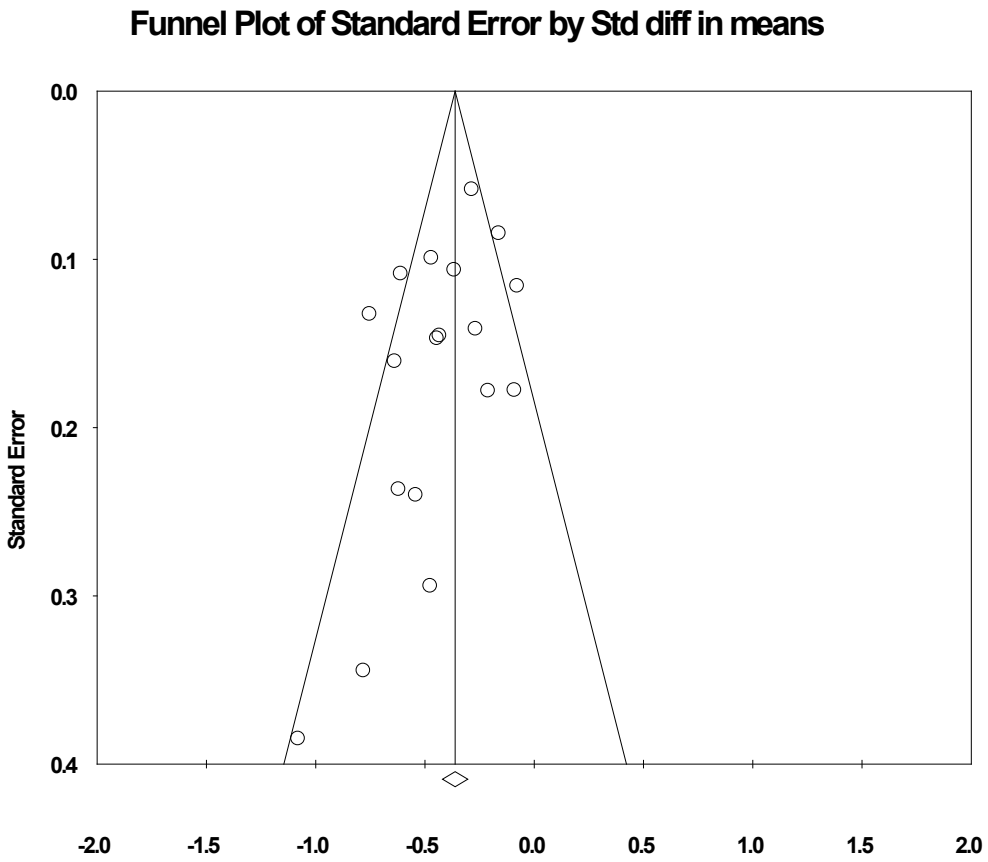
Group by: Disorder	Study name	Comparison	Outcome	Std diff in means	Lower limit	Upper limit	p-Value
Dep Sxs	Clarke 2002	cCBT v Control	Sx Severity	-0.08	-0.30	0.15	0.50
Dep Sxs	de Graaf 2009	cCBT1 v Control	Sx Severity	-0.21	-0.56	0.14	0.24
Dep Sxs	de Graaf 2009	cCBT2 v Control	Sx Severity	-0.09	-0.44	0.26	0.61
Dep Sxs	Farrer 2011	cCBT1 v Control	Sx Severity	-1.08	-1.83	-0.33	0.01
Dep Sxs	Farrer 2011	cCBT2 v Control	Sx Severity	-0.78	-1.46	-0.11	0.02
Dep Sxs	Glozier 2013	cCBT v Control	Sx Severity	-0.16	-0.33	0.00	0.06
Dep Sxs	Griffiths 2012	cCBT1 v Control	Sx Severity	-0.61	-0.82	-0.40	0.00
Dep Sxs	Griffiths 2012	cCBT2 v Control	Sx Severity	-0.47	-0.66	-0.28	0.00
Dep Sxs	Hickie 2010	cCBT v Control	Sx Severity	-0.47	-1.05	0.10	0.11
Dep Sxs	Levine 2011	cCBT v Control	Sx Severity	-0.44	-0.73	-0.16	0.00
Dep Sxs	Lintvedt 2013	cCBT v Control	Sx Severity	-0.64	-0.95	-0.32	0.00
Dep Sxs	McKinnon 2008	cCBT v Control	Sx Severity	-0.37	-0.57	-0.16	0.00
Dep Sxs	Moritz 2012	cCBT v Control	Sx Severity	-0.43	-0.72	-0.15	0.00
Dep Sxs	Spek 2007	cCBT v Control	Sx Severity	-0.27	-0.54	0.01	0.00
Dep Sxs	van Bastelaar 2008	cCBT v Control	Sx Severity	-0.29	-0.40	-0.17	0.00
Dep Sxs	van der Zanden 2012	cCBT v Control	Combined	-0.75	-1.01	-0.49	0.00
Dep Sxs	Warmerdam 2008	cCBT1 v Control	Combined	-0.62	-1.08	-0.16	0.01
Dep Sxs	Warmerdam 2008	cCBT2 v Control	Combined	-0.54	-1.01	-0.07	0.02
Dep Sxs				-0.40	-0.49	-0.31	0.00
MDD	Andersson 2005	cCBT v Control	Combined	-0.88	-1.33	-0.43	0.00
MDD	Berger 2011	cCBT1 v Control	Sx Severity	0.63	-1.31	0.06	0.07
MDD	Berger 2011	cCBT2 v Control	Sx Severity	-1.13	-1.84	-0.41	0.00
MDD	Carlbring 2013	cCBT v Control	Combined	-0.75	-1.20	-0.30	0.00
MDD	Choi 2012	cCBT v Control	Combined	-0.70	-1.25	-0.16	0.01
MDD	Johansson 2012	cCBT1 v Control	Combined	-0.83	-1.40	-0.26	0.00
MDD	Johansson 2012	cCBT2 v Control	Combined	-0.57	-1.13	0.00	0.05
MDD	Kessler 2009	cCBT v Control	Sx Severity	-0.61	-0.89	-0.33	0.00
MDD	Perini 2009	cCBT v Control	Combined	-0.76	-1.44	-0.07	0.03
MDD	Titov 2010	cCBT1 v Control	Combined	-1.17	-1.73	-0.61	0.00
MDD	Titov 2010	cCBT2 v Control	Combined	-1.19	-1.77	-0.62	0.00
MDD	Vernmark 2010	cCBT1 v Control	Combined	-0.88	-1.42	-0.34	0.00
MDD	Vernmark 2010	cCBT2 v Control	Combined	-0.47	-1.12	0.18	0.15
MDD	Williams 2013	cCBT v Control	Combined	-0.98	-1.50	-0.45	0.00
MDD	Wright 2005	cCBT v Control	Combined	-1.33	-2.17	-0.49	0.00
MDD				-0.82	-0.98	-0.67	0.00



Abbreviations: CI=confidence interval; Dep Sxs=depressive symptoms; cCBT=computerized cognitive behavioral therapy; MDD=major depressive disorder; Std diff=standardized difference; Sx=symptom

Of all of the patient groups we analyzed, only the depressive symptom group and MDD group had enough studies (≥10) to conduct an analysis of potential publication bias using funnel plots (Figures 4 and 5). Visual inspection of the depressive symptoms funnel plot suggests possible publication bias, though testing was not statistically significant (Kendall's *Tau*=-0.24; *p*=0.16). Adjustment for publication bias using Duval and Tweedie's trim and fill method resulted in a small but still statistically significant difference for the cCBT intervention (SMD -0.33; 95% CI, -0.44 to -0.22).

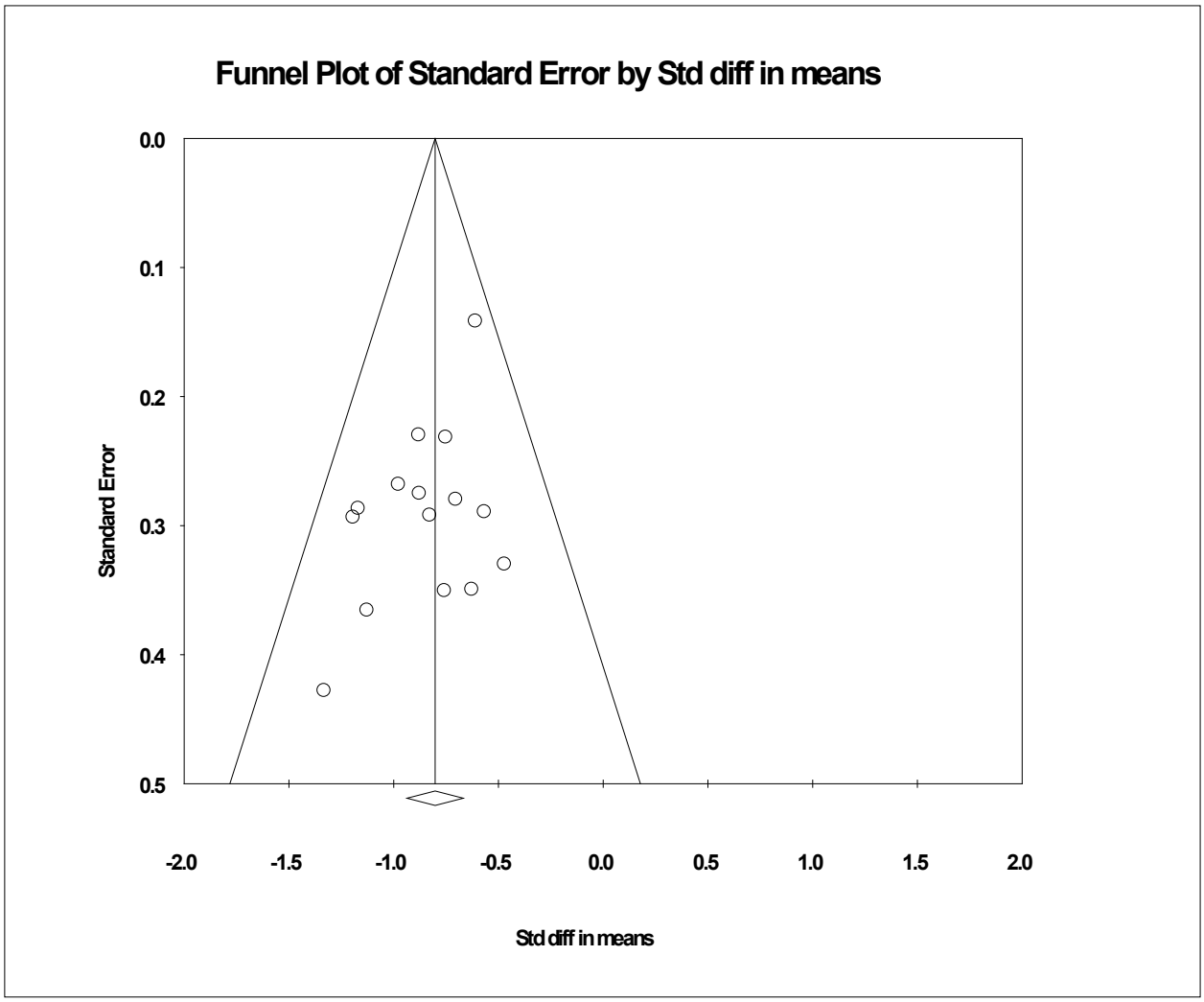
Figure 4. Funnel plot of studies conducted in patients with depressive symptoms



Abbreviations: Std diff=standardized difference

Visual inspection of the MDD funnel plot was not suggestive of publication bias, and the statistical test was not significant (Kendall's *Tau*=-0.36; *p*=0.15).

Figure 5. Funnel plot of studies conducted in patients with major depressive disorder



Abbreviations: Std diff=standardized difference

Eleven trials (15 comparisons) examining patients with major depressive disorder provided end-of-treatment outcome data. In these comparisons, cCBT was associated with a large difference in depressive symptoms compared with control groups (SMD -0.82; 95% CI, -0.98 to -0.67). There was no evidence of heterogeneity between comparisons (Q=10.33; p =.74; I^2=0%). Treatment effects differed significantly between comparisons enrolling patients based on symptom thresholds and those confirming major depressive disorder with a diagnostic interview (Q=20.84, p<.001).

Subgroup Analyses

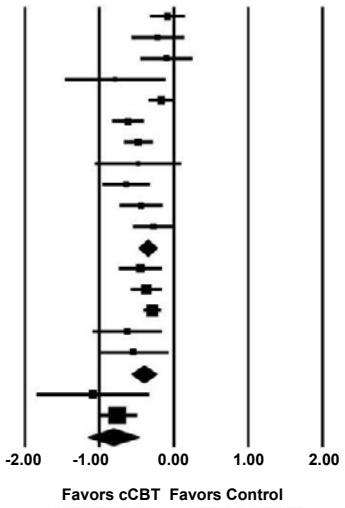
To examine treatment heterogeneity, we conducted mixed-treatment effects subgroup analyses for two prespecified factors: (1) level of cCBT support and (2) type of control group.

Level of cCBT Support

To examine potential influences of different levels of human support for cCBT interventions, we classified interventions into the four categories (defined in Methods) based on the level of cCBT support involved. Because treatment effects varied significantly between comparisons where participants exceeded depressive symptom thresholds and comparisons where participants were diagnosed with major depressive disorder, the influence of level of support was analyzed separately by type of sample. Figure 6 shows a forest plot of SMDs for all trials conducted in patients with depressive symptoms by level of support. A mixed-treatment effects subgroup analysis with participants enrolled on the basis of self-reported depressive symptom thresholds suggested that more intensive support resulted in stronger effects ($Q\ (2)$=6.35, p=.042). Two studies with two comparisons examining patients with depressive symptoms found that the cCBT-LS interventions reported large differences compared with control. Of these, one included weekly 10-minute phone calls with a counselor (SMD -1.08; 95% CI, -1.83 to -0.33).[44] Another used live chat rooms for facilitators to present material and respond to participant questions (SMD -0.75; 95% CI, -1.01 to -0.49).[42] Approximately 25 percent of the variability in treatment effect was explained by the category of cCBT support.

Figure 6. Forest plot of cCBT versus control in patients with depression symptoms by level of support

Group by: cCBT Type	Study name	Comparison	Outcome	Std diff in means	Lower limit	Upper limit	p-Value
cCBT-NS	Clarke 2002	cCBT v Contro1	SxSeverity	-0.08	-0.30	0.15	0.50
cCBT-NS	deGraaf 2009	cCBTl v Contro1	SxSeverity	-0.21	-0.56	0.14	0.24
cCBT-NS	deGraaf 2009	cCBT2 v Contro1	SxSeverity	-0.09	-0.44	0.26	0.61
cCBT-NS	Farrer 2011	cCBT v Contro1	SxSeverity	-0.78	-1.46	-0.11	0.02
cCBT-NS	Glozier 2013	cCBT v Contro1	SxSeverity	-0.16	-0.33	0.00	0.06
cCBT-NS	Griffiths2012	cCBTl v Contro1	SxSeverlty	-0.61	-0.82	-0.40	0.00
cCBT-NS	Griffiths2012	cCBT2 v Contro1	SxSeverity	-0.47	-0.66	-0.28	0.00
cCBT-NS	Hickie 2010	cCBT v Contro1	SxSeverlty	-0.47	-1.05	0.10	0.11
cCBT-NS	Lintvedt 2013	cCBT v Contro1	SxSeverity	-0.64	-0.95	-0.32	0.00
cCBT-NS	Moritz 2012	cCBT v Contro1	SxSeverity	-0.43	-0.72	-0.15	0.00
cCBT-NS	Spek 2007	cCBT v Contro1	SxSeverity	-0.27	-0.54	0.01	0.06
cCBT-NS				-0.35	-0.47	-0.23	0.00
cCBT-S	Levin 2011	cCBT v Contro1	SxSeverity	-0.44	-0.73	-0.16	0.00
cCBT-S	McKinnon 2008	cCBT v Contro1	SxSeverity	-0.37	-0.57	-0.16	0.00
cCBT-S	vanBaslelaar 2008	cCBT v Contro1	SxSeverity	-0.29	-0.40	-0.17	0.00
cCBT-S	Warmerdam 2008	cCBTl v Contro1	Combined	-0.62	-1.08	-0.16	0.01
cCBT-S	Warmerdam 2008	cCBT2 v Contro1	Combined	-0.54	-1.01	-0.07	0.02
cCBT-S				-0.40	-0.57	-0.22	0.00
cCBT-LS	Farrer 2011	cCBT v Control	SxSeverlty	-1.08	-1.83	-0.33	0.01
cCBT-LS	vanderZanden 2012	cCBT v Controt	Combined	-0.75	-1.01	-0.49	0.00
cCBT-LS				-0.81	-1.15	-0.47	0.00

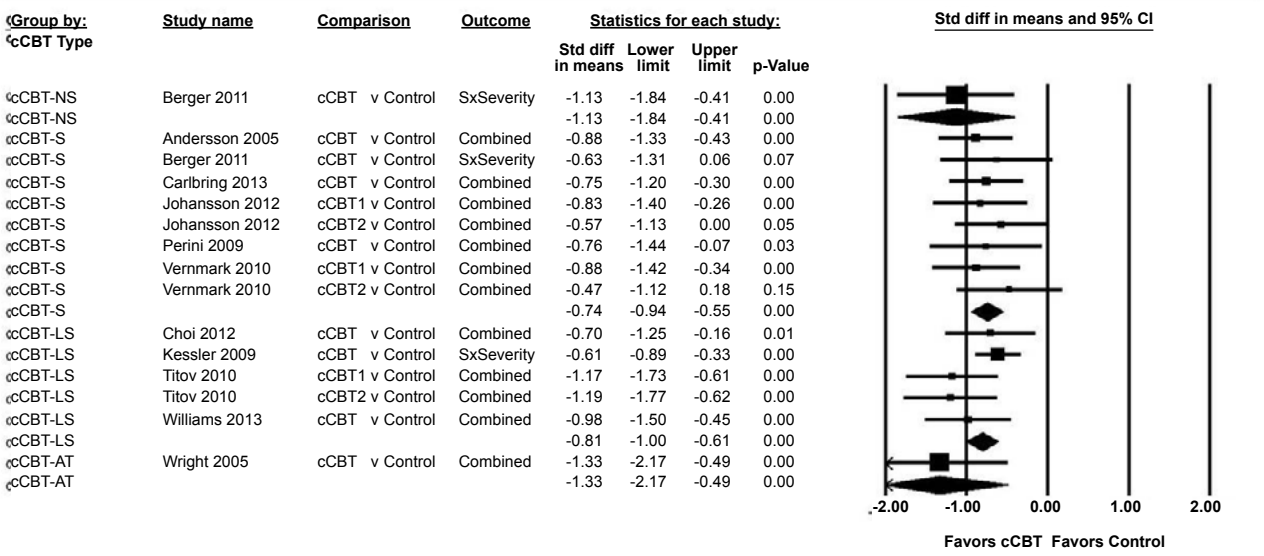


Abbreviations: CI=confidence interval; cCBT=computerized cognitive behavioral therapy; NS=no support; S=support; LS=live support; Sx=symptoms

Figure 7 shows a forest plot of SMDs for all studies involving participants with major depressive disorder. Though all types of comparisons reported relatively large effect sizes, the influence of level of support among participants with diagnosed major depressive disorder was not clear.

A mixed-treatment effects subgroup analysis did not provide evidence of differences among this group of comparisons based on level of support (*Q (3)*=2.67, *p*=0.45). However, there were limited numbers of comparisons in each category of support, and treatment effects were consistently large, so there was limited power to find any effect of level of support.

Figure 7. Forest plot of cCBT versus control in patients with major depressive disorder by level of support



Abbreviations: CI=confidence interval; cCBT=computerized cognitive behavioral therapy; NS=no support; S=support; LS=live support; Sx=symptoms; AT=adjunct to therapy

Type of Control Group

To examine potential influences of the type of control group selected for comparison with the cCBT group, we classified control groups into three categories (defined in Methods): waitlist, treatment as usual, and attention/information. As before, we analyzed trials of depressive symptoms separately from trials of major depressive disorder. In patients with depressive symptoms, five trials (seven comparisons) used a treatment-as-usual control, six trials (seven comparisons) used waitlist, and three trials (four comparisons) used an attention/information control. Treatment effects varied across a narrow range (SMD -0.32 to -0.48) and did not differ significantly by the type of control (*p*=0.50).

Analyses of the influence of type of control group were inconclusive for major depressive disorder comparisons because all but four employed waitlist control groups, and effects were consistently large in the included trials. A mixed-treatment effects subgroup analysis showed no statistically significant difference by control group type (*Q (2)*=2.83, *p*=.24).[64]

Health-Related Quality-of-Life Outcomes

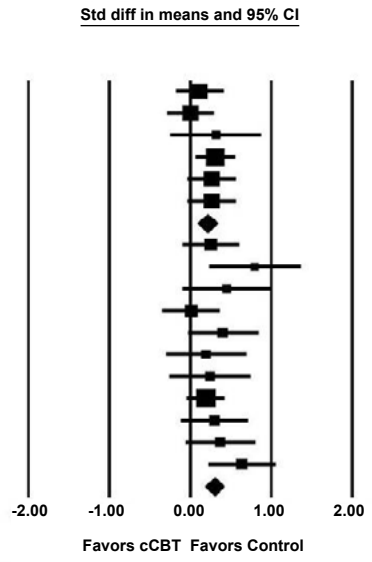
Twelve trials (17 comparisons) examining patients with depressive symptoms or major depressive disorder provided end-of-treatment data for HRQOL outcomes (Figure 8). Four trials (6 comparisons) were in patients with depressive symptoms, and 8 trials (11 comparisons) were in patients with diagnosed major depressive disorder. Trials of patients with depressive symptoms

found a small difference (SMD 0.26; 95% CI, 0.11 to 0.41) in favor of increased HRQOL in the cCBT group without significant heterogeneity in treatment effect (*Q (5)*=3.41, *p*=.64). Trials of patients with major depressive disorder also found a relatively small difference (SMD 0.37; 95% CI, 0.23 to 0.52) with heterogeneity analyses that were not statistically significant (*Q (10)*=9.98, *p*=.44). A mixed-treatment effects subgroup analysis found no statistically significant difference between the depressive symptom and major depressive disorder samples (*Q (1)*=1.04, *p*=.31).

We used a mixed-treatment effects subgroup analysis across all 17 comparisons in patients with depression to examine the influence of the level of support. In the four studies with five cCBT-NS interventions, cCBT resulted in a small difference in HRQOL compared with control groups (SMD 0.25; 95% CI, 0.07 to 0.43). Six trials (nine comparisons) of cCBT-S interventions found a small to moderate difference (SMD 0.33; 95% CI, 0.18 to 0.49) in HRQOL. In three trials with three cCBT-LS interventions, cCBT resulted in a small to moderate difference in HRQOL compared with control groups (SMD 0.40; 95% CI, 0.17 to 0.63). A mixed-treatment effects subgroup analysis did not find a significant difference in HRQOL by level of support (*Q (2)*=1.10, *p*=.58). Overall, the effects of cCBT on HRQOL in trials of depression were statistically significant but relatively small.

Figure 8. Forest plot of cCBT versus control in patients with major depressive disorder or depressive symptoms for HRQOL outcomes

Group By Disorder	Study name	Comparison	Outcome	Statistics for each study: Std diff In means	Lower limit	Upper limit	p-Value
Dep Sxs	de Graaf 2009	cCBT1 v Control	Combined	0.15	-0.21	0.51	0.41
Dep Sxs	de Graaf 2009	cCBT2 v Control	Combined	0.01	-0.35	0.37	0.97
Dep Sxs	Glozier 2013	cCBT v Control	HRQoL	0.40	-0.30	1.10	0.26
Dep Sxs	Moritz 2012	cCBT v Control	HRQoL	0.39	0.09	0.70	0.01
Dep Sxs	Warmerdam 2008	cCBT1 v Control	HRQoL	0.33	-0.03	0.70	0.07
Dep Sxs	Warmerdam 2008	cCBT2 v Control	HRQoL	0.33	-0.03	0.70	0.07
Dep Sxs				0.26	0.11	0.41	0.00
MDD	Andersson 2005	cCBT v Control	HRQoL	0.32	-0.11	0.76	0.14
MDD	Berger 2011	cCBT1 v Control	HRQoL	1.00	0.30	1.71	0.01
MDD	Berger 2011	cCBT2 v Control	HRQoL	0.57	-0.11	1.25	0.10
MDD	Carlbring 2013	cCBT v Control	HRQoL	0.02	-0.42	0.46	0.94
MDD	Choi 2012	cCBT v Control	HRQoL	0.51	-0.03	1.05	0.06
MDD	Johansson 2012	cCBT1 v Control	HRQoL	0.25	-0.36	0.86	0.42
MDD	Johansson 2012	cCBT2 v Control	HRQoL	0.31	-0.31	0.92	0.33
MDD	Kessler 2009	cCBT v Control	Combined	0.24	-0.04	0.53	0.10
MDD	Vernmark 2010	cCBT1 v Control	HRQoL	0.38	-0.14	0.90	0.15
MDD	Vernmark 2010	cCBT2 v Control	HRQoL	0.47	-0.06	1.00	0.08
MDD	Williams 2013	cCBT v Control	HRQoL	0.80	0.29	1.32	0.00
MDD				0.37	0.23	0.52	0.00



Abbreviations: cCBT=computerized cognitive behavioral therapy; CI=confidence interval; Dep Sxs=depressive symptoms; HRQoL=health-related quality of life; MDD=major depressive disorder

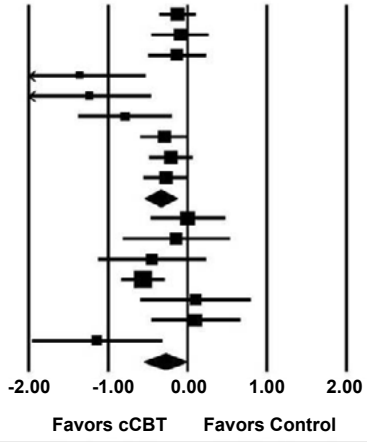
Long-Term Followup

Figure 9 shows a forest plot of SMDs for all trials conducted in patients with depressive symptoms or major depressive disorder that reported symptom severity at least 6 months after randomization. Twelve trials (16 comparisons) examining patients with depressive symptoms or disorders provided followup data at least 6 months after the baseline assessment. In the seven trials (nine comparisons) involving participants with depressive symptoms, cCBT was associated with a small difference (SMD -0.33; 95% CI, -0.53 to -0.13).

In the five trials (seven comparisons) of participants with major depressive disorder, cCBT was associated with a similarly small difference (SMD -0.28; 95% CI, -0.55 to -0.01). A mixed-treatment effects subgroup analysis found no significant difference between depressive symptom and major depressive disorder samples (*Q (1)*=0.57, *p*=.45). Compared with the effect sizes for end-of-treatment outcomes, longer term followup data from trials of major depressive disorder suggested diminishing effects at followup. Due to the relatively small number of comparisons with 6-month followup data for both treatment and control groups, subgroup analyses examining level of support and type of control group are not included in this report. Overall, for the trials providing followup data on patients with depressive symptoms or major depressive disorder, the differences in outcomes for the cCBT groups compared with the control groups were small.

Figure 9. Forest plot of cCBT versus control in patients with major depressive disorder or depressive symptoms for most distal assessment of depression

Group By Disorder	Study name	Comparison	Outcome	Timepoint	Statistics for each study			
					Std diff In means	Lower limit	Upper limit	p-Value
Dep Sxs	Clarke 2002	cCBT v Control	Sx Severity	8 months	-0.13	-0.35	0.10	0.28
Dep Sxs	de Graaf 2009	cCBT1 v Control	Sx Severity	12 months	-0.09	-0.45	0.27	0.62
Dep Sxs	de Graaf 2009	cCBT2 v Control	Sx Severity	12 months	-0.13	-0.48	0.23	0.49
Dep Sxs	Farrer 2011	cCBT1 v Control	Sx Severity	6 months	-1.36	-2.18	-0.53	0.00
Dep Sxs	Farrer 2011	cCBT2 v Control	Sx Severity	6 months	-1.23	-2.01	-0.46	0.00
Dep Sxs	Hickie 2010	cCBT v Control	Sx Severity	6 months	-0.79	-1.37	-0.20	0.01
Dep Sxs	Levin 2011	cCBT v Control	Sx Severity	6 months	-0.29	-0.59	0.20	0.06
Dep Sxs	McKinnon 2008	cCBT v Control	Sx Severity	12 months	-0.20	-0.47	0.06	0.14
Dep Sxs	Spek 2007	cCBT v Control	Sx Severity	12 months	-0.27	-0.54	0.01	0.06
Dep Sxs					-0.33	-0.53	-0.13	0.00
MDD	Andersson 2005	cCBT v Control	Combined	6 months	0.01	-0.46	0.47	0.98
MDD	Berger 2011	cCBT1 v Control	sx Severity	6 months	-0.14	-0.81	0.53	0.68
MDD	Berger 2011	cCBT2 v Control	sx Severity	6 months	-0.44	-1.12	0.23	0.20
MDD	Kessler 2009	cCBT v Control	sx Severity	8 months	-0.56	-0.83	-0.28	0.00
MDD	Vermark 2010	cCBT2 v Control	Combined	6 months	0.11	-0.59	0.80	0.77
MDD	Vermark 2010	cCBT1 v Control	Combined	6 months	0.11	-0.45	0.67	0.70
MDD	Wright 2005	cCBT v Control	Combined	6 months	-1.14	-1.95	-0.32	0.01
MDD					-0.28	-0.55	-0.01	0.04



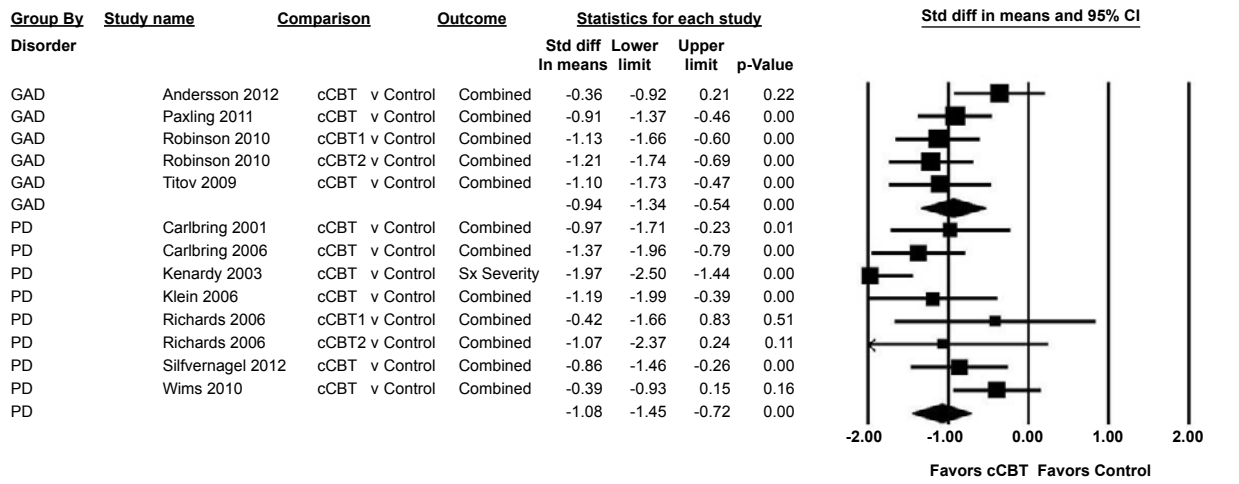
Abbreviations: cCBT=computerized cognitive behavioral therapy; CI=confidence interval; Dep Sxs=depressive symptoms; MDD=major depressive disorder; Sx=symptom

Effects of cCBT Interventions in Patients With Anxiety Disorders

End-of-Treatment Outcomes

Seventeen trials (19 comparisons) examining patients with anxiety symptoms or disorders provided end-of-treatment outcome data. Only trials of generalized anxiety disorder and panic disorder had enough comparisons to calculate a valid summary SMD. Figure 10 shows a forest plot of SMDs for all comparisons in participants with generalized anxiety disorder or panic disorder. Four trials (five comparisons) in patients with generalized anxiety disorder found that cCBT was associated with a large difference compared with control groups (SMD -0.94; 95% CI, -1.34 to -0.54). Significance testing provided no strong evidence of heterogeneity (*Q (4)*=5.867, *p*=.209; I^2 = 32%). Seven trials (eight comparisons) examining patients with panic disorder found that cCBT was also associated with a large difference compared with control groups (SMD -1.08; 95% CI, -1.45 to -0.72). However, there was evidence of heterogeneity between studies (*Q (7)*=19.80, *p*<.01; I^2=64%).

Figure 10. Forest plot of cCBT versus control in patients with generalized anxiety disorder and panic disorder



Abbreviations: cCBT=computerized cognitive behavioral therapy; CI=confidence interval; GAD=generalized anxiety disorder; PD=panic disorder; Sx=symptom

Anxiety Symptoms

Two trials (two comparisons) examining patients with significant anxiety symptoms provided end-of-treatment outcome data. One found that cCBT was associated with a small difference (SMD -0.28; 95% CI, -0.74 to 0.18) that was not statistically significant.[76] Similarly, the other trial of participants meeting panic symptom thresholds found that cCBT was associated with a small to moderate difference (SMD -0.42; 95% CI, -0.94 to 0.10), which was not statistically significant.[77]

Depression, Anxiety, or Mixed Anxiety/Depression

Two trials (two comparisons) examining effects of cCBT in participants with a mixed group of disorders found that differences in favor of cCBT were similar. One study yielded a difference of -0.50 (95% CI, -0.91 to -0.08),[70] while the other found a difference of -0.50 (95% CI, -0.79 to -0.21).[68]

Posttraumatic Stress Disorder

Two trials (two comparisons) assessing PTSD both trended in the direction of symptom reduction in the cCBT group, but neither was statistically significant. The differences in these two studies were -0.42 (95% CI, -1.13 to 0.29)[61] and -0.46 (95% CI, -1.09 to 0.17).[47]

Subgroup Analyses

To examine treatment heterogeneity, we conducted mixed-treatment effects subgroup analyses for two prespecified factors: (1) level of cCBT support and (2) type of control group.

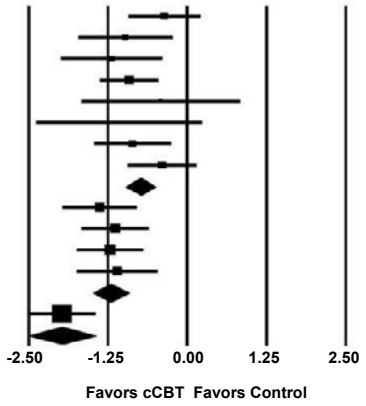
Level of cCBT Support

Because of the insufficient number of trials conducted in patients with other disorders, our additional analyses of level of cCBT support focused on trials in those with generalized

anxiety disorder or panic disorder. Figure 11 shows a forest plot of SMDs for all comparisons in participants with generalized anxiety disorder or panic disorder. Analyses of the influence of level of support on effect sizes examined 13 comparisons among 10 trials and found an association (*Q (2)*=14.70, *p*=.001), explaining 25 percent of the observed variability in treatment effect. However, this analysis was limited by the absence of studies in the cCBT-NS category and only one study in the cCBT-AT category. Seven trials (eight comparisons) of cCBT-S interventions compared with control resulted in a large difference in favor of cCBT (SMD -0.73; 95% CI, -0.96 to -0.50). Unfortunately, it is difficult to evaluate the cCBT-LS interventions because of an insufficient number of trials using more intensive support to treat generalized anxiety disorder or panic disorder.

Figure 11. Forest plot of cCBT versus control in patients with generalized anxiety disorder and panic disorder by level of support

Group By Disorder	Study name	Comparison	Outcome	Std diff In means	Lower limit	Upper limit	p-Value
cCBT-S	Andersson 2012	cCBT v Control	Combined	-0.36	-0.92	0.21	0.22
cCBT-S	Carlbring 2001	cCBT v Control	Combined	-0.97	-1.71	-0.23	0.01
cCBT-S	Klein 2006	cCBT v Control	Combined	-1.19	-1.99	-0.39	0.00
cCBT-S	Paxling 2011	cCBT v Control	Combined	-0.91	-1.37	-0.46	0.00
cCBT-S	Richards 2006	cCBT1 v Control	Combined	-0.42	-1.66	0.83	0.51
cCBT-S	RIchards 2006	cCBT2 v Control	Combined	-1.07	-2.37	0.24	0.11
cCBT-S	Silfvernagel 2012	cCBT v Control	Combined	-0.86	-1.46	-0.26	0.00
cCBT-S	Wims 2010	cCBT v Control	Combined	-0.39	-0.93	0.15	0.16
cCBT-S				-0.73	-0.96	-0.50	0.00
cCBT-LS	Carlbring 2006	CCBT v Control	Combined	-1.37	-1.96	-0.79	0.00
cCBT-LS	Robinson 2010	cCBT1 v Control	Combined	-1.13	-1.66	-0.60	0.00
cCBT-LS	Robinson 2010	cCBT2 v Control	Combined	-1.21	-1.74	-0.69	0.00
cCBT-LS	Titov 2009	cCBT v Control	Combiried	-1.10	-1.73	-0.47	0.00
eCBT-LS				-1.20	-1.48	-0.92	0.00
cCBT-AT	Kenardy 2003	cCBT v Control	SxSeverlty	-1.97	-2.50	-1.44	0.00
cCBT-AT				-1.97	-2.50	-1.44	0.00



Abbreviations: CI=confidence interval; cCBT=computerized cognitive behavioral therapy; S=support; LS=live support; Sx=symptoms; AT=adjunct to therapy

Type of Control Group

Examination of potential influences of the type of control group on effect sizes in trials of generalized anxiety disorder or panic disorder included the same 13 comparisons across 10 trials used to evaluate the level of support. Nine trials (10 comparisons) compared cCBT interventions with waitlist control, and 2 trials (3 comparisons) compared cCBT with an attention/information control group. No studies used treatment as usual for the control group. A mixed-treatment effects subgroup analysis showed no evidence of differences in treatment effect by type of control group (*Q (1)*=0.003, *p*=.87).

Health-Related Quality-of-Life Outcomes

HRQOL data were available for three trials (three comparisons) of generalized anxiety disorder and five trials (seven comparisons) of panic disorder. The comparisons involving generalized anxiety disorder showed a moderate difference indicating a better effect in cCBT groups compared with control groups (SMD 0.57; 95% CI, 0.27 to 0.87). A similar moderate difference was observed in the panic disorder comparisons (SMD 0.49; 95% CI, 0.23 to 0.75).

There were also some data for other patient groups. Two comparisons for samples with mixed anxiety and depressive symptoms resulted in a small to moderate difference on HRQOL outcomes (SMD 0.30, 95% CI, -0.10 to 0.69[70] and SMD 0.42, 95% CI, 0.15 to 0.69[68]). One comparison reporting HRQOL in PTSD found an SMD of 0.60 (95% CI, -0.04 to 1.23).[47] For generalized anxiety disorder and panic disorder, end-of-treatment data suggest a moderate level of improvement in HRQOL.

Long-Term Followup

Due to the lack of trials reporting at least 2 months of followup data for cCBT interventions for anxiety disorders, no summary mean differences are available. Effect sizes were generally small to moderate. Our review found one comparison in a trial enrolling patients on the basis of baseline anxiety symptoms (SMD -0.21; 95% CI, -0.82 to 0.40),[69] two comparisons of generalized anxiety disorder (SMD -0.48; 95% CI, -1.09 to 0.14[40] and SMD -0.14; 95% CI, -0.69 to 0.41[46]), two comparisons of mixed anxiety and depressive symptoms (SMD -0.43; 95% CI, -0.87 to 0.01[70] and SMD -0.40; 95% CI, -0.69 to -0.10[68]), and one comparison from a PTSD sample (SMD -0.94, 95% CI, -1.92 to 0.04).[61] We did not conduct additional analyses of potential influences of level of support or type of control group.

Treatment Adherence for All Clinical Disorders

Treatment adherence was reported as the percentage of patients completing all planned sessions or as the mean number of sessions completed. These data were reported in 27 of the 43 trials included in KQ 1 (33 comparisons). Patients completing the intervention was reported in 24 trials (30 comparisons), shown in Table 6. The mean number of sessions completed was reported in 16 trials (20 comparisons), shown in Table 7. Sessions completed was relatively consistent (median 65%, range 25-93%). Studies reporting completion rates found substantial variability in the proportion of participants completing the treatment (median 49.5%; range 11% to 100%). While treatment completion was quite high in several interventions, it was quite low in several interventions. Low adherence may account for diminished treatment effects in some studies.

Table 6. Treatment adherence: percentage of patients completing all sessions by condition

Condition	cCBT level	Patients completing intervention	Patients starting intervention	Percentage completing
Depressive symptoms				
de Graaf, 2009	NS	12	95	13%
de Graaf, 2009	NS	36	95	38%
Farrer, 2011	NS	6	38	16%
Farrer, 2011	LS	7	41	17%
Griffiths, 2012	NS	32	73	44%
Griffiths, 2012	NS	48	74	65%
Lintvedt, 2013	NS	42	81	52%
Moritz, 2013	NS	82	105	78%
Spek, 2007	NS	49	102	47%
van Bastelaar, 2008	S	53	125	42%
van der Zanden, 2012	LS	24	121	20%
Warmerdam, 2008	S	33	88	38%
Warmerdam, 2008	S	34	88	39%
Major depressive disorder				
Andersson, 2005	S	24	57	42%
Berger, 2011	NS	9	25	36%
Berger, 2011	S	14	25	56%
Carlbring, 2013	S	11	40	28%
Choi, 2012	LS	17	25	68%
Perini, 2009	S	20	27	74%
Titov, 2010	LS	32	46	70%
Titov, 2010	LS	33	41	80%
Williams, 2013	LS	19	25	76%
Wright, 2005	AT	13	13	100%
Generalized anxiety disorder				
Paxling, 2011	S	4	38	11%
Titov, 2009	LS	18	24	75%
Panic disorder				
Carlbring, 2006	LS	24	30	80%
Klein, 2006	S	18	19	95%
Silfvernagel, 2012	S	7	29	24%
Wims, 2010	S	23	29	79%
Mixed				
Newby, 2013	LS	41	46	89%

Abbreviations: AT=adjunct to therapy; cCBT=computerized cognitive behavioral therapy; LS=live support; NS=no support

Table 7. Treatment adherence: mean and percentage of sessions completed by condition

Condition	cCBT level	Mean sessions completed	Sessions planned	Percentage sessions completed
Depression symptoms				
Farrer, 2011	NS	1.5	6	25%
Farrer, 2011	LS	2	6	33%
Griffiths, 2012	NS	8	12	66%
Griffiths, 2012	NS	10	12	83%
Lintvedt, 2013	NS	3.1	5	62%
Moritz, 2013	NS	6.3	10	63%
van der Zanden, 2012	LS	3.2	6	53%
Major depressive disorder				
Andersson, 2005	S	3.7	10	37%
Berger, 2011	NS	6.8	10	68%
Berger, 2011	S	8.5	10	85%
Carlbring, 2013	S	5.1	7	73%
Choi, 2012	LS	5.56	6	93%
Johansson, 2012	S (s)	6.5	8	81%
Johansson, 2012	S (t)	7.5	9.7	77%
Generalized anxiety disorder				
Andersson, 2012	S	5.1	8	64%
Paxling, 2011	S	4.8	8	60%
Panic disorder				
Carlbring, 2006	LS	8.9	10	89%
Silfvernagel, 2012	S	5	8	63%
Anxiety symptoms				
Kenardy, 2006	NS	3.3	6	55%
Mixed				
Newby, 2013	LS	5.6	6	93%

Abbreviations: AT=adjunct to therapy; cCBT=computerized cognitive behavioral therapy; LS=live support; NS=no support; (s)=standard; S=support; (t)=tailored

To explore the influence of psychiatric condition on adherence, we further examined treatment completion by condition type. While these data were only available in 24 trials, some basic differences were observed, resulting in a statistically significant difference across condition ($Q(4) = 45.86$, $p<.01$). In 13 comparisons of participants with depressive symptoms, the median completion rate was 39% (range 13% to 78%). In nine comparisons of participants with major depressive disorder, the median completion rate was 68% (range 28% to 100%). In the four studies reporting panic disorder, completion rates had a median of 79.5% (range 24% to 95%). In two studies reporting generalized anxiety disorder, the completion rates were 11 percent and 75 percent. Finally, in one study of mixed disorders, the completion rate was 89 percent. Generally, completion was lower for the depressive symptoms group, which did not receive diagnostic assessment.

KEY QUESTION 2. For cCBT interventions, what level, type, and modality of user support is provided (e.g., daily telephone calls, weekly email correspondence); who provides this support (e.g., therapist, graduate student, peer); what is the clinical context (primary intervention, adjunct); and how is this support related to patient outcomes?

Key Points

- Of the 57 cCBT intervention arms examined, 15 (26.3%) were classified as not supported, 26 (45.6%) were supported, 14 (24.6%) were supported with live features, and 2 (3.5%) were used as adjuncts to therapy.
- All but three trials allowed patients to access the program from a nonclinical location (e.g., home, library, or community facility), and an advertisement on the internet was the most common means of recruitment (53%).
- Most trials used email in some form (74%), while phone support by clinical staff (35%) and peer support via discussion board or chat room (25%) were used less often. Instant messaging was used in one study.
- The intervention components of studies classified as supported and supported with live features were highly variable, making firm conclusions difficult to draw.
- Exploratory subgroup analysis, using indirect comparisons, showed an association between higher levels of support and greater treatment effects. Two small studies directly compared different levels of therapist support and did not find a differential treatment effect.

Overview of cCBT Programs

Overall, cCBT interventions lasted from 5 to 16 weeks and were designed around a median of 7 treatment modules. Over half (53%) of the interventions were 8 to 9 weeks in duration. Eighty-five percent of interventions contained 6 to 10 treatment modules. Thirty-one trials used preexisting cCBT programs.[42-45,48,49,51-53,56-62,65,68,70-73,75,77,78,80-85] The other 16 trials developed their own programs or did not name a preexisting program.[39-41,46,47,50,54,55,63,64,66,67,69,74,76,79]

The available programs used for each disorder were different. For major depressive disorder, the Sadness Program was used four times and Deprexis® was used once. For depressive symptoms, MoodGYM was used four times; Color Your Life, E-couch, and adaptations of Coping with Depression were each used twice. Overcoming Depression over the Internet, Master Your Mood, and the Wellness Workshop CD were each used once. The Worry Program was used in three of the four trials of generalized anxiety disorder. Panic Online was used three times, and the Panic Program was used once in trials for panic disorder. DE-STRESS was used in one of the two trials on PTSD. Interapy® was used in one of the two trials on anxiety symptoms. Beating the Blues® and a combination of Worry and Sadness programs were used in the three trials examining mixed depression and anxiety. In the trials we examined, authors tended to develop their own programs when addressing a full diagnosis. In interventions targeting major depressive disorder, six trials (55%) used preexisting computerized therapy programs,[43,45,52,57,80,81] while the other five

devised their own programs.[39,54,55,64,67] However, for depressive symptoms, most trials (80%) used preexisting computerized therapy programs.[42,44,48,49,56,58,60,62,71,72,78,82-84]

Table D-2 in Appendix D describes the particular components delivered in the cCBT programs, which included psychoeducation, cognitive restructuring, behavioral activation, breathing retraining, progressive muscle relaxation, interoceptive and situational-graded exposure, and relapse prevention. In many cases, the components of the intervention were not well described, especially the presence or absence of psychoeducation, which was a part of most of the cCBT programs. All of the cCBT interventions featured cognitive restructuring and used homework in some form, but the type of homework and how well it was completed was often not addressed. For depressive disorders, the other components most commonly found were behavioral activation and modification of lifestyle factors. For panic disorder, PTSD, and anxiety symptoms, the other major components were exposure, relaxation, and relapse prevention. For generalized anxiety disorder, interpersonal skills and lifestyle factors were emphasized.

Study Characteristics

For KQ 2, all 47 included trials used at least one category of cCBT intervention (defined in Methods). Ten trials[39,44,45,52-54,56,58,72,75] contained more than one cCBT study arm, usually differing in degree of support, for a total of 57 cCBT arms across the 47 trials. Table 8 summarizes the intervention characteristics, and Tables D-3 and D-4 in Appendix D provide detailed descriptions of the interventions and types of support for each of the 57 arms, organized by target condition.

Table 8. Intervention characteristics of cCBT programs

Intervention characteristics (57 arms unless otherwise noted)	Number of arms
Category for degree of clinical support:	
No support	15
Support	26
Live support	14
Adjunct to therapy	2
Technical support to navigate program provided:	
Yes	17
No/not reported	40
Number of treatment modules: median (range)	7 (5 to 12)
Duration of intervention in weeks: median (range)	8 (5 to 16)
Setting where cCBT was delivered:	
Nonclinical (e.g., home, work, library, other community setting)	54
Clinical (i.e., at the therapist's or general practitioner's office or clinic)	3
Therapist training (n=42 arms):[a]	
Licensed professional	13
Supervised trainee	14
Study used both licensed professionals and trainees	5
"Other" staff	7
Not reported	3
Therapist time spent on intervention communications (n=42 arms):[a]	
Estimate of minutes per patient per week: median (range)[b]	13.5(<10 to 90)
Not reported	7 arms
Highly variable	4 arms

Mode of communication with therapist (n=42 arms):[a]	
Email, text, or instant messaging	
Reminder to complete modules only	33
Not reported	11
Other	11
Telephone conversation	2
Only called if needed (e.g., did not respond to email)	12
No/not reported	8
Peer component (online discussion forum or chat room:[c]	37
Yes	
No/not reported	14
	43

[a] These characteristics apply only to 42 of the 57 intervention arms since they are not applicable to arms categorized as "no support."
[b] The maximum of the range represents one study[42] that used a 90-minute chat room as a vehicle for group therapy for five patients at a time.
[c] These characteristics are for all 57 arms since one of the "no support" arms used an online support group that was moderated only for observation of the group rules.

Setting and Clinical Context of cCBT Interventions

The most common means of patient recruitment was over the internet, usually via a website on mental health disorders (25 studies, 53%). Fifteen of these trials also used more traditional means of advertisement (newspapers, newsletters, mailings). Over 50 percent of trials that sought patients with major depressive disorder, generalized anxiety disorder, or panic disorder used the internet as the primary means of recruitment. One of the web-only trials[61] was a Department of Defense website seeking PTSD cases from the 9/11 attack on the Pentagon.

Nine trials recruited patients from clinics.[49,50,55,67-71,78] These included one[71] that recruited patients from the membership rolls of a health maintenance organization, both of the cCBT-AT trials,[67,69] and the two trials that located the program in the general practitioner's office.[68,70] Otherwise, there was no pattern based on the degree of support provided or the diagnosis sought.

Eleven of the remaining 13 trials recruited via newspaper advertisements, mailings, or waitlists from previous studies. One trial[44] invited callers to a 24-hour counseling line to participate. One trial examining the effect of cCBT on anxiety symptoms[76] recruited students from college psychology classes. A majority of trials (70%) allowed concurrent, stable doses of psychotropic medications; 13 percent excluded patients taking psychotropic medication while 17 percent did not report how medication was handled.

All but three trials allowed patients to access the program from a nonclinical location (e.g., home, a library, or other community facility). Two trials that addressed depression, anxiety, or mixed depression and anxiety[68,70] located the cCBT program in the general practitioner's office, and one cCBT-AT intervention[67] located the program in the therapist's office.

Modalities of cCBT Communication

We classified 13 trials (15 arms) as unsupported (cCBT-NS).[44,45,56,62,68,70-72,76,78,82-84] Most of the trials addressed subthreshold symptoms of depression or anxiety and did not provide support beyond automated feedback given within the cCBT program. Studies that used automated emails to remind participants to complete modules were also considered cCBT-NS.

Two trials (two arms) used cCBT as an adjunct to face-to-face therapy (cCBT-AT).[67,69] Wright et al.[67] addressed major depressive disorder by splitting a standard 50-minute therapy session into 25 minutes spent with a therapist in-person (PhD, MD, MS, or LCSW) and 25 minutes spent working through a computer module that complemented the therapy in the clinician's office. Kenardy et al.[69] addressed panic disorder with six full therapy sessions plus the provision of an auxiliary palmtop device providing supportive information, exposure exercises, and five prompts per day to practice the exposure exercises.

Of the 40 remaining arms, the cCBT intervention was supported by study staff to varying degrees through email, text, instant messaging, phone, discussion forums, or chat rooms. We classified 22 trials (26 arms) as supported interventions (cCBT-S).[39-41,45,46,48-51,54,57-60,64-66,74,75,77,79,80] Twelve trials (14 arms) used live support (cCBT-LS).[42-44,47,52,53,55,61,63,73,81,85] We found these classifications occasionally difficult to make as some of these studies employed different types of media to very different degrees.

Email and Texting

Communication was most often described as bidirectional (i.e., both staff-to-patient and patient-to-staff). It was unclear in five trials[49,54,58,59,64] whether participants could contact staff or their assigned therapist. Forty-four arms used email or text as a mode to communicate with patients. Thirty-three of these arms used email to provide support and feedback on homework. Of the 24 studies that reported amount of time spent by the therapist on email communication per patient per session (which did not include instant messaging or online groups), the median was 13.5 minutes, but varied from less than 10 minutes to 90 minutes. Four trials used email only to send reminders to patients and used a different medium (instant messaging, phone, or chat room) for the therapeutic communication. For example, Kessler et al.[55] used instant messaging to conduct a standard 50- to 55-minute therapy session over the internet; an email simply reminded the participant of the appointment.

Phone Conversations

Ten trials (12 arms) used phone conversations weekly or as needed. Six arms recommended phone conversations be kept to 10 minutes per week; other durations of phone conversations were variable or not reported.[43,44,47,52,60,61,63,73,81,85] For example, Choi et al.[43] provided each patient with a weekly phone call from a Chinese-speaking therapist that could last as long as a standard therapy session. In another six trials (eight arms),[49,51,53,54,72,82] the call was limited to reminding the patient to work on the module or move to the next module; or the patient was called only when he or she did not respond to email or did not log on for several weeks.

Online Peer Communication

Fourteen arms used some type of online peer communication. One trial arm[42] used a 90-minute chat room in place of a therapy session for five patients at a time. Eleven trials used moderated discussion forums where patients could post questions or comments.[47,48,50-53,57,63,64,66,73] Therapists responded within 72 hours. One arm of a cCBT-NS intervention provided a moderated support forum, but the moderator did not participate except to enforce forum conduct rules.[72] One study for Chinese-speaking participants[43] provided translations of previous online discussion groups.

All 27 trials treating major depressive disorder, panic disorder, generalized anxiety disorder, or PTSD were supported interventions to some degree except for one arm of a depression

study;[45] however, at least 50 percent of the trials on depressive and anxiety symptoms were not supported interventions. Thus, there was a qualitative correlation between increased support and increased illness severity. In cCBT-S studies, it was common for therapists to interact with patients on a weekly basis. Similarly, interventions that addressed a mental health diagnosis such as major depressive disorder tended to be longer—up to 16 weeks—than interventions aimed at addressing subthreshold mental health symptoms, which lasted up to 12 weeks.

Who Provides cCBT Intervention Support?

Support for cCBT was provided by licensed professionals (i.e., MD, PhD, MS, or LCSW) in 13 trials (13 arms)[47,49,50,52,53,55,57,59,67,69,73,79,81] and by graduate students supervised by a licensed professional, usually at the PhD level, in 11 trials (14 arms).[39-41,43,46,48,54,58,63,66,80] In four trials (five arms), both professionals and students were used as therapists,[45,65,75,77] while in seven trials (seven arms), staff was described as "mental health promotion workers," "trained lay counselors," or "technicians."[42,44,51-53,60,85] Training level of the therapists was not reported in four trials.[60,61,64,74] One study arm[45] did not provide staff support.

Support was given more often by licensed professionals when the intervention was used to treat patients with full criterion diagnosis of a disorder, rather than simply exceeding a symptom threshold on a severity measure. Again, using major depressive disorder compared with depressive symptoms as an example, support in the major depressive disorder trials was provided by licensed professionals in 40 percent of the arms. By contrast, support provided for patients enrolled for depressive symptoms was given via supervised graduate students or lay support staff in all but one instance (5%).[79]

Relationship Between cCBT Support and Patient Outcomes

We considered two types of analyses to examine the relationship between level of support and treatment outcomes. First we used mixed-treatment effects subgroup analyses, which examined whether treatment effects varied across studies with differing levels of support for the cCBT intervention. These indirect comparisons—reported in detail in KQ 1—are subject to confounding and should be considered exploratory. In this section, we summarize patterns across conditions. Second, we used direct comparisons of different levels of therapist support. While these trials have the potential to give the most robust evidence, only two small studies made direct comparisons.

Another challenge was the difficulty of classifying intervention arms into differing levels of support and the variability within those categories. For example, we categorized a large set of studies as cCBT-S (supported). This designation covered a broad scope: the amount of email contact was highly variable (as described previously); the content of contacts ranged from simple encouragement to detailed feedback on homework assignments; and half these trials included a discussion forum while the other half did not. The same breadth of scope held true for the cCBT-LS (live support) interventions: contact varied from a phone call lasting less than 10 minutes once a week to a 90-minute chat room session in addition to individual contact.

Indirect Comparisons

The results of the mixed-treatment effect subgroup analyses, using symptom severity at end of treatment, are summarized in Table 9. Because there were relatively few trials for each condition, we conducted analyses separately for all depressive disorders and those for generalized anxiety

disorder combined with panic disorder. For both of these analyses, there was a strong association between the level of cCBT support and the treatment effect ($p<0.001$). For trials of generalized anxiety disorder and panic disorder, there were no unsupported interventions and only one intervention using cCBT-AT (adjunct to therapy). Therefore, that analysis primarily compares cCBT-S with cCBT-LS. Because each of these analyses included only a single intervention using cCBT-AT, we conducted a sensitivity analysis that excluded these studies. For depressive disorders and anxiety disorders, the association between level of cCBT support and treatment effect remained statistically significant.

For major depressive disorder and depressive symptoms, there were sufficient studies to analyze the level of support for each disorder separately. This stratified analysis has the advantage of controlling for the disorder but has lower statistical power since there are few studies in some categories. For depressive symptoms, there remained an association between level of cCBT support and treatment effect (p=0.04); for major depressive disorder, there was no association.

Table 9. Mixed-treatment effects in indirect comparisons

Disorder	cCBT-NS SMD (95% CI)	cCBT-S[a] SMD (95% CI)	cCBT-LS SMD (95% CI)	cCBT-AT SMD (95% CI)
Major depressive disorder and depressive symptoms	N=12 -0.37 (-0.50 to -0.24)	N=13 -0.54 (-0.69 to -0.40)	N=7 -0.85 (-1.05 to -0.64)	N=1 -1.33 (-2.17 to -0.49)
Depressive symptoms	N=11 -0.35 (-0.47 to -0.23)	N=5 -0.40 (-0.57 to -0.22)	N=2 -0.81 (-1.15 to -0.47)	No studies
Major depressive disorder	N=1 -1.13 (-1.84 to -0.41)	N=8 -0.74 (-0.94 to -0.55)	N=5 -0.81 (-1.00 to -0.61)	N=1 -1.33 (-2.17 to -0.49)
Generalized anxiety disorder and panic disorder	No studies	N=8 -0.73 (-0.96 to -0.50)	N=4 -1.20 (-1.48 to -0.92)	N=1 -1.97 (-2.50 to -1.44)

[a] Wagner, 2013; Bergstrom, 2010; Carlbring, 2005 and Kiropoulos, 2008, are not included in this analysis because the control group is active (face-to-face therapy) rather than inactive (e.g., waitlist).
Abbreviations: AT=adjunct to therapy; cCBT=computerized cognitive behavioral therapy; CI=confidence interval; LS=live support; N=number of studies; NS=no support; S=support; SMD=standardized mean difference

For depressive disorders, the effect was diminished, but the general pattern remained when we examined differences at the most distal time point (≥6 months, 16 arms; data not shown). Few anxiety trials reported distal outcomes, and treatment effects did not vary by condition for the anxiety disorders, so we did not analyze these data further.

Direct Comparisons and Subgroup Analyses

There were only three trials, two with low risk of bias[45,54] and one with moderate risk of bias,[44] that examined different levels of cCBT support. Farrer et al.[44] examined the use of an available cCBT program, MoodGYM, with and without the support of a weekly phone call from a lay counselor (length of call not reported) in 155 participants with depressive symptoms recruited from a national telephone helpline service. Although depression scores on the CES-D scale were lower in both cCBT conditions with and without phone support compared with treatment as usual, the study did not find a difference between the two cCBT interventions. SMDs were -13.9 (NR) for cCBT with phone tracking compared with -10.6 (NR) for cCBT only (p=NS).

Berger et al.[45] examined the use of another available cCBT program, Deprexis, with and without the support of a weekly email providing feedback on homework and progress through the program (about 10 minutes per week) in 76 participants with major depressive disorder recruited from website advertisements. Again, although depression scores on the Beck Depression Inventory-II (BDI-II) were lower in both cCBT conditions with and without email support compared with waitlist, the trial did not find a significant difference between the cCBT interventions. Mean differences were -12.5 (NR) for "guided self-help" (cCBT with email feedback) compared with -9.0 (NR) for "unguided self-help" (cCBT only) (p=NS). This trial was confounded by the fact that the diagnosis was made via an initial phone call from a therapist in both groups.

Vernmark et al.[54] evaluated the effects of a standardized cCBT program developed for an earlier study[64] with positive reinforcement on progress via email (therapist time 53 ± 28 total minutes per patient) versus a tailored cCBT program delivered via email, essentially "email therapy," (509 ± 176 total minutes per patient) in 88 patients with major depressive disorder recruited via university media. As in the other two studies, depression scores on both the BDI-II and the Montgomery-Asberg Depression Rating Scale (MADRS) were significantly lower in both cCBT conditions compared with control conditions. The difference between guided self-help and tailored email therapy was small and favored the tailored therapy but was not significant (p=0.41). On the BDI-II, the end-of-treatment effect sizes were 2.27 (email group) compared with 1.46 (self-help group). On the MADRS, the end-of-treatment effect sizes were 2.04 (email group) compared with 1.11 (self-help group).

We examined two other variables to determine whether there was an effect from the level of cCBT support: (1) HRQOL and (2) whether the support was provided by a licensed clinician or a nonlicensed technician or lay counselor. The comparison for HRQOL had limited power due to few trials (cCBT-NS=5, cCBT-S=9, cCBT-LS=3, cCBT-AT=0). The gradient was in the expected direction (cCBT-NS=SMD +0.25; 95% CI, +0.07 to +0.43; cCBT-S=SMD +0.33; 95% CI, +0.18 to +0.49; cCBT-LS=SMD +0.40; 95% CI, +0.17 to +0.63); however, the association was not significant (p=0.58).

There were only two trials (four arms) that examined who delivered the intervention—a proxy for the importance of level of training. Studies by Titov et al.[52] and Robinson et al.[53] were conducted by the same group at St. Vincent's Hospital in Sydney, Australia, using the same method adapted for two different disorders, major depressive disorder[52] and generalized anxiety disorder.[53] Completion rates were high in all four arms. Neither trial found significant differences due to clinician versus technician support. In Titov et al.,[52] within-group effect sizes on the BDI-II were 1.27 (clinician-assisted group) and 1.20 (technician-assisted group) (p=0.07). On the Personal Health Questionnaire-9 scale, effect sizes were 1.54 (clinician-assisted group) and 1.60 (technician-assisted group) (p=0.07). In Robinson et al.,[53] within-group effect sizes on the Penn State Worry Questionnaire were 1.16 (clinician-assisted group) and 1.07 (technician-assisted group) (p=0.07), and on the Generalized Anxiety Disorder-7 scale were 1.55 (clinician-assisted group) and 1.73 (technician-assisted group) (p=0.11).

In summary, indirect evidence supports a possible association between the level of cCBT support and treatment effect. A small number of trials directly comparing different levels of support did not find clinically important differences; however, these trials may be underpowered to detect a differential effect.

KEY QUESTION 3. For adults with depressive disorder, posttraumatic stress disorder, panic disorder, or generalized anxiety disorder, what are the effects of cCBT interventions compared with face-to-face therapy?

Key Points

- Only seven trials directly compared cCBT interventions with standard face-to-face therapy. Five trials used an internet-based platform, while two trials incorporated a computerized complement to face-to-face therapy.
- For patients with anxiety disorders or symptoms, only panic disorder had enough trials to provide a summary effect size. Evidence suggests there is minimal difference between cCBT and face-to-face therapy for panic disorder (SMD -0.07; 95% CI, -0.34 to 0.21).
- For patients with depressive disorders or symptoms, more data are needed to evaluate the differential effect between cCBT and face-to-face therapy.
- No trials of this type were conducted in patients with PTSD.

Study Characteristics

We identified 7 trials involving 664 patients that met inclusion criteria for evaluating KQ 3.[50,59,62,66,67,69,79] Four trials focused on treatment for panic disorder, two for subthreshold depressive symptoms, and one for major depressive disorder. Risk of bias was rated low for three trials[50,59,62] and moderate for four trials.[66,67,69,79] Overall, the majority of trial participants were female (range 62% to 76%). Over half of the trials reported current medication use in the sample.

Effects of cCBT Interventions in Patients With Depressive Disorders and Symptom Thresholds

End-of-Treatment Outcomes

In the first of three trials[62,67,79] evaluating cCBT versus face-to-face therapy, Spek et al.[62] randomized 301 adults over the age of 50 with subthreshold depressive symptoms into one of three groups: (1) cCBT, (2) face-to-face group treatment, or (3) waitlist. For inclusion, participants were required to have elevated symptoms of depression but were excluded if they met full diagnostic criteria for depression based on the DSM-IV. Participants underwent either an 8-week cCBT intervention or a 10-week face-to-face group intervention for depressive symptoms using the Coping with Depression (CWD) program. The cCBT protocol was based on the CWD protocol but provided no additional support (cCBT-NS). Overall, the face-to-face group completed approximately 98 percent of the sessions (9.1 of 10 sessions), while the cCBT group completed approximately 78 percent of the sessions (5.5 of 8 sessions). Therefore, the face-to-face group intervention was longer and had greater adherence. After end-of-treatment evaluation, the two treatments did not significantly differ (SMD 0.06; 95% CI, -0.21 to 0.34; p=0.66). In a followup trial assessing predictor variables, Spek et al.[62] found that having higher baseline depressive symptoms, being female, and having lower neuroticism scores were associated with better outcomes regardless of treatment type.

The second trial[79] also focused on subthreshold depressive symptomology in adults between the ages of 19 and 67. Treatment in both arms of the study included "intensive therapist contact" and consisted of a manual-based CBT program delivered in eight weekly sessions. The sessions

were given in the same sequential order and were provided with the same psychoeducation as the face-to-face group, but the cCBT group received texts and feedback on their progress and written assignments. At baseline, there were significant differences between groups with more females in the cCBT group compared with the face-to-face group. At end of treatment, the two treatments did not significantly differ (SMD 0.01; 95% CI: -0.53 to 0.55; p=0.98). In addition, these findings remained stable at 3-month followup.

The third trial[67] focused on major depressive disorder in adults between the ages of 18 and 65 who were not currently taking any antidepressant medication. Treatment in both arms of the study involved a face-to-face component to the treatment. The standard cognitive therapy program consisted of eight weekly sessions compared with a modified computerized version of the program that reduced the amount of time spent with therapist. At baseline, there were significant differences between groups, with cCBT participants reporting greater symptomatology on both the BDI-II (p=0.001) and the Automatic Thoughts Questionnaire p=0.03) compared with the face-to-face unassisted participants. At end of treatment, the two treatments did not significantly differ (SMD 0.062; 95% CI, -0.22 to 0.34; p=0.66). These findings also were maintained at both 3- and 6-month followup.

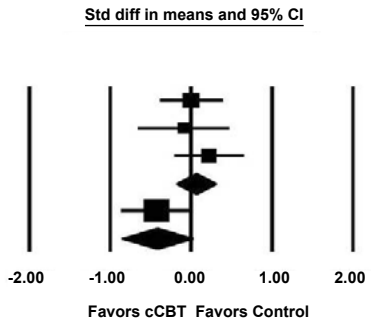
Effects of cCBT Interventions in Patients With Panic Disorder

End-of-Treatment Outcomes

Three interventions were categorized as cCBT-S,[50,59,66] and one used a mobile palmtop as an adjunct to therapy.[69] Face-to-face therapy consisted of ten 2-hour group sessions in one study[50] and ranged from 6 to 12 individual sessions in the other three studies. Figure 12 shows a forest plot of SMDs for all comparisons in participants with panic disorder, grouped by category of support. In the three comparisons, cCBT was not more effective than face-to-face therapy (SMD 0.06; 95% CI, -0.19 to 0.31). In the single study evaluating cCBT as an adjunct, symptoms improved more than face-to-face therapy (SMD -0.42; 95% CI, -0.87 to 0.02), but this result could have been due to chance.

Figure 12. Forest plot of cCBT versus face-to-face therapy in patients with panic disorder

Group By cCBT Type	Study name	Outcome	Statistics for each study: Std diff In means	Lower limit	Upper limit	p-Value
cCBT-S	Bergstrom 2010	SxSeverity	0.00	-0.38	0.38	1.00
cCBT-S	Carlbring 2005	Combined	-0.10	-0.66	0.47	0.74
cCBT-S	Kiropoulos 2008	Combined	0.22	-0.20	0.55	0.30
cCBT-S			0.06	-0.19	0.31	0.64
cCBT-AT	Kenardy 2003	SxSeverity	-0.42	-0.87	0.02	0.06
cCBT-AT			-0.42	-0.87	0.02	0.06



Abbreviations: A=adjunct to therapy; cCBT=computerized cognitive behavioral therapy; S=support; Std diff=standardized difference; Sx=symptoms

Health-Related Quality of Life Outcomes

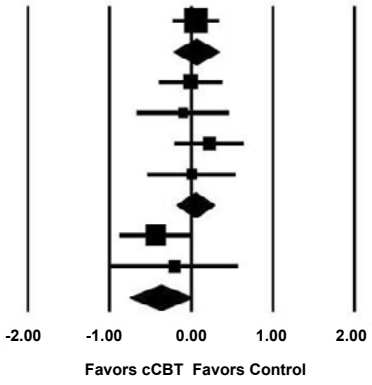
HRQOL outcome data were available for three comparisons across three trials of patients with panic disorder[50,59,66] but were not reported in the other trials. The cCBT intervention group was not found to be significantly better compared with the face-to-face therapy group (SMD -0.07; 95% CI, -0.34 to 0.21).

Combined Level of Support Across Diagnosis

Because of the small number of studies, we conducted mixed-treatment effect subgroup analyses using symptom severity as the outcome, to examine the influence of level of support across all seven trials that compared cCBT with face-to-face interventions. Figure 13 shows a forest plot of SMDs for comparisons involving participants with depression or panic disorder. In the four comparisons of cCBT-S interventions, effect sizes were generally small (SMD 0.05; 95% CI, -0.18 to 0.28). The two comparisons of cCBT-AT versus face-to-face therapy resulted in moderate, but statistically nonsignificant, differences in favor of cCBT (SMD -0.37; 95% CI, -0.75 to 0.02). There was only one trial of cCBT-NS, and intervention effects did not differ.

Figure 13. Forest plot of cCBT versus face-to-face therapy in patients with depression or panic disorder by level of cCBT support

Group By cCBT Type	Study name	Outcome	Statistics for each study: Std diff In means	Lower limit	Upper limit	p-Value
cCBT-NS	Spek 2007	Sx Severity	0.06	-0.21	0.34	0.66
cCBT-NS			0.06	-0.21	0.34	0.66
cCBT-S	Bergstrom 2010	Sx Severity	0.00	-0.38	0.38	1.00
cCBT-S	Carlbring 2005	Combined	-0.10	-0.66	0.47	0.74
cCBT-S	Kiropoulos 2008	Combined	0.22	-0..20	0.65	0.30
cCBT-S	Wagner 2013	Sx Severity	0.01	-0.53	0.55	0.98
cCBT-S			0.05	-0.18	0.28	0.66
cCBT-AT	Kenardy 2003	Sx Severity	-0.42	-0.87	0.02	0.06
cCBT-AT	Wright 2005	Combined	-0.20	-0.98	0.57	0.61
cCBT-AT			-0.37	-0.75	0.02	0.06



Abbreviations: AT=adjunct to therapy; cCBT=computerized cognitive behavioral therapy; CI=confidence interval; NS=no support; S=support; Std diff=standardized difference; Sx=symptom

Treatment Adherence and Patient Satisfaction for Disorders

Treatment adherence was reported in four of the seven comparisons of cCBT and face-to-face therapy. The percentage of patients completing the intervention was reported in three comparisons, and the mean and standard deviation of sessions completed were reported in two. Adherence outcomes by study are presented in Table 10. The studies reporting the proportion of completers generally found that the majority of participants completed the face-to-face interventions, but completion was inconsistent in the cCBT intervention.[62,67,79] In regard to the number of sessions completed versus planned, the cCBT patients completed on average 71.5 percent of sessions compared with 90.5 percent of face-to-face sessions.[62,66]

Table 10. Treatment adherence for cCBT interventions compared with face-to-face therapy

Study	Disorder	Proportion completing all planned sessions	
		cCBT	*Face-to-face therapy*
Spek, 2007	Depressive symptoms	49/102 (48%)	94/99 (94.5%)
Wagner, 2013	Depressive symptoms	25/32 (78%)	28/30 (93%)
Wright, 2005	Major depression, dysthymia	13/13 (100%)	14/14 (100%)
		Mean sessions completed/total planned sessions	
Spek, 2007	Depressive symptoms	5.5/8	9.1/10
Carlbring, 2005	Panic disorder	7.4/10	9.0/10

Patient satisfaction was reported in three trials.[59,66,79] Generally, the studies reported equal satisfaction between cCBT and face-to-face groups. However, participants in the face-to-face group in one trial[59] reported significantly higher levels of "enjoyment for communicating with therapist."

SUMMARY AND DISCUSSION

The demand for mental health services in VHA is increasing, with depressive disorders, anxiety disorders, and PTSD among the most common diagnoses. Yet, there are important barriers to in-person, evidence-based therapy, including stigma associated with mental healthcare and logistical barriers such as transportation challenges, time constraints, and limited available appointments. The VA/DoD have begun to invest in web-based self-help programs such as cCBT to help overcome these barriers; for example, people can participate when convenient for them from home. Thus, this evidence review was commissioned to inform development of such programs.

We identified 47 randomized controlled trials involving 7270 patients that were relevant to our study questions. The most studied conditions were depressive disorders, generalized anxiety disorder, and panic disorder. Participants in these included trials were typically mid-life adults with moderate symptom severity. The cCBT interventions were delivered most often through web-based applications with at least a limited degree of remote therapist support. All studies reported short-term effects on symptom severity, with a subset of studies also reporting longer term effects on HRQOL. When meta-analysis was possible, treatment effects were summarized using the SMD. Adverse effects were not reported systematically in the included studies. Next, we summarize our findings and the overall strength of evidence (SOE) by KQ.

SUMMARY OF EVIDENCE BY KEY QUESTION

KQ 1. Effects of cCBT Interventions Compared With Controls

We found at least moderate SOE that cCBT interventions improved symptoms to a greater degree than control conditions (usual care, waitlist, or attention controls) for depressive symptoms, major depressive disorder, generalized anxiety disorder, and panic disorder (Table 11). For the latter three conditions, the effects measured at end of treatment were large. For PTSD and anxiety symptoms, however, there were few trials, and our confidence in the estimate of treatment effect was low. Patterns were similar for effects on HRQOL.

The literature on major depressive disorder indicates that an increase in depressive symptoms months after the end of cCBT is to be expected; however, one review found that a minority of patients (approximately 26% to 31%) relapse to significant depressive symptoms.[86] For the subset of trials included in our systematic review that evaluated outcomes at 6 months or longer, treatment effects were smaller but remained statistically significant.

Adherence to treatment was highly variable with fewer than one-half of participants completing all planned treatment sessions (median 44%; range 11% to 95%). This rate of adherence is low compared with general estimates of treatment completion for major depressive disorder[87] and generalized anxiety disorder,[88], as well as studies using in-person CBT with Veterans.[89,90] The limited adherence rates in trials, where patients are often more adherent than in typical practice, is a concern for effective implementation of cCBT.

Table 11. Summary of the strength of evidence for KQ 1: cCBT compared with control at end of treatment by disorder

Outcome	Strength of Evidence Domains				Effect Estimate (95% CI)[a]	SOE
	Number of Studies (Patients)	Study Design/ Risk of Bias	Consistency Directness	Precision Publication Bias		
Adults with depressive symptoms						
Symptom severity	13 (3010)	RCT/Moderate	Inconsistent Direct	Precise None detected	SMD = -0.38 (-0.50 to -0.27)	Moderate
HRQOL	4 (1269)	RCT/Moderate	Consistent Direct	Precise None detected	SMD = 0.26 (0.11 to 0.41)	Moderate
Adults with major depressive disorder or dysthymia						
Symptom severity	11 (931)	RCT/Moderate	Consistent Direct	Precise None detected	SMD = -0.84 (-1.01 to -0.67)	High
HRQOL	8 (941)	RCT/Moderate	Consistent Direct	Precise None detected	SMD = 0.37 (0.22 to 0.52)	High
Adults with generalized anxiety disorder						
Symptom severity	4 (321)	RCT/Low	Consistent Direct	Imprecise None detected	SMD = -0.94 (-1.34 to -0.54)	Moderate
HRQOL	3 (176)	RCT/Moderate	Consistent Direct	Imprecise None detected	SMD = 0.57 (0.27 to 0.87)	Low
Adults with panic disorder						
Symptom severity	7 (333)	RCT/Moderate	Consistent Direct	Imprecise None detected	SMD = -1.08 (-1.45 to -0.72)	Moderate
HRQOL	6 (250)	RCT/Moderate	Consistent Direct	Imprecise None detected	SMD = 0.49 (0.23 to 0.75)	Moderate
Adults with PTSD						
Symptom severity	2 (71)	RCT/Moderate	Consistent Direct	Imprecise None detected	No summary estimate. SMD range from -0.42 to -0.46	Low
HRQOL	1 (40)	RCT/Moderate	NA Direct	Imprecise None detected	No summary estimate. SMD = 0.60 (-0.04 to 1.23) from one study	Insufficient
Adults with anxiety symptoms						
Symptom severity	2 (132)	RCT/High	Consistent Direct	Imprecise None detected	No summary estimate. SMD range from -0.28 to -0.42	Low
HRQOL	0 (0)	NA	NA NA	NA NA	NA	Insufficient

[a] For symptom severity, a negative effect estimate favors cCBT; for health-related quality of life, a positive effect estimate favors cCBT.

Abbreviations: CI=confidence interval; HRQOL=health-related quality of life; NA=not applicable; PTSD=posttraumatic stress disorder; RCT=randomized controlled trial; SMD=standardized mean difference; SOE=strength of evidence

KQ 2. Characteristics and Effects of User Support Provided in cCBT Programs

Most of the cCBT interventions were accessed via the internet from nonclinical locations and were supported by a therapist. Approximately one-third included a peer support discussion board. The level of therapist support varied widely, ranging from minimal feedback on homework assignments via email to a full therapy session via instant messaging or a chat room format. In two studies, cCBT was used as an adjunct to face-to-face therapy, but for most interventions, cCBT was a standalone treatment. Exploratory subgroup analysis, using indirect comparisons, showed an association between higher levels of support and greater treatment effects. Two small studies directly compared different levels of therapist support and did not find a differential treatment effect.

KQ 3. Effects of cCBT Interventions Compared With Face-to-Face Therapy

Seven studies directly compared cCBT with face-to-face therapy (Table 12). Panic disorder was the only condition with more than two studies making this comparison, and these trials showed no difference in effects on symptom severity or HRQOL (moderate SOE). Two studies, a relatively large, high-quality trial[62] and a smaller, fair-quality trial,[79] found no difference in treatment effects for participants with depressive symptoms (low SOE). The sample size in the single pilot study on major depressive disorder was too small to determine SOE. Therefore, we conclude the current literature is generally insufficient for making a determination about whether the efficacy of cCBT is comparable to traditional, face-to-face therapy.

Table 12. Summary of the strength of evidence for KQ 3

Outcome	Strength of Evidence Domains				Effect Estimate (95% CI)[a]	SOE
	Number of Studies (Patients)	Study Design/ Risk of Bias	Consistency Directness	Precision Publication Bias		
Adults with depressive symptoms						
Symptom severity	2 (254)	RCT/Low	Consistent Direct	Imprecise None detected	No summary estimate. SMD range (0.01 to 0.06)	Low
HRQOL	0 (0)	NA	NA NA	NA NA	No studies	Insufficient
Adults with major depression or dysthymia						
Symptom severity	1 (26)	RCT/Moderate	NA Direct	Imprecise None detected	No summary estimate. SMD = -0.20 (-0.98 to 0.57) from one study	Insufficient
HRQOL	0 (0)	NA	NA NA	NA NA	No studies	Insufficient
Adults with panic disorder						
Symptom severity	4 (319)	RCT/Low	Consistent Direct	Imprecise None detected	SMD = -0.07 (-0.34 to 0.21)	Moderate
HRQOL	3 (239)	RCT/Low	Consistent Direct	Imprecise None detected	SMD = -0.07 (-0.34 to 0.21)	Moderate

[a] For symptom severity, a negative effect estimate favors cCBT; for health-related quality of life, a positive effect estimate favors cCBT.
Abbreviations: HRQOL=health related quality of life; NA=not applicable; RCT=randomized controlled trial; SMD=standardized mean difference; SOE=strength of evidence

CLINICAL AND POLICY IMPLICATIONS

Computerized CBT, through the internet or computer-based applications, has the potential to overcome barriers to evidence-based therapies—particularly for patients who live long distances from trained clinicians. This mode of delivery also has the potential to address shortages in the number of trained mental health professionals and might possibly lower the cost of care. Computerized CBT is estimated to cost $50 to $550 per client episode of completed treatment. By comparison, fees for individual psychotherapy, typically range from $80 to $160 per single session in the United States. Despite this potential, however, few clinical guidelines address cCBT, including those from the VA/DoD,[91] American Psychiatric Association,[92] and the Canadian Network for Mood and Anxiety Treatments.[93] In the United Kingdom, the National Institute for Health and Care Excellence (NICE) depression guideline recommends, "For people with persistent subthreshold depressive symptoms or mild to moderate depression, consider offering … computerised cognitive behavioural therapy."[94] Further, the guidelines state the computerized CBT be "provided via a stand-alone computer-based or web-based programme, include an explanation of the CBT model, encourage tasks between sessions, and use thought-challenging and active monitoring of behaviour, thought patterns and outcomes, be supported by a trained practitioner, who typically provides limited facilitation of the programme and reviews progress and outcome, and typically take place over 9 to 12 weeks, including follow-up."[94] NICE makes similar recommendations for generalized anxiety disorder.[95] Our systematic review is consistent with these guideline recommendations. That is, cCBT programs, supported by trained practitioners, have short-term benefits for individuals with major depression, generalized anxiety disorder, panic disorder, and, to a lesser extent, people with depressive symptoms.

Although our review supports cCBT for selected conditions, a number of cautions relate to applicability to Veterans and issues of how best to implement cCBT in the VA health system. Because most of the cCBT interventions excluded participants with active suicidal ideation or severe symptoms, very little information is available on the efficacy of cCBT for managing patients in crisis. Current evidence does not support cCBT for patients in crisis or with severe illness. Also, the use of cCBT technology brings with it privacy and information security risks that must be addressed to ensure that these risks are eliminated or at least communicated to Veterans using cCBT. For treatments that use electronic messaging from hospital staff to remind patients to complete modules or to address questions, secure messaging systems will need to be integrated with the treatment. Because cCBT often utilizes web-based modules, the security of information transmitted and stored on these sites will need to be addressed.

Veterans enrolled in the VA health system are older, on average, than those in the clinical trials and have higher levels of chronic health conditions. Information on comorbid conditions was reported infrequently in the trials of cCBT. Patients with mental health conditions and severe comorbid physical or mental conditions (e.g., depressive disorder plus PTSD or diabetes) may be less responsive to treatment, or they may find that distance-based treatment is isolating, particularly when it involves briefer and fewer instances of asynchronous communication.[96] Despite this caution, there is some evidence that cCBT is acceptable to older adults.[97] Younger, more tech-savvy Veterans may be particularly appropriate candidates for cCBT.

In the studies we reviewed, older individuals were not included (median age 39.8, range 20 to 58), so the utility of cCBT in Veterans age 60 and older is unknown. It is also worth considering that most of the cCBT interventions reviewed required computer and internet access at home. While internet access in the Veteran population is likely to increase over time, results from the 2010 National Survey of Veterans indicated that 71 percent were using the internet,[98] so cCBT is likely not an ideal choice for the minority of Veterans who do not use the internet.

Interest in undertaking cCBT could vary substantially across patients. As a consideration in implementing cCBT, some clinics might offer it as an alternative to face-to-face therapy, to be selected only by patients that prefer the accessibility of cCBT. If clinics are considering this implementation method, it would be helpful to conduct more research on the influence of treatment choice on outcomes. This could be accomplished with trial designs that randomized to choice versus no-choice conditions. Alternatively, clinics might consider using cCBT in a stepped-care model that offers cCBT as a first-line psychotherapy. In this model, patients who do not report benefit from cCBT could then be referred for face-to-face therapy. Clinics implementing cCBT also need to consider the staffing needs of these interventions. While therapist burden is expected to be reduced, at least some level of therapist involvement is reasonable to ensure that patients receive reinforcement of material presented in cCBT. Some of the studies we reviewed used technicians, as opposed to clinicians, to provide human support. While few studies have compared technicians with clinicians, those that did generally found that technicians performed well. As a result, clinics could consider nonclinician staff members to be used in resolving questions about procedural problems with the cCBT program or routine questions about treatment content. However, therapists must remain available for consultation, because there will continue to be a potential for crisis issues that demand clinical expertise.

Some cCBT programs, including Beating the Blues and FearFighter™, are included as a covered benefit by the national health services of the United Kingdom, Australia, New Zealand, and Canada.[99] In the United States, Ultrasis partnered with University of Pittsburgh to form U2 Interactive to market Beating the Blues.[100] The VHA will need to determine whether to make an existing program available to its patients or develop its own programs. Especially for disorders like major depressive disorder or generalized anxiety disorder, for which we found no statistically significant evidence of heterogeneity in treatment effects across studies, it is reasonable to expect that VHA researchers could develop programs that will achieve treatment outcomes similar to those observed in previous studies. For either approach, issues of privacy, including HIPAA compliance, and how to make the program available—through referral by VA clinicians or more widely to any Veteran—will require careful consideration. New programs could be tailored to a Veteran sample and could incorporate recent developments in treatment as well as be adapted for increasingly prevalent technologies such as smartphones. VHA has introduced some smartphone apps (e.g., PTSD Coach, www.ptsd.va.gov/apps/ptsdcoachonline/default.htm) that offer assessment, basic coping tools, and referral to treatment resources. The methods used to communicate and disseminate these apps to Veterans could serve as a foundation for providing cCBT, which is a more in-depth treatment modality.

Our review suggests greater effects for patients meeting criteria for full disorders and mild to moderate symptom severity. Requiring a diagnosis and clinician referral to the program could ensure more careful diagnostic evaluations and closer followup. However, this approach could

partially negate some of the advantages of the cCBT format, such as anonymity and overcoming time constraints and travel barriers. If the VHA were to develop its own cCBT programs, they should utilize the approaches found in the more effective interventions and be sensitive to the user interface, which could affect engagement and treatment adherence. For major depression, our review provides support for a fairly uniform benefit from multiple cCBT interventions, suggesting that treatment benefit is derived from the general principles of CBT rather than any one specific cCBT program. In contrast, studies of patients with anxiety disorders had more variability in treatment effects, raising the possibility that effects are specific to the type of program used.

Another consideration is how much therapist support to provide with cCBT treatments. Psychotherapy models typically include the therapeutic alliance between patient and therapists as an important mechanism of achieving improved psychiatric symptoms. At this point, it is unclear to what extent a relationship with a therapist is needed to optimize cCBT treatment outcomes, but there is reason to suspect it will be an important consideration. Based on indirect comparisons, we found a relatively consistent gradient showing greater treatment effects with greater support. However, very few studies evaluated more intensive human support for some conditions, and we were unable to isolate the specific features or degree of support associated with treatment benefit. Based on current evidence, we conclude that health systems implementing cCBT should include therapist support via email or brief telephone sessions, or both. The studies we reviewed did not provide reliable estimates of the panel size that a single therapist could support, but based on the median of approximately 15 minutes devoted to each patient weekly, a therapist supporting cCBT could provide care to a substantially larger cohort than those utilizing face-to-face therapy.

Finally, the VHA should not underestimate the challenge of introducing different approaches to care delivery. Successful implementation of cCBT will likely require a carefully planned approach.

STRENGTHS AND LIMITATIONS

Our study has a number of strengths, including a protocol-driven review, a comprehensive search, a careful quality assessment, and rigorous quantitative synthesis methods. Our report, and the literature, also has limitations. Important limitations of the literature include the few studies in conditions of high priority to the VA (e.g., PTSD), few studies with longer term outcomes, and few studies directly comparing cCBT with differing levels of therapist support, such as length of the interaction, speed of the interaction (i.e., instant messaging vs. email), and the mode of support (email vs. chat room vs. phone). To more definitively address cCBT effectiveness in patients with PTSD, anxiety symptoms, or multiple/comorbid diagnoses—as well as the association between therapist support and treatment benefit—additional carefully designed trials will be needed.

Other limitations include the choice of controls for some trials, patient recruitment through advertisement, and relatively high dropout rates in many studies. Selection of the most appropriate control in trials of psychotherapy is challenging, but waitlist controls may overestimate the treatment benefit compared with studies that use treatment as usual or attention controls. Patient recruitment through advertisements, particularly over the internet, may select patients who are more adept users of internet technology but who may not have a medical home if a crisis arises. In addition, high dropout rates, even when appropriate statistical correction is

employed, may bias toward greater treatment effect. Last, we were concerned about the lack of systematic reporting of safety data.

Limitations of our review methodology include a limited ability to detect publication bias due to small numbers of studies in the meta-analyses as well as the challenge of classifying the levels of cCBT support even though we used relatively broad categories. We supplemented our statistical assessment for publication bias (using funnel plots) with a search of www.clinicaltrials.gov and did not identify a pattern of completed but unpublished studies. Although we classified studies into broad categories of support, which would act to minimize the association with treatment outcomes, our mixed-treatment effect subgroup analyses found an important association, which suggests that this approach did not obscure the association.

RECOMMENDATIONS FOR FUTURE RESEARCH

We used the framework recommended by Robinson et al.[101] to identify gaps in evidence and classify why these gaps exist. This approach considers PICOTS (population, intervention, comparator, outcomes, timing, and setting) to identify gaps and classifies them as due to (1) insufficient or imprecise information, (2) biased information, (3) inconsistency or unknown consistency, and (4) not the right information. Using this structure, we have identified gaps in evidence and propose study designs to address these gaps (Table 13). VA and other healthcare systems should consider their clinical and policy needs when deciding whether to invest in research to address gaps in evidence.

Table 13. Evidence gaps and future research needs

Evidence Gap	Reason	Type of Studies to Consider
Patients		
Effects in patients with PTSD or anxiety symptoms	Insufficient information	Randomized controlled trials
Effects on access to care	Insufficient information	Observational studies to evaluate if cCBT users differ from users of traditional mental health services and changes in proportion of veterans with mental illness receiving evidence-based therapies
Identifying factors (such as severity, educational level) that predict successful treatment with cCBT	Insufficient information	Large trials, observational studies, or patient level meta-analysis
Interventions		
Optimal level of therapist support	Insufficient information Exploratory analysis suggest possible differential effect	RCTs or quasi-experimental studies of limited versus more robust therapist support
Optimal mode of support delivery, i.e., phone vs. email vs. chat-room, etc.	Insufficient information	Head-to-head comparisons of mode, duration and intensity of therapist support.
Amount of therapist support. i.e., frequency and duration of contact independent of mode	Insufficient information	Head-to-head comparisons of mode, duration and intensity of therapist support.
Optimal case-load for a therapist supporting cCBT interventions	Insufficient information	Time-in-motion or related study designs
Optimal platform (e.g., web or mobile device) and interface design	Insufficient information: few studies of mobile devices; no detailed analysis of web design features	RCTs, quasi-experimental, and single case experimental designs to test novel technology. Studies should contain multiple platform comparisons including web-only, web + mobile, web on mobile, and mobile-only. Also include various mobile features such as text messaging, video messaging, and mobile applications.
Comparator		
Effectiveness compared to in person treatment	Insufficient information	Trials with end or treatment and 6 to 12 month outcome assessments
Outcomes		
Effects on adherence rates	Insufficient information	Trials with 6- to 12-month outcome assessments
Durability of treatment effects beyond the end of treatment	Insufficient information	Trials with 6- to 12-month outcome assessments
Uncertain effects on adverse events and patient safety	Insufficient information	Multisite observational studies; patient registries

Abbreviation: cCBT=computerized cognitive behavioral therapy; PTSD=posttraumatic stress disorder; RCT=randomized controlled trial

CONCLUSION

We found moderate to strong evidence that cCBT is effective in improving short-term symptoms for mid-life patients with major depressive disorder, generalized anxiety disorder, and panic disorder. Treatment effects were smaller for patients with depressive symptoms. We found evidence suggesting that the level of therapist support was related to the magnitude of benefit, but additional head-to-head trials are needed to address this issue definitively. VA/DoD should consider this body of evidence when updating their clinical guidelines for depression and anxiety disorders.

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APPENDIX A. SEARCH STRATEGIES

Table A-1. Search strategy for PubMed (August 30, 2013)

Set #	Terms	Results
1	"Behavior Therapy"[Mesh] OR ((behavior[tiab] OR behaviour[tiab]) AND (therapy [tiab] OR therapies[tiab)) OR Aversive[tiab] OR Biofeedback[tiab] OR Feedback[tiab] OR Neurofeedback[tiab] OR Desensitization[tiab] OR Virtual Reality[tiab] OR Exposure[tiab] OR Relaxation[tiab] OR Meditation[tiab] OR chronotherapy[tiab] OR commitment[tiab] OR dialectical[tiab] OR "Cognitive Therapy"[Mesh] OR ((cognitive[tiab] OR cognition[tiab]) AND (therapy[tiab] OR therapies[tiab])) OR "Psychotherapy, Brief"[Mesh] OR ((brief[tiab] OR short-term[tiab]) AND (psychotherapy[tiab] OR psychotherapies[tiab]))	**784265**
2	"Depressive Disorder"[Mesh] OR "Dysthymic Disorder"[Mesh] OR "Adjustment Disorders"[Mesh] OR "Stress Disorders, Post-Traumatic"[Mesh] OR Dysthymia[tiab] OR Minor Depression[tiab] OR Adjustment disorder[tiab] OR ptsd[tiab] OR generalized anxiety disorder[tiab] OR Depression[Mesh] OR Anxiety[Mesh:noexp] OR "Anxiety Disorders"[Mesh:noexp] OR "Panic Disorder"[Mesh] OR "Obsessive-Compulsive Disorder"[Mesh] OR anxiety disorder nos[tiab] OR mixed anxiety[tiab] OR subthreshold depression[tiab] OR minor depression[tiab] OR subsyndromal depression[tiab] OR panic[Mesh]	**213813**
3	(Computer-assisted Psychotherapy[tiab] OR Computerized Cognitive Behavioral Therapy[tiab] OR Low Intensity[tiab]) OR ("Internet"[Mesh] OR internet[tiab] OR web[tiab] OR social-media[tiab] OR "Therapy, Computer-Assisted"[Mesh]) OR (online[tiab] OR computer[tiab] OR computers[tiab] OR computerized[tiab] OR mobile[tiab] OR smartphone[tiab] OR smartphones[tiab] OR tablet[tiab] OR tablets[tiab] OR self-paced[tiab] OR computers[Mesh])	**456239**
4	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR control[tiab] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp])	**3151494**
5	#1 AND #2 AND #3 AND #4 Filters: Publication date from 1990/01/01 to 2013/12/31; English	**442**

APPENDIX B. CRITERIA USED IN RISK OF BIAS ASSESSMENT

Guidance on Assessing Risk of Bias for Randomized Controlled Trials

General instructions: (1) Rate each risk of bias item listed below as Low risk/ High risk/ Unclear risk (refer to Cochrane guidance to inform judgements). Add comments to justify ratings.
(2) After considering each quality item, give the study an overall rating of "Low risk," "Moderate risk," or "High risk" (see below).

Rating of individual items

* Indicates items contained in Cochrane Risk of Bias Tool.

1. **Selection bias:**
   a. *Randomization adequate (Adequate methods include random number table, computer-generated randomization, minimization without a random element.) **Low risk/ High risk/ Unclear risk**
   b. *Allocation concealment (Adequate methods include pharmacy-controlled randomization, numbered sealed envelopes, central allocation.) **Low risk/ High risk/ Unclear risk**
   c. Baseline characteristics (Consider whether there were systematic differences observed in baseline characteristics and prognostic factors between groups, and if important differences were observed, if the analyses controlled for these differences.) **Low risk/ High risk/ Unclear risk**

2. **Performance bias:**
   a. *Concurrent interventions or unintended exposures (Consider concurrent intervention or an unintended exposure (e.g., crossovers; contamination – some control group gets the intervention) that might bias results) **Low risk/ High risk/ Unclear risk**
   b. Protocol variation (Consider whether variation from the protocol compromised the conclusions of the study.) **Low risk/ High risk/ Unclear risk**

3. **Detection bias:**
   a. *Subjects blinded (Consider measures used to blind subjects to treatment assignment and any data presented on effectiveness of these measures.) **Low risk/ High risk/ Unclear risk**
   b. *Outcome assessors blinded, hard outcomes (Outcome assessors blind to treatment assignment for "hard outcomes" such as mortality.) **Low risk/ High risk/ Unclear risk**
   c. *Outcome assessors blinded, soft outcomes (Outcome assessors blind to treatment assignment for "soft outcomes" such as symptoms.) **Low risk/ High risk/ Unclear risk**
   d. Measurement bias (Reliability and validity of measures used.) **Low risk/ High risk/ Unclear risk**

4. **Attrition bias:**
   a. *Incomplete outcome data (Consider whether incomplete outcome data were adequately addressed, including systematic differences in attrition between groups [differential attrition]; overall loss to followup [overall attrition]; and whether an "intention-to-treat"

[ITT; all eligible patients that were randomized are included in analysis] analysis was performed.) (Note: mixed models and survival analyses are, in general, ITT.) **Low risk/ High risk/ Unclear risk**

5. **Reporting bias:**
   a. *Selective outcomes reporting (Consider whether there is any suggestion of selective outcome reporting; e.g., systematic differences between planned and reported findings.) **Low risk/ High risk/ Unclear risk**

Overall study rating

Please assign each study an overall quality rating of "Low risk," "High risk," or "Unclear risk" based on the following definitions:

A "**Low risk**" study has the least bias, and results are considered valid. A low risk study uses a valid approach to allocate patients to alternative treatments; has a low dropout rate; and uses appropriate means to prevent bias, measure outcomes, and analyze and report results. [Items 1a and 1c; 2a; 3b and 3c; and 4a are all rated low risk]

A "**Moderate risk**" study is susceptible to some bias but probably not enough to invalidate the results. The study may be missing information, making it difficult to assess limitations and potential problems (unclear risk). As the moderate risk category is broad, studies with this rating vary in their strengths and weaknesses. [Most, but not all of the following items are rated low risk: Items 1a and 1c; 2a; 3b and 3c; and 4a]

A "**High risk**" rating indicates significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; have large amounts of missing information; or have discrepancies in reporting. The results of a high risk study are at least as likely to reflect flaws in the study design as to indicate true differences between the compared interventions. [At least one-half of the individual quality items are rated high risk or unclear risk]

Conflict of interest (recorded but not used as part of Risk of Bias Assessment)

Was there the absence of potential important conflict of interest? The focus here is financial conflict of interest. If no financial conflict of interest (e.g., if funded by government or foundation and authors do not have financial relationships with drug/device manufacturer), then answer "Yes." **Yes /No /Unclear**

APPENDIX C. PEER REVIEW COMMENTS

Reviewer	Comment	Response
Question 1: Are the objectives, scope, and methods for this review clearly described?		
1	Yes.	Thank you.
2	Yes, the objectives, scope and methods were clearly described.	Thank you.
3	Overall, the objectives, scope, and methods are clear, and it appears that the investigators' approach was thorough and descriptive. Below are some specific comments that hopefully will be helpful in finalizing the report. 1. Many studies excluded patients with severe symptoms – this is an important limitation given that the mean baseline scores on symptom measures of Veterans receiving CBT and other evidence-based psychotherapies are typically in the severe range. This may affect the generalizability of the findings to the Veteran patient population. At minimum, recommend that this be emphasized and included as a limitation in the executive summary. 2. Similarly, studies examined generally included few older individuals (who represent the majority of the Veteran patient population) and seemingly included primarily individuals with significant interest and experience using computers and/or the Internet. While this is appropriately noted in the discussion of the findings, I think the implications of this should be further emphasized. In fact, it appears that no one truly older individual, using the conventional definition for this age group (65+), was included in any of the studies. 3. In addition, examinations of CBT with Veterans, specifically, have shown that the therapeutic alliance (emphasized in in-person VA CBT protocols) is significantly related to outcome – and this relationship is even greater among older Veterans. This seems at least worthy of mention. 4. There is limited mention of to what extent and how the quality of studies was considered. Were only studies of certain quality included and how many studies were excluded? 5. Psychotropic medication was allowed in 75 percent of the studies examined – if individuals were newer to treatment and not receiving psychotropic medication for some time, improvements could have been due to the psychotropic medication. Were studies excluded if this potential confound was not addressed? If not, this should be noted as a limitation 6. I do not recommend combining studies examining PTSD and anxiety disorder and reporting the effect size across these studies.	1. We agree that this issue is important for applicability to the Veteran population. We have given this point greater prominence (see pages 56-58). We think that CBT delivered via computer might be well suited to patients seen in primary care, who typically have mild to moderate severity. We agree that the evidence does not directly address patients with severe symptoms and that these patients might be served better by a clinic-based therapist in case of the need for crisis intervention. 2. We agree that this is an important issue related to applicability of the findings. Older adults may respond differentially to treatment compared with younger adults and may have different facility with or different response to computerized CBT. We have emphasized the absence of studies in older adults in the Executive Summary and Discussion. 3. This is an important consideration, and we think our analysis of the level of human support for cCBT is relevant to this question. As a result, we have added some discussion of the potentially important role of therapeutic alliance to the section of the Clinical and Policy Implications that addresses cCBT support. 4. Otherwise eligible studies were included without regard to the quality rating. Quality ratings are detailed in Appendix B and provided for each study in Appendix D. Quality rating (Risk of Bias) is included in the qualitative description of the studies and considered explicitly in the SOE rating (see Methods section). 5. With the literature from the updated search added, this falls to 70 percent. The reviewer makes a good point; however, all studies that allow for concurrent medication required that patients be on a stable dose for a period of time prior to study enrollment or the patients were excluded. This clarification has been added. 6. We did not combine studies to compute a summary estimate of effect for studies examining PTSD and anxiety disorders. We combined major depressive disorder and depressive symptoms.

Reviewer	Comment	Response
3 (continued)	7. The method of calculating the SMD by dividing the result by the pooled standard deviations of the two groups is considered by some to be a less conservative method for calculating the effect size.	7. We acknowledge that there are different approaches to calculating the SMD, including approaches that correct for small sample sizes. We conducted a sensitivity analysis and found little impact on the estimates (≤0.01SMD) across methods.
4	Yes. The authors prepared a very clear and comprehensive review of the topic.	Thank you.
Question 2: Is there any indication of bias in our synthesis of the evidence?		
1	No. The systematic review was clearly well done and free of bias, following all standards in existence regarding transparency in review.	Thank you.
2	Yes, bias was examined and was minimal	Thank you.
3	No.	Thank you.
4	No.	Thank you.
Question 3: Are there any published or unpublished studies that we may have overlooked?		
1	No. The internet based and computer based projects are all well represented. You will need to do a new review in a few years to include apps and mobile mental health games (once data from the Harnessing Technologies RFA are published).	Thank you for the suggestion.
2	Yes. The authors refer to additional studies that will be included in the manuscript and it was not clear why these studies were not included in the current report or at least at a minimum, discussion provided as to whether these studies influence outcomes reported in anyway	All but one of the additional eight studies referred to were published in 2013 and found when we updated the literature search on August 30, 2013. We have rerun all analyses and updated all outcomes affected by these new studies.
3	No. None identified.	Thank you.
4	No.	Thank you.
Question 4: Please write additional suggestions or comments below. If applicable, please indicate the page and line numbers from the draft report.		
1	The review as comprehensive, I have no other comments	Thank you.
2	May highlight in the review articles that specifically included veterans. In general, the report was clearly written, justifications for decisions were sound, and the report addresses an important topic. Page 34 – 35 the x axis changes from figure 7 to figure 8. Helpful to ensure that the labels are consistent for all graphs Worth considering for the paper, the role of adherence. Did interventions that have higher rates of intervention adherence result in better outcomes? What aspects of treatment intervention adherence were helpful?	Our review of the literature found only one article specifically addressing Veterans. This is given special emphasis in the report. We chose the X axis such that the effect estimate and 95% CI for most studies is included. This means the X axis is ± 2.0 for almost all graphs but in selected cases had to be modified to meet our graphical display criteria. We conducted a meta-regression analysis for the subset of studies reporting proportion of patients completing all modules. There was no association with the estimate of treatment effect. With regard to the relationship between the treatment intervention and adherence, there was not sufficient detail or number of studies reporting these characteristics to evaluate this association.

Reviewer	Comment	Response
3	1. Electronic CBT (eCBT) is not typically the standard term used for referring to computerized CBT. This is more commonly referred to as "computer-assisted", "computer-administered", "computerized", "computer-based", etc. Further, "eCBT" is the name of a specific, proprietary phone app for CBT for depression.	1. We have revised the report to use the term computerized CBT (cCBT).
	2. The low completion rate observed appears to be significantly lower than that for in-person CBT (e.g., Eftekhari et al., 2013; Karlin et al., 2012).	2. We agree and have noted in the summary of evidence that the adherence rates were relatively low compared with those observed for in-person therapy. In addition, improved adherence/completion was identified as a future direction for cCBT.
	3. "Mental health disorders" should read "mental disorders."	3. We have made the correction.
	4. I appreciate the investigators' focus on the relationship between eCBT support and patient outcomes. The issue of therapist support has been an important one in this area, as it has appeared that level of therapist supported is positively associated with outcomes and adherence. As noted by the investigators, the "supported" category included a broad range of support types, making it difficult to fully examine this question. Additional, systematic research examining this issue would be worthwhile. However, the current investigation appears to confirm previous findings.	4. Acknowledged; thank you for your comment.
	5. It would likely be useful to report the adherence/completion rate by condition cluster, in addition to or place of the overall rate across diagnostic areas. Looking at the rates reported for each individual study, there appears to be very wide variability. Is there evidence of why this was? Presumably, this may be related to level of therapist involvement, as some previous research had suggested. Thank you for the opportunity to review this report.	5. Thank you for this suggestion. We found the proportion completing all modules does vary by condition cluster. We have added this information to the results and discussion of adherence. There were not sufficient studies reporting adherence to the control group within condition clusters to examine an association between therapist support and adherence.
4	Very minor comments: 1. There was a possible typo on page 24, should be 218 excluded rather than 220 to get numbers to add up	1. We have updated and corrected the numbers in the literature flow.
	2. In cases when there were multiple measures in the same study, the authors chose to calculate the mean effect from all instruments (Page 21). While this sounds reasonable to me, I wonder if the authors chose the same approach if a study pre-specified a primary outcome.	2. We compared the authors' prespecified primary measure(s) to the outcome measures included in our analyses. In almost all instances there was perfect agreement.

Reviewer	Comment	Response
Optional Dissemination and Implementation Questions		
Question 5: Are there any clinical performance measures, programs, quality improvement measures, patient care services, or conferences that will be directly affected by this report? If so, please provide detail.		
1	All I am aware of is the National Center for PTSD and their work around mobile mental health – they would benefit from this report. Worthwhile at some point to do a review for older adults and technology interventions, given the aging of the veteran population	Thank you for the suggestion.
2	If issues related to IT and confidentiality are addressed in the VA, the report may be able to influence policy by providing electronic CBT to veterans to address the continued lack of adequate mental health providers	Thank you for the suggestion about IT. This has been discussed in a little more detail in the revised discussion section.
3	No comments	Thank you.
4	No comments	Thank you.
Question 6: Please provide any recommendations on how this report can be revised to more directly address or assist implementation needs.		
1	Maybe more on how these data affect older populations.	Thank you for the suggestion.
2	Further clarify what the recommendations the VA can use to implement electronic CBT. A recommendation for a comparator may be examining outcomes of individuals who can select receiving cognitive behavioral interventions via life person, or computer based. In reality, this is likely the way these programs would likely be introduced. Consider providing more comment on the resources and staffing of the use of ECBT? If there are a limited of mental health clinicians, is using computer based CBI a way to offset these challenges?	Thank you, we have provided further explanation in the Discussion section of the report.
3	No comments	Thank you.
4	No comments	Thank you.
Question 7: Please provide us with contact details of any additional individuals/stakeholders who should be made aware of this report.		
1	David Mohr at NorthWestern	Thank you for the suggestion.
2	No comments	Thank you.
3	No comments	Thank you.
4	No comments	Thank you.

APPENDIX D. STUDY CHARACTERISTICS TABLES

Table D-1. Detailed study characteristics of cCBT interventions

Study	Location Recruitment Setting Organization Total N	Age in Years (SD) % Female % Race/ethnicity Baseline differences?	Target Condition Baseline Severity Medications	Study Duration Outcomes Reported	Number of Arms Intervention Comparator	Design Quality
Major depressive disorder (11 trials)						
Andersson, 2005[1]	Europe (Sweden) Newspaper advertisement Government 117	Total: 36.14 (NR) Grand mean: 75% NR No	MDD CIDI-SF Allowed, not managed	EOT: 10 wk (mean) Followup: 26 wk BDI BAI MADRS Quality of life Adherence Therapist productivity	2 cCBT Attention control (online discussion group)	RCT Fair
Berger, 2011[2]	Europe (Switzerland and Germany) Advertisement and website University affiliated 76	Grand mean: 38.8 (NA) Grand mean: 69.7% NR No	MDD, dysthymia BDI-II >13 Allowed, not managed	EOT: 10 wk; Followup: 26 wk BDI WHOQOL-BREF Adherence Therapist productivity	3 cCBT (guided) cCBT (unguided) Waitlist	RCT Good
Carlbring, 2013[3]	Europe (Sweden) Advertisement: website, newspaper Government 80	Total: 44.4 (13.5) Total: 82.5% NR No	MDD MADRS SCID Allowed, not managed	EOT: 8 wk Followup: 13 wk BDI-II BAI MADRS HRQOL	2 cCBT (BA) Waitlist	RCT Good
Choi, 2012[4]	Australia Mass media Government 63	Grand mean: 39.2 (NA) Grand mean: 80.5% Asian: 100% No	MDD NR Allowed, not managed	EOT: 8 wk Followup: 26 wk BDI (Chinese version) PHQ-9 (Chinese version) HRQOL: SDS ≥50% reduction in BDI Adherence	2 cCBT Waitlist	RCT Fair
Johansson, 2012[5]	Europe (Sweden) Newspaper advertisement, waitlist from prior study Government 121	Total: 45 (12.1) Total: 71.1% NR No	MDD MADRS >14 and <36 Allowed, not managed	EOT: 10 wk Followup: 6 mo BDI-1 MADRS BAI QOLI	3 Standard cCBT Tailored cCBT Attention control	RCT Fair

Study	Location Recruitment Setting Organization Total N	Age in Years (SD) % Female % Race/ethnicity Baseline differences?	Target Condition Baseline Severity Medications	Study Duration Outcomes Reported	Number of Arms Intervention Comparator	Design Quality
Kessler, 2009[6]	Europe (UK) Within 3 primary care centers Government 297	Grand mean: 34.95 (NA) Grand mean: 68% NR No	New episode of depression BDI ≥14 Allowed, not managed	EOT: 16 wk Followup: 34.8 wk HRQOL: SF-12 EQ5D BDI Reduction to BDI <10	2 IPCRESS study TAU	Cluster RCT Fair
Perini, 2009[7]	Australia Web University affiliated 48	Grand mean: 49.3 (NA) Grand mean: 76% NR No	MDD PHQ-9 >5 Allowed, not managed	EOT: 8 wk No followup BDI-II PHQ-9 Adherence Therapist productivity	2 cCBT Waitlist	RCT Fair
Titov, 2010[8]	Australia Website Government 141	Grand mean: 43.3 (NA) Grand mean: 73.3% NR No	MDD PHQ-9 Allowed, not managed	EOT: 9 wk Followup: 17.4 wk PHQ-9 BDI-II Adherence Therapist productivity	3 cCBT (clinician assisted) cCBT (technician assisted) Waitlist	RCT Good
Vernmark, 2010[9]	Europe (Sweden) University campus mail and newspaper; radio interview Government 88	Grand mean: 36.6 (NA) Grand mean: 68.2% NR No	MDD MADRS-S >14 Allowed, not managed	EOT: 8 wk Followup: 26 wk Quality of life inventory BID BAI MADRS-SR SCID (no depression diagnosis); value reflects N without depression Therapist productivity	3 cCBT (supported) cCBT (self-help) Waitlist	RCT Good
Williams, 2013[10]	Australia Website Government 297	Grand mean: 44.81 (NA) Grand mean: 76% NR No	MDD MINI NR	EOT: 11 wk No followup BDI-II PHQ-9 K10 AST-D SST STAI-T HRQoL	2 CBM + cCBT Waitlist	RCT Fair
Wright, 2005[11]	US (Kentucky) Advertisement, referral University affiliated 45	Grand mean: 40.2 (NA) Grand mean: 75.5% NR No	MDD, dysthymia BDI ≥14 Not allowed	EOT: 8 wk Followup: 26 wk HADS BDI Cognitive therapy awareness Adherence Therapist productivity	3 cCBT Standard CBT Waitlist	RCT Fair

Study	Location Recruitment Setting Organization Total N	Age in Years (SD) % Female % Race/ethnicity Baseline differences?	Target Condition Baseline Severity Medications	Study Duration Outcomes Reported	Number of Arms Intervention Comparator	Design Quality
Depressive symptoms (15 trials)						
Clarke, 2002[12]	US (Oregon) Mailing to HMO members Kaiser HMO 299	Grand mean: 43.9 (NA) Grand mean: 75.5% White: 94.5% No	MDD, minor depression NR Allowed, not managed	EOT: 17 wk Followup: 34.8 wk CES-D	2 cCBT Waitlist	RCT Good
de Graaf, 2009[13]	Europe (Netherlands) Mailed invitation to complete online screening questionnaire Government 303	Grand mean: 44.9 (NA) Grand mean: 55.7% NR No	Significant depressive symptoms BDI-II >16 Not allowed	EOT: 13 wk Followup: 52.1 wk SF-36 BDI-II BDI decrease ≥9 points WSAS Adherence	3 cCBT + TAU cCBT (no support) TAU	RCT Fair
Farrer, 2011[14]	Australia Callers to lifeline telephone counseling service Government 188	Grand mean: 41.0 (NA) Grand mean: 82.7% NR No	Significant depressive symptoms K10 ≥22 NR	EOT: 6 wk Followup: 26 wk CES-D CES-D <16 Adherence	3 cCBT (supported) cCBT (not supported) TAU	RCT Fair
Glozier, 2013[15]	Australia Recruited from cohort study University affiliated 562	Grand mean: 58.0 (NA) Grand mean: 61.4% NR No	Depression symptoms (mild to moderate) PHQ-9 >8 Allowed, not managed	EOT: 12 wk No followup PHQ-9 GAD-7 WHODAS	2 cCBT Attention control	RCT Good
Griffiths, 2012[16]	Australia Mailing to general population Government 355	Grand mean: 43.7 (NR) Grand mean: 70.0% NR No	Depressive symptoms K10 >22 NR	EOT: 13 wk Followup: 52.1 wk CES-D <16 Adherence	3 cCBT cCBT + internet support Attention control	RCT Fair
Hickie, 2010[17]	Australia Primary care Government 83	Grand mean: 33.4 (NA) Grand mean: 71.5% NR No	Significant depressive symptoms K10 >19 Not allowed	EOT: 8 wk Followup: 52.1 wk K10 <16	2 cCBT TAU	Cluster RCT Poor

Study	Location Recruitment Setting Organization Total N	Age in Years (SD) % Female % Race/ethnicity Baseline differences?	Target Condition Baseline Severity Medications	Study Duration Outcomes Reported	Number of Arms Intervention Comparator	Design Quality
Levin, 2011[18]	US (Oregon) Primary care Kaiser HMO 191	Grand mean: 43.5 (NA) Grand mean: 77% Grand mean: White: 90.15% Black: 2.2% Hispanic: 3.1% Asian: 0.5% Other: 4.1% No	Significant depressive symptoms NR Allowed, not managed	6 wk 26 wk SCID CES-D STAI S-STAI	2 cCBT (supported) TAU	RCT Good
Lintvedt, 2013[19]	Europe (Norway) University (mailed questionnaire to all students) University affiliated 163	28.2 (7.4) 76.7% NR No	Depressive symptoms 62.8% "unmet need for help" NR	8 wk No followup K10 screening CES-D ATQ Treatment depression literacy	2 Informational website + cCBT Waitlist/TAU	RCT Fair
McKinnon, 2008[20]	Australia Community (mailed questionnaire to participants from electoral roll) University affiliated 525	Grand mean: 36.0 (NA) Grand mean: 72.5% NR No	Significant depressive symptoms K10 ≥22 NR	EOT:6 wk Followup:52 wk CES-D ATQ	3 cCBT Information control (Blue Pages) Attention control	RCT Fair
Moritz, 2012[21]	Western Europe (Germany) Online advertising University affiliated 210	Grand mean: 38.6 (NA) Grand mean: 78.6% NR No	Depressive symptoms NR Allowed, not managed	EOT: 8 wk No followup BDI-II DAS WHOQOL	2 cCBT Waitlist	RCT Fair
Spek, 2007[22]	Europe (Netherlands) Mail; newspaper and letter of invitation to all older adults in the city Government 301	Grand mean: 54.7 (NA) Grand mean: 63.4% NR No	Minor depression Edinburgh depression scale >12 NR	10 wk 52.1 wk BDI-II Adherence	3 cCBT Group CBT Waitlist	RCT Good
van Bastelaar, 2008[23]	Europe (Netherlands) Web/mail: Open-access study website University medical center 255	Total: 50.0 (12.0) Total: 61% White: 89% Yes	MDD, dysthymia, minor depression, or significant depressive symptoms and type 1 or type 2 diabetes mellitus CES-D ≥16 Allowed, not managed	12 wk No followup Perceived health status: SF-12 CES-D PAID (diabetes-specific emotional distress) Adherence	2 cCBT Waitlist	RCT Poor

Study	Location Recruitment Setting Organization Total N	Age in Years (SD) % Female % Race/ethnicity Baseline differences?	Target Condition Baseline Severity Medications	Study Duration Outcomes Reported	Number of Arms Intervention Comparator	Design Quality
van der Zanden, 2012[24]	Europe (Netherlands) Advertisement: promotional material in physician's office and educational institutions and websites Mental health clinics 244	Total: 20.9 (2.2) Total 84.4% NR No	Significant depressive symptoms CES-D: 10 to 45 NR	EOT: 12 wk Followup: 6 mo CES-D HADS Adherence	2 cCBT Waitlist	RCT Fair
Wagner, 2013[25]	Europe (Germany, Switzerland) Advertisements in newspapers, local facilities, university websites Government 62	Grand mean: 38.0 Grand mean: 65% NR Yes: gender	Depressive symptoms BDI-II Grand mean: 23.2 Allowed, not managed	EOT: 8 wk Followup: 3 mo BDI-II BSI SCL anxiety subscale ATQ	2 cCBT Face-to-face	RCT Fair
Warmerdam, 2008[26]	Europe (Netherlands) Website, newspaper advertisement Government 263	Grand mean: 45.0 (NA) Grand mean: 71.1% NR No	Significant depressive symptoms CES-D ≥16 NR	EOT: 8 wk No followup EQ5D CES-D HADS Clinically significant change Adherence Therapist productivity Cost	3 cCBT PST Waitlist	RCT Fair
Mixed depression and anxiety (3 trials)						
Newby, 2013[27]	Australia Previous interest, internet advertising University affiliated 109	44.30(12.2) 77.8% NR Yes	GAD and/or MDD MINI Allowed, not managed	EOT: 10 wk Followup: 3 mo PHQ-9 GAD-7 WHODAS-II Adherence	2 cCBT Waitlist	RCT Good
Proudfoot, 2003[28]	Europe (UK) Primary care Government 274	Grand mean: 43.5 (NA) Grand mean: 73.8% Grand mean: White: 80% Black: 3.6% Asian: 1.95% Other: 4.75% No	Minor depression, significant depressive symptoms, GAD, panic disorder, anxiety NOS, significant anxiety symptoms, and phobia GHQ-12 ≥4 CIS-R ≥12 Not allowed	EOT: 9 wk Followup: 26 wk WSAS BDI BAI Hospitalization Cost	2 cCBT TAU	RCT Fair

Study	Location Recruitment Setting Organization Total N	Age in Years (SD) % Female % Race/ethnicity Baseline differences?	Target Condition Baseline Severity Medications	Study Duration Outcomes Reported	Number of Arms Intervention Comparator	Design Quality
Proudfoot, 2004[29]	Europe (UK) Primary care General practice in London and southeast England 167	Grand mean: 44.7 (NA) Grand mean: 73.7% Grand mean: White: 88% Black: 5% Asian: 3.5% Other: 4% No	Significant depressive symptoms, anxiety NOS, significant anxiety symptoms, and other (anxious and/or depressed) GHQ-12 ≥4 CIS-R (PROQSY) ≥12 Not allowed	EOT: 89 wk Followup: 26 wk WSAS BDI BAI	2 cCBT TAU	RCT Fair
Generalized anxiety disorder (4 trials)						
Andersson, 2012[30]	Europe (Sweden) Advertisement (website, newspaper) Not described 81	Grand mean: 42 (NA) Grand mean: 76% NR No	GAD NR Allowed, not managed	EOT: 8 wk Followup: 21 to 22 wk QOLI BDI-II PSWQ BAI (0-63) Adherence	2 cCBT Waitlist	RCT Good
Paxling, 2011[31]	Europe (Sweden) Advertisement in newspaper, website Academic clinics 89	Grand mean: 39.3 (NA) Grand mean: 80% NR No	GAD PSWQ >53 GAD-Q-IV >5.7 Allowed, not managed	EOT: 8 wk Followup: 52.1 wk QOLI BDI PSWQ BAI Adherence	2 cCBT Waitlist	RCT Fair
Robinson, 2010[32]	Australia Website www.virtualclinic.org.au NR 150	Grand mean:47(NA) Grand mean: 68.4% NR Yes: marital status, age	GAD NR Allowed, not managed	EOT: 11 wk Followup: 13 wk PHQ-9 PSWQ GAD-7 Therapist productivity	3 cCBT (clinician) cCBT (technician) Waitlist	RCT Good
Titov, 2009[33]	Australia Website www.virtualclinic.org.au Government 48	Total: 44.0 (12.98) Total: 75% NR No	GAD GAD section of MINI to determine if patient met DSM-IV criteria for GAD Allowed, not managed	EOT: 10 wk No followup SDS PHQ-9 PSWQ GAD-7	2 cCBT Waitlist	RCT Fair

Study	Location Recruitment Setting Organization Total N	Age in Years (SD) % Female % Race/ethnicity Baseline differences?	Target Condition Baseline Severity Medications	Study Duration Outcomes Reported	Number of Arms Intervention Comparator	Design Quality
Panic disorder (10 trials)						
Bergstrom, 2010[34]	Europe (Sweden) Primary care, self-referral Government 113	Grand mean: 34.2 (NA) Grand mean: 61.5% NR No	Panic disorder DSM-IV criteria for panic disorder with or without agoraphobia on MINI Allowed, not managed	EOT: 10 wk Followup: 26 wk SDS MADRS ASI PDSS Response on PDSS ≥40% Cost	2 cCBT Group CBT	RCT Good
Carlbring, 2001[35]	Europe (Sweden) Website and mail advertisement Government 31	Total: 34 (7.5); range (21 to 51) Total: 70.7% NR No	Panic disorder No Allowed, not managed	6 to 14 wk postrandomization QOLI BDI BAI MADRAS-SR Therapist productivity	2 cCBT Waitlist	RCT Poor
Carlbring, 2005[36]	Europe (Sweden) Waitlist of participants from Carlbring, 2001, study Government 49	Grand mean: 35.0 (NA) Grand mean: 71.5% NR No	Panic disorder No Allowed, not managed	EOT: 10 wk Followup: 52 wk QOLI MADRS-SR BDI BAI ACQ Adherence	2 cCBT Face-to-face CBT	RCT Fair
Carlbring, 2006[37]	Europe (Sweden) Waitlist of people who had expressed interest in participating in internet-administered self-help program on panic disorder Government 60	Total: 36.7 (10.0) Total: 60% NR No	Panic disorder DSM-IV criteria for panic disorder Allowed, not managed	EOT: 10 wk Followup: 9 mo QOLI MADRS BDI BAI Body sensations Questionnaire Adherence	2 cCBT Waitlist	RCT Good
Kenardy, 2003[38]	Europe (Scotland) and Australia Primary care and mental health specialty University affiliated 121	Total: 36.8 (10.0) Total: 75.5% NR Yes: education	Panic disorder No Allowed, not managed	EOT: 3 wk Followup: 26 wk Composite panic-anxiety measure STAI-Trait Change on STAI-Trait Cost	3 cCBT Face-to-face Waitlist	RCT Fair

Study	Location Recruitment Setting Organization Total N	Age in Years (SD) % Female % Race/ethnicity Baseline differences?	Target Condition Baseline Severity Medications	Study Duration Outcomes Reported	Number of Arms Intervention Comparator	Design Quality
Kiropoulos, 2008[39]	Australia Website, advertisement Government 86	Total Age: 39.0 (11.13) Grand mean: 72.5% NR No	Panic disorder No Allowed, not managed	EOT: 12 wk No followup WHO QOL DASS ADIS clinician overall panic disorder rating PDSS Adherence Therapist productivity	2 cCBT Face-to-face	RCT Good
Klein, 2006[40]	Australia Website, mail advertisement Government 55	Range: 18 to 70 years Total: 81% NR NR	Panic disorder No Allowed, not managed	EOT: 12 wk Followup: 3 mo HRQOL "health rating" DASS depression PDSS (interview) BVS Panic disorder clinician ratings Adherence Therapist productivity Cost	2 cCBT Information control	RCT Fair
Richards, 2006[41]	Australia Website, advertisement Government 32	Grand mean: 36.9 (NA) Grand mean: 30.7% NR Yes: gender	Panic disorder 2 points greater than any secondary diagnosis on the clinician's 9-point severity rating scale in the ADIS-IV Allowed, not managed	EOT: 8 wk Followup: 13 wk QOL (psychological) DASS (depression) PDSS ACQ Therapist productivity GP visits pre-post	3 cCBT cCBT + stress management Information control	RCT Poor
Silfvernagel, 2012[42]	Europe (Sweden) Information on web; recruited via email Not specified 57	Grand mean: 32.4 (NA) Grand mean: 64.8% NR Yes: gender	Panic symptoms with significant comorbid depressive or anxiety symptoms No Allowed, not managed	EOT: 8 wk Followup: 60 wk QOLI MADRS-S PDSS BAI PDSS score decrease by ≥40% Adherence (# of patients completed sessions) Therapist productivity	2 cCBT Waitlist	RCT Fair
Wims, 2010[43]	Australia Website University affiliated 141	Grand mean: 42.3 (NA) Grand mean: 76% NR No	Panic disorder No Allowed, not managed	EOT: 9 wk Followup: 13 wk SDS PHQ-9 ACQ PDSS Adherence Therapist productivity	2 cCBT Waitlist	RCT Good

Study	Location Recruitment Setting Organization Total N	Age in Years (SD) % Female % Race/ethnicity Baseline differences?	Target Condition Baseline Severity Medications	Study Duration Outcomes Reported	Number of Arms Intervention Comparator	Design Quality
PTSD (2 trials)						
Litz, 2007[44]	US Advertisement on website U.S. Department of Defense 45	Grand mean: 39.2 (NA) Grand mean: 22% Black: 77.5% No	PTSD NR Allowed, not managed	EOT: 8 wk Followup: 6 mo PTSD-SS BDI-II BAI	2 cCBT Internet support group	RCT Fair
Spence, 2011[45]	Australia Website www.virtualclinic.org.au, email newsletter from www.beyondblue.org.au, mail advertisement, local newspaper NR 44	Grand mean: 42.5 (NA) Grand mean: 81.5% NR No	PTSD No Allowed, not managed	EOT: 8 wk Followup: 13 wk PHQ-9 PCL-C GAD-7 SDS Therapist productivity	2 cCBT Waitlist	RCT Fair
Anxiety symptoms (2 trials)						
Kenardy, 2006[46]	Australia Psychology class Academic clinics 83	Total: 20.7 (6.29) Total: 78.3% NR NR	Significant anxiety symptoms Anxiety sensitivity >24 Not allowed	EOT: 6 wk Followup: 26 wk CES-D ASI BSQ Adherence	2 cCBT Waitlist	RCT Poor
Ruwaard, 2010[47]	Europe (Netherlands) Website, mail advertisement Government 58	Grand mean: 38.5 (NA) Grand mean: 73% NR Yes: gender	Greater than or equal to subsyndromal panic disorder NR Allowed, not managed	EOT: 13 wk (variable) Followup: 156 wk DASS-Depression PDSS-SR PDSS-SR Responder (<8) BSQ Therapist productivity	2 cCBT Waitlist	RCT Fair

Table D-2. Program components of cCBT interventions

Study Program Name cCBT Level	Behavior Activation	Cognitive Restructuring	Exposure	Interpersonal Skills Assertiveness	Lifestyle Factors	Problem Solving	Relapse Prevention	Relaxation Training	Other Components
Major depressive disorder: 11 trials, 15 arms									
Andersson, 2005[1] No name cCBT-S	Yes	Yes	No	NR	Yes	NR	Yes	NR	NR
Berger, 2011[2] DEPREXIS Arm 1: cCBT-S Arm 2: cCBT-NS	Yes	Yes	No	Yes	Yes	Yes	NR	Yes	Arm 1: Psychoeducation, dreamwork, emotional work Arm 2: NA
Carlbring, 2013[3] Depressionshjälpen cCBT-S	Yes	Yes	No	NR	Yes	NR	Yes	NR	Acceptance and commitment therapy—mindfulness
Choi, 2012[4] SADNESS (adapted to Chinese) cCBT-LS	Yes	Yes	No	Yes	Yes	Yes	NR	NR	NR
Johansson, 2012[5] No name Arm 1: cCBT-S Arm 2: cCBT-S	Yes	Yes	No	NR	Yes	Yes (Tailored only)	Yes	Yes (Tailored only)	Arm 1: Tailored sleep management, mindfulness, Arm 2: Panic, social anxiety, worrying stress
Kessler, 2009[6] No name cCBT-LS	55 minutes of instant messaging for 10 sessions	NA	No	NA	NA	NA	NA	NA	NR
Perini, 2009[7] SADNESS cCBT-S	Yes	Yes	No	Yes	Yes	Yes	NR	NR	NR
Titov, 2010[8] SADNESS Arm 1: cCBT-LS Arm 2: cCBT-LS	Yes	Yes	No	Yes	Yes	Yes	NR	Yes	Arm 1: Topics that came up on discussion forum Arm 2: Program script only
Vernmark, 2010[9] No name Arm 1: cCBT-S Arm 2: cCBT-S	Yes	Yes	No	NR	Yes	NR	Yes	NR	Arm 1: Goal setting Arm 2: Topics that came up while tailoring to the individual patient

Study Program Name cCBT Level	Behavior Activation	Cognitive Restructuring	Exposure	Interpersonal Skills Assertiveness	Lifestyle Factors	Problem Solving	Relapse Prevention	Relaxation Training	Other Components
Williams, 2013[10] CBM +Sadness CBT-LS	Yes	Yes	No	Yes	Yes	Yes	NR	NR	Cognitive bias modification
Wright, 2005[11] No name cCBT-AT	Yes	Yes x 3	No	NR	Yes	Yes	Yes	NR	Task breakdown
Depressive symptoms: 15 trials, 19 arms									
Clarke, 2002[12] Overcoming Depression via the Internet cCBT-NS	NR	Yes	No	NR	NR	NR	NR	NR	Skills training, psychoeducation
de Graaf, 2009[13] CYL[a] + treatment as usual Arm 1: cCBT-NS Arm 2: cCBT-NS	NR	NR	No	Yes	NR	Yes	NR	NR	Arm 1: Stress management, planning Arm 2: NA
Farrer, 2011[14] MoodGYM Arm 1: cCBT-LS Arm 2: cCBT-NS	Yes	Yes	No	Yes	NR	Yes	NR	Yes	Arm 1: Psychoeducation Arm 2: NA
Glozier, 2013[15] E-couch cCBT-NS	NR	Yes	No	Yes	Yes	NR	NR	NR	Psychoeducation based on Blue Pages
Griffiths, 2012[16] E-couch Arm 1: cCBT-NS Arm 2: cCBT-NS	NR	NR	No	Yes	Yes	NR	NR	Yes	Arm 1: Psychoeducation, internet support group Arm 2: Psychoeducation
Hickie, 2010[17] MoodGYM cCBT-NS	Yes	Yes	No	Yes	NR	Yes	NR	Yes	Psychoeducation
Levin, 2011[18] Wellness Workshop[a] cCBT-NS	Yes	Yes	No	Yes	Yes	Yes	NR	Yes	NA

Study Program Name cCBT Level	Behavior Activation	Cognitive Restructuring	Exposure	Interpersonal Skills Assertiveness	Lifestyle Factors	Problem Solving	Relapse Prevention	Relaxation Training	Other Components
Lintvedt, 2013[19] MoodGYM + Blue Pages cCBT-NS	Yes	Yes	No	Yes	Yes	NR	NR	Yes	Psychoeducation
McKinnon, 2008 #290[20] MoodGYM cCBT-S	Yes	Yes	No	Yes	NR	Yes	NR	Yes	Psychoeducation
Moritz, 2012[21] Deprexis cCBT-NS	Yes	Yes	No	Yes	Yes	Yes	NR	Yes	Arm 1: Psychoeducation, dreamwork, emotional work Arm 2: NA
Spek, 2007[22] No name[a] cCBT-NS	Yes	Yes	No	Yes	NR	NR	NR	Yes	Psychoeducation
van Bastelaar, 2008[23] CYL-DM[a] cCBT-S	Yes	Yes	No	Yes	Yes	Yes	NR	Yes	Adapted specifically for patients with diabetes
van der Zanden, 2012[24] Master Your Mood[a] cCBT-LS	Yes	Yes	No	Yes	NR	NR	Yes	NR	Psychoeducation
Wagner, 2013[25] No name cCBT-S	Yes	Yes	No	Yes	NR	NR	Yes	NR	Psychoeducation
Warmerdam, 2008[26] No named programs Arm 1: cCBT-S[a] Arm 2: cCBT-S	Arm 1: Yes Arm 2: No	Yes	No	Yes	NR	Arm 1: NR Arm 2: Yes	Yes	NR	Arm 1: Psychoeducation, based on classic CBT[a] Arm 2:Based on classic problem-solving therapy
Mixed depression and anxiety: 3 trials, 3 arms									
Newby, 2013[27] Worry and Sadness Program cCBT-LS	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Psychoeducation
Proudfoot, 2003[28] Beating the Blues cCBT-NS	Yes	Yes x 3	No	NR	Yes	Yes	Yes	NR	Introduction is psychoeducation, goal-setting planning; task breakdown

Study Program Name cCBT Level	Behavior Activation	Cognitive Restructuring	Exposure	Interpersonal Skills Assertiveness	Lifestyle Factors	Problem Solving	Relapse Prevention	Relaxation Training	Other Components
Proudfoot, 2004[29] Beating the Blues cCBT-LS	Yes	Yes x 3	No	NR	Yes	Yes	Yes	NR	Introduction is psychoeducation, goal-setting planning; task breakdown
Generalized anxiety disorder: 4 trials, 5 arms									
Andersson, 2012[30] No name cCBT-S	NR	Yes	Yes	Yes	Yes	Yes	NR	Yes	Psychoeducation, worry exposure
Paxling, 2011[31] No name cCBT-S	NR	Yes	Yes	Yes	Yes	Yes	NR	Yes	Psychoeducation, worry exposure
Robinson, 2010[32] Worry program Arm 1: cCBT-LS (clinician) Arm 2: cCBT-LS (technician)	NR	Yes	Yes	Yes	Yes	Yes	NR	Yes	Arm 1: Psychoeducation, worry exposure, online discussion forum Arm 2: Same, but no forum
Titov, 2009[33] Worry program cCBT-LS	NR	Yes	Yes	Yes	Yes	Yes	NR	Yes	Psychoeducation, worry exposure
Panic disorder: 10 trials, 11 arms									
Bergstrom, 2010[34] No name cCBT-S	NR	Yes	Yes	NR	NR	NR	Yes	NR	Psychoeducation, panic exposure
Carlbring, 2001[35] No name cCBT-S	NR	Yes	Yes	Yes	NR	NR	Yes	Yes (breathing)	Psychoeducation, panic exposure
Carlbring, 2005[36] No name cCBT-S	NR	Yes	Yes	Yes	NR	NR	Yes	Yes (breathing)	Psychoeducation, panic exposure
Carlbring, 2006[37] No name cCBT-LS	NR	Yes	Yes	Yes	NR	NR	Yes	Yes (breathing)	Psychoeducation, panic exposure
Kenardy, 2003[38] No name cCBT-AT	NR	Yes	Yes	NR	NR	NR	NR	Yes (breathing)	Goal-setting, panic exposure

Study Program Name cCBT Level	Behavior Activation	Cognitive Restructuring	Exposure	Interpersonal Skills Assertiveness	Lifestyle Factors	Problem Solving	Relapse Prevention	Relaxation Training	Other Components
Kiropoulos, 2008[39] Panic Online cCBT-S	NR	Yes	Yes	NR	NR	NR	Yes	Yes	Psychoeducation, panic exposure
Klein, 2006[40] Panic Online cCBT-S	NR	Yes	Yes	NR	NR	NR	Yes	Yes	Psychoeducation, panic exposure
Richards, 2006[41] Panic Online Arm 1: cCBT-S Arm 2: cCBT-S	NR	Yes	Yes	Arm1: NR Arm 2: Yes in stress modules	Arm1: NR Arm 2: Yes in stress modules	NR	Yes	Yes	Arm 1: Psychoeducation, panic exposure Arm 2: Same + 6 modules on stress management
Silfvernagel, 2012[42] No name cCBT-S	NR	NR	Yes	NR	NR	NR	Yes	NR	Psychoeducation, panic exposure
Wims, 2010[43] Panic Program cCBT-S	NR	Yes	Yes	NR	NR	NR	Yes	NR	Psychoeducation, de-arousal, panic exposure
PTSD: 2 trials, 2 arms									
Litz, 2007[44] DE-STRESS cCBT-LS	Yes	NR	Yes	NR	NR	NR	Yes	Yes	Planning, trauma exposure, stress management
Spence, 2011[45] No name cCBT-LS	Yes	Yes	Yes	Yes	Yes	Managing panic attacks	Yes	NR	De-arousal, trauma exposure
Anxiety symptoms: 2 trials, 2 arms									
Kenardy, 2006[46] Anxiety Prevention Program cCBT-S	NR	Yes	Yes	NR	NR	NR	Yes	Yes	Psychoeducation, anxiety exposure
Ruwaard, 2010[47] Interapy cCBT-S	NR	Yes	Yes	NR	NR	NR	Yes	Yes	Psychoeducation, awareness, anxiety exposure

[a] Interventions that are loosely based on Lewinsohn's model of depression: Lewinsohn PM, Youngren MA, Grosscup SJ. Reinforcement and depression. In RA Dupue (Ed*.),* The psychobiology of depressive disorders: Implications for the effects of stress (pp. 291-316). New York: Academic Press, 1979.

Table D-3. General characteristics of cCBT interventions

Study Comparison and Arm (if applicable)	Recruitment	Clinical Context	Program Name	Setting	Technical Support	Duration (Weeks)	Module Number	Planned Contacts
Major depressive disorder: 11 trials, 15 arms								
Andersson, 2005[1] cCBT-S vs. AC	Advertisements in newspapers	Not established, but AC was moderated online group	No name	Nonclinical	NR	8-10	5	≥6
Berger, 2009[2] Arm 1: cCBT-S vs. cCBT-NS Arm 2:cCBT-NS vs. WL	Advertisement and website	No established clinical relationship	Deprexis®	Nonclinical	NR	10	10	10
Carlbring, 2013[3] cCBT-S vs. WL	Advertisement and website	No established clinical relationship	*Depression-shjälpen*	Nonclinical	Yes	8	7	7
Choi, 2012[4] cCBT-LS vs. WL	Mass media (unspecified)	No established clinical relationship	Sadness (adapted to Chinese)	Nonclinical	NR	8	6	6
Johansson, 2012[5] Arm 1: cCBT-S (standard) Arm 2: cCBT-S (tailored) vs. AC	Advertisements in newspaper (waiting list)	No established clinical relationship	No name	Nonclinical	Yes	10	8 (standard) 8-10 (tailored)	10
Kessler, 2009[6] cCBT-LS vs. TAU	Primary care	Yes, medical home	No name	Nonclinical	NR	16	10	10
Perini, 2009[7] cCBT-S vs. WL	Website	No established clinical relationship	Sadness	Nonclinical	NR	8	6	6
Titov, 2010[8] Arm 1: cCBT-LS (clinician) vs. cCBT-LS (technician) Arm 2: cCBT-LS (either) vs. WL	Website virtualclinic.org.au	No established clinical relationship	Sadness	Nonclinical	NR	8	6	≥6
Vernmark, 2010[9] Arm 1: cCBT-S vs. cCBT-NS Arm 2: cCBT-S vs. WL	University mail newspaper and radio	No established clinical relationship	No name	Nonclinical	Yes	8	7	Variable, minimum 8
Williams, 2013[10] cCBT-LS vs. WL	Website	No established relationship	CBM + Sadness	Non clinical	Yes	11 (1 CBM, 10 CBT)	CBM=7 sessions CBT=6 modules	NR
Wright, 2005[11] cCBT-AT vs. WL	Advertisement or referral	Yes, medical home at university-affiliated psychiatric hospital	No name	Clinical	Yes, in person	8–9	8	9
Depressive symptoms: 15 trials, 19 arms								
Clarke, 2002[12] cCBT-NS vs. WL	Mailing to HMO members	Yes, had medical home	ODIN	Nonclinical	NR	NR	7	NA

Study Comparison and Arm (if applicable)	Recruitment	Clinical Context	Program Name	Setting	Technical Support	Duration (Weeks)	Module Number	Planned Contacts
de Graaf, 2009[13] Arm 1: cCBT-NS + TAU vs. cCBT-NS or WL Arm 2: cCBT-NS vs. TAU	Mailed invitation to the general population	No established clinical relationship	a) CYL + TAU b) CYL only	Nonclinical	No	8 plus 9th booster session	9	4-5 consults with GP NA for cCBT arm
Farrer, 2011[14] Arm 1: cCBT-LS vs. cCBT-NS Arm 2: cCBT-NS vs. TAU	Callers to 24-hr telephone counseling service were invited to participate	No established clinical relationship	Blue Pages and MoodGYM	Nonclinical	a) Yes, via phone b) No	6	6	a) 6 b) none
Glozier, 2013[15] cCBT-NS vs. AC	Recruited through cohort study (age:≥45 yrs)	No established clinical relationship	E-couch	Nonclinical	Yes	12	12	NR
Griffiths, 2012 [16] Arm 1: cCBT-NS + ISG vs. cCBT-NS Arm 2: cCBT-NS vs. AC	Mailing to general populations	No established clinical relationship	a) E-couch (with ISG) b) E-couch	Nonclinical	No	12	12	NA
Hickie, 2010[17] cCBT-NS vs. TAU	Primary care	Yes, medical home	MoodGYM	Nonclinical	No	8 (for taking five 20-40 min modules)	5	NA
Levin, 2011[18] cCBT-S vs. TAU	Primary care	Yes, medical home	Wellness Workshop CD	Nonclinical	Yes, once via phone	6	5	1
Lintvedt, 2013[19] cCBT-NS vs. WL	Mailing to all registered students	No established clinical relationship	MoodGYM + Blue Pages	Nonclinical	NR	8	5	NA
McKinnon, 2008[20] cCBT-S vs. AC/IC (lifestyle)	Mailed questionnaire via voter rolls	No established clinical relationship	MoodGYM	Nonclinical	Yes, via phone	6	5	6
Moritz, 2012[21] cCBT-NS vs. WL	Online advertising	No established clinical relationship	Deprexis	Nonclinical	NR	8	10	NR
Spek, 2007 [22] cCBT-NS vs. traditional CBT or WL	Mailed invitation letter to all older adults	No established clinical relationship	Based on CWD	Nonclinical	Yes, could call or email	10	8	NA
van Bastelaar, 2008[23] cCBT-S vs. WL	Website/mail: Open-access study website	No established clinical relationship	CYL-DM	Nonclinical	No	8	8	8
Van der Zanden, 2012[24] cCBT-LS vs. WL	Mixed ads: GP offices, educational institutions, websites	Population was mixed: some had GP and others may not have had GP relationship	Master Your Mood	Nonclinical	NR	6	6	6
Wagner, 2013[25] cCBT-S vs. Face-to-face	Newspaper advertisements, websites, local facilities	No established clinical relationship	No name	Nonclinical	Yes, via therapist	8	8	16
Warmerdam, 2008[26] Arm 1: cCBT-S vs. WL Arm 2: cPST-S vs. WL	Website and newspaper advertisement	No established clinical relationship	a) CWD b) PST	Nonclinical	No	a) 8 9th (review) 12 wk later b) 5	a) 8 b) 5	a) 8 b) At least 5

Study Comparison and Arm (if applicable)	Recruitment	Clinical Context	Program Name	Setting	Technical Support	Duration (Weeks)	Module Number	Planned Contacts
Mixed depression and anxiety: 3 trials, 3 arms								
Newby, 2013[27] cCBT-LS vs. WL	Waitlist from previous studies and online advertising	No established clinical relationship	Worry and Sadness Program	Nonclinical	NR	10	6 (with additional supple-mental modules)	NR; received regular contact via email and telephone
Proudfoot, 2003[28] cCBT-NS vs. TAU	Primary care	Yes, medical home	Beating the Blues®	Clinical, GP clinics	Yes, limited from RN	8	1, 15-min intro video, then 8 modules	NR
Proudfoot, 2004[29] cCBT-NS vs. TAU	Primary care	Yes, medical home	Beating the Blues®	Clinical, GP clinics	Yes, limited from RN	8	1, 15-min intro video, then 8 modules	NR
Generalized anxiety disorder: 4 trials, 5 arms								
Anderson, 2012[30] cCBT-S vs. WL	Advertisement (Website and newspaper)	No established clinical relationship	No name	Nonclinical	NR	8	8	8
Paxling, 2011[31] cCBT-S vs. WL	Advertisement (newspaper and website) to general population	No established clinical relationship	No name	Nonclinical	NR	8	8	8
Robinson, 2010[32] Arm 1: cCBT-LS (clinician) vs. WL Arm 2: cCBT-LS (technician) vs. WL	Website www.virtualclinic.org.au	No established clinical relationship	Worry Program	Nonclinical	yes	10	6	At least 6
Titov, 2009[33] cCBT-LS vs. WL	Website www.virtualclinic.org.au	No established clinical relationship	Worry Program	Nonclinical	NR	9	6	Variable depending on patient's questions
Panic disorder: 10 trials, 11 arms								
Bergstrom, 2010[34] cCBT-S vs. traditional CBT	Primary care or self-referral	May or may not have medical home	No name	Nonclinical	NR	10	10	10 or more
Carlbring, 2001[35] cCBT-S vs. WL	Website for panic disorder and mass media advertisements	May or may not have had clinical relationship	No name	Nonclinical	NR	6–12	6	At least 6
Carlbring, 2005[36] cCBT-S vs. F2F	Recruited from WL from another study (initially, website or media ad)	May or may not have had clinical relationship	No name	Nonclinical	NR	10	10	At least 1 per wk
Carlbring, 2006[37] cCBT-LS vs. WL	Recruited from WL from another study (initially, website or media ad)	May or may not have had clinical relationship	No name	Nonclinical	NR	10	10	At least 1 per wk

Study Comparison and Arm (if applicable)	Recruitment	Clinical Context	Program Name	Setting	Technical Support	Duration (Weeks)	Module Number	Planned Contacts
Kenardy, 2003[38] cCBT-AT vs. WL	Primary care and mental health specialty	Yes, medical home	No name	Nonclinical (palmtop)	NR	6	6	6
Kiroupolos, 2008[39] cCBT-S vs. F2F	Website advertisement	No established clinical relationship	Panic Online	Nonclinical	NR	12	6	6
Klein, 2006[40] cCBT-S vs. IC	Website and mail advertisement	No established clinical relationship	Panic Online	Nonclinical	NR	6	6	6
Richards, 2006[41] Arm 1: cCBT-S vs. IC Arm 2: cCBT-S + SM vs. IC	From panic website, links to other mental health websites and mass media	No established clinical relationship	a) Panic Online b) Panic Online + stress management	Nonclinical	Yes, via therapist	8	a) 6 Panic Online b) 6 Panic Online, 6 stress management	Variable
Silfvernagel, 2012[42] cCBT-S vs. WL	Information on website; recruited via email	No established clinical relationship	No name	Nonclinical	NR	8	6-8 (2 fixed, 4-6 chosen from menu)	Variable, but minimum of 8
Wims, 2010[43] cCBT-S vs. WL	Website gave information about study, link to apply to study	No established clinical relationship	Panic Program	Nonclinical	NR	8	6	Variable
PTSD: 2 trials, 2 arms								
Litz, 2007[44] cCBT-LS vs. AC (self-monitor ADL)	Ad on Department of Defense website (PTSD from 9/11 Pentagon attack)	May or may not have had clinical relationship with VA or other medical facility	DE-STRESS	Nonclinical	yes	8	8	8 or more, variable
Spence, 2011[45] cCBT-LS vs. WL	Email news and mail, newspaper ads referring to website www.virtualclinic.org.au	No established clinical relationship	No name	Nonclinical	Yes	8	7	8 or more, variable
Anxiety symptoms: 2 trials, 2 arms								
Kenardy, 2006[46] cCBT-NS vs. WL	Psychology classes	No established clinical relationship	No name	Nonclinical	NO	6	6	NA
Ruwaard, 2010[47] cCBT-S vs. WL	Mail and media advertisements referred to a website	No established clinical relationship	Interapy	Nonclinical	NR	11	7	14 "feedback moments"

Table D-4. Type and intensity of support in cCBT interventions

Study	cCBT level Program Name[a]	Therapist Training	Therapist Time per Patient	Email or Text	Phone	Online Group Component	Instant Messaging	Face to Face
Major depressive disorder: 11 trials, 15 arms								
Andersson, 2005[1]	cCBT-S No name	NR	NR	Feedback on end of module quizzes	NR	Moderated discussion group	NR	No
Berger, 2011[2]	Arm 1: cCBT-S Deprexis Arm 2: cCBT-NS	Arm 1: licensed professionals & supervised students Arm 2: NA	Arm 1: 10 min per session Arm 2: NA	Arm 1: Supportive feedback via email from therapist weekly Arm 2: Program is interactive	NR	NR	NR	No
Carlbring, 2013[3]	cCBT-S *Depressionshjalpen*	Supervised PhD students	12 min (average)/wk	Feedback support	NR	No	NR	No
Choi, 2012[4]	cCBT-LS Sadness (adapted to Chinese)	Supervised PhD graduate student	NR, variable because over phone	Autoreminders	Yes, weekly	No, but access to prior transcriptions	No	No
Johansson, 2012[5]	Arm 1: CCBT-S (Standard) No name Arm 2: cCBT-S (tailored)	Supervised MS graduate students	Arm1 standard 74.1 min total, 9.3 min/ module Arm 2 tailored 95.2 min total, 9.7 min/ module	Feedback on homework support	NR	Control was online discussion group	No	No
Kessler, 2009[6]	cCBT-LS No name	Licensed MS or PhD	55 min/ session	Autoreminders	No	No	Yes, entire session	No
Perini, 2009[7]	cCBT-S Sadness	PhD	Variable; emailed response to forum post within 24 hr	Autoreminders, reinforcement and feedback	NR	Discussion forum	No	No
Titov, 2010[8]	Arm 1: cCBT-LS SADNESS Arm2: cCBT-LS	Arm 1: clinician Arm 2: technician	Average 10 min per session by forum, email or phone	Arm 1: feedback, goal-setting, problem-solving, therapeutic strategies Arm 2: scripted feedback on module and support	Yes, weekly	Arm 1: Moderated discussion forum Arm 2: No	No	No
Vernmark, 2010[9]	Arm 1: cCBT-S (self-help) No name Arm 2: cCBT-S (tailored)	Supervised master's students	Arm 1: 53 ± 28 min For all sessions Arm 2: 509 ±176 min	Arm 1: Supportive feedback on progress Arm 2: All materials and discussion over individualized, tailored email	Only if no response to email	No	No	No
Williams, 2013[10]	CCBT-LS Sadness	Licensed MS or PhD	NR, but no difference between groups	Email support but no feedback on homework	Yes	No	No	No
Wright, 2005[11]	cCBT-AT No name	PhD, master, MD, LCSW	25 min/ 50 min session	NR	NR	No	No	Yes

Study	cCBT level Program Name[a]	Therapist Training	Therapist Time per Patient	Email or Text	Phone	Online Group Component	Instant Messaging	Face to Face
Depressive symptoms: 15 trials, 19 arms								
Clarke, 2002[12]	cCBT-NS ODIN	NA	NA	NR	NA	NA	NA	No
de Graaf, 2009[13]	Arm 1: cCBT-NS CYL + TAU Arm 2: cCBT-NS CYL	Arm 1: GP for TAU Arm 2: NA	NA	Arm 1: If part of TAU Arm 2: NA	Arm 1: If part of TAU Arm 2: NA	NA	NA	No
Farrer, 2011[14]	cCBT-LS MoodGYM cCBT-NS	Arm 1: Lay crisis counselor Arm 2: NA	Arm 1: NR Arm 2: NA	Feedback on homework is automated within program	Arm 1: Yes, for weekly support Arm 2: NA	NA	NA	No
Glazier, 2013[15]	cCBT-NS E-couch	Arm 1: NA Arm 2: NA	NA	Reminders to complete next module	Reminders to complete next module	NR	NR	No
Griffiths, 2012[16]	Arm 1: cCBT-NS eCOUCH + ISG Arm 2: cCBT-NS eCOUCH	Arm 1: No therapist Arm 2: No therapist	NA - staff only moderated forum to enforce rules	Autoreminders via email	Automated phone reminder if needed	Arm 1: Support forum moderated only for rules Arm 2: NA	NA	No
Hickie, 2010[17]	cCBT-NS MoodGYM	NA	NA	NR	No	NR	NR	No
Levin, 2011[18]	cCBT-S Wellness Workshop	Licensed therapist does initial interview	After initial assessment, only once, <5 min via phone	NR	Yes, brief prompt to begin	NR	NR	No
Lintvedt, 2013[19]	cCBT-NS MoodGYM/ Blue Pages	NA	NA	NA	NA	NA	NA	No
McKinnon, 2008[20]	cCBT-S MoodGYM	Technician discussed lifestyle	NR	NR	Yes, weekly	No	No	No
Moritz, 2012[21]	cCBT-NS Deprexis	Arm 1: NA	Arm 1: NA	Reminders to complete modules	NR	NR	NR	No
Spek, 2007[22]	cCBT-NS No name	No therapist after intake	Initial assessment only for all patients	NR	NR	NR	NR	No
van Bastelaar, 2008[23]	cCBT-S CYL-DM	Supervised graduate students & psychiatry residents	NR	Autoreminders, feedback on homework	NR	Moderated discussion group forum	No	No
van der Zanden, 2012[24]	cCBT-LS Master Your Mood	Trained MH promotion workers	90 min/ chat room session	Autoreminders	NR	Web chat between therapist and up to 5 patients	NR	No

Study	cCBT level Program Name[a]	Therapist Training	Therapist Time per Patient	Email or Text	Phone	Online Group Component	Instant Messaging	Face to Face
Wagner, 2013[25]	cCBT-S No name	Psychologists or psychotherapists	20-50 min/text	Feedback on homework and answers to questions	NR	NR	NR	No
Warmerdam, 2008[26]	Arm 1: cCBT-S No name Arm 2: cPST-S	Supervised master's students	20 min per wk	Autoreminders, feedback on homework, support, suggestions	NR	NR	NR	No
Mixed depression and anxiety: 3 trials, 3 arms								
Newby, 2013[27]	cCBT-S Worry and Sadness Program	Supervised practice manager	23.37 min on average	Email as required based on elevated distress scores	Yes; not described in detail	NR	NR	No
Proudfoot, 2003[28]	cCBT-NS BTB	NA	NA	NA	NA	NA	NA	No
Proudfoot, 2004[29]	cCBT-NS BTB	NA	NA	NA	NA	NA	NA	No
Generalized anxiety disorder: 4 trials, 5 arms								
Andersson, 2012[30]	cCBT-S no name	Supervised graduate students	92 +/- 61 min for all sessions	Feedback, responses to questions	NR	NR	NR	No
Paxling, 2011[31]	cCBT-S No name	Supervised graduate students	97 +/- 52 min for all sessions	Feedback, responses to questions	NR	NR	NR	No
Robinson, 2010[32]	Arm 1: cCBT-LS (clinician) Worry program Arm 2: cCBT-LS (technician)	Arm 1: PhD-level clinician Arm 2: technician	Arm 1: 10 min per wk + discussion forum Arm 2: 10 min per wk + discussion forum	Arm 1: Encouragement, problem-solving, goal setting Arm 2: Support from script	Yes, if not responsive over email	Arm 1: Moderated discussion forum Arm 2: No	NR	No
Titov, 2009[33]	cCBT-LS Worry program	PhD	Weekly, no more detail given	Reminders & feedback	Yes	Moderated discussion forum	Yes	No
Panic disorder: 10 trials, 11 arms								
Bergstrom, 2010[34]	cCBT-S No name	Staff psychologist	35 min average for program	Responses to questions	NR	Moderated discussion forum	NR	No
Carlbring, 2001[35]	cCBT-S No name	NR	90 min total for all sessions; average 7-8 email exchanges	Feedback on homework, answers to questions	NR	NR	NR	No
Carlbring, 2005[36]	cCBT-S No name	Supervised graduate students	150 min for all sessions	Feedback on homework, answers to questions	NR	Moderated discussion board; mandatory to post weekly	NR	No

Study	cCBT level Program Name[a]	Therapist Training	Therapist Time per Patient	Email or Text	Phone	Online Group Component	Instant Messaging	Face to Face
Carlbring, 2006[37]	cCBT-LS No name	Supervised graduate students	10-12 min per session or wk	Reminders, feedback on progress	Yes	Moderated discussion board; mandatory to post weekly	NR	No
Kenardy, 2003[38]	cCBT-AT No name	Licensed psychologist	6, 1-hr sessions	5 daily palmtop reminders for patients to practice exposure	NR	NR	NR	Yes
Kiropoulos, 2008[39]	cCBT-S Panic Online	Licensed psychologist	Average of 352 min for all sessions	Feedback weekly	NR	NR	NR	No
Klein, 2006[40]	cCBT-S Panic Online	Both professionals and supervised graduate students	Average of 87 min for all sessions	Support and feedback	NR	NR	NR	No
Richards, 2006[41]	Arm 1: cCBT-S Panic Online alone Arm 2: cCBT-S Panic Online with stress modules	Both professionals and supervised graduate students	Arm 1: NR Arm 2: NA	Support and feedback on Panic Online modules; Stress management was just reading material	NR	NR	NR	No
Silfvernagel, 2012[42]	cCBT-S No name	Supervised graduate students	Averaged 19 emails for program	Reminders, feedback on homework	NR	NR	NR	No
Wims, 2010[43]	cCBT-S Panic Program	"Psychiatry registrar"	NR	Reminders, feedback, responses to questions	Called if patient did not log-in for 2 wk	Moderated discussion forum; mandatory to post weekly	NR	No
PTSD: 2 trials, 2 arms								
Litz, 2007[44]	cCBT-LS DE-STRESS	NR	Highly variable	Yes, as needed	Yes, as needed and at wk 6 prior to trauma narrative exercise	NR	NR	Yes, one initial session
Spence, 2011[45]	cCBT-LS No name	PhD	10 min per session	Reminders and feedback	Yes, as needed	Moderated discussion forum	Yes, if needed	No
Anxiety symptoms: 2 trials, 2 arms								
Kenardy, 2006[46]	cCBT-NS No name	No therapist	NA	Progress through modules monitored	NA	NA	NA	No
Ruwaard, 2010[47]	cCBT-S Interapy	Both professionals and supervised graduate students	20-40 min per session	Feedback including help structuring planned exposure assignments	NR	NR	NR	No

[a] All programs included some type of homework.

ABBREVIATIONS USED IN APPENDIX D TABLES

Abbreviation	Term
AC	attention control
ACQ	Agoraphobic Cognitions Questionnaire
ADIS	Anxiety Disorder Interview Schedule
ASI	Anxiety Sensitivity index;
ATQ	Adult Temperament Questionnaire
BA	behavior activation
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
BSQ	Body Shape Questionnaire
BVS	Body Vigilance Scale
CBT	cognitive behavioral therapy
CBM	cognitive bias modification
cCBT	computerized cognitive behavioral therapy
cCBT-AT	cCBT adjunct to therapy
cCBT-LS	cCBT live support
cCBT-NS	cCBT no support
cCBT-S	cCBT supported
CES-D	Center for Epidemiologic Studies Depression scale
CIDI-SF	Composite International Diagnostic Interview-Short Form
CIS-R	Clinical Interview Schedule-Revised
CYL	Color Your Life
CWD	Coping With Depression
DASS	Depression Anxiety Stress Scale
DM	diabetes mellitus
DSM	Diagnostic and Statistical Manual for Mental Disorders
EOT	end of treatment
EQ5D	European Quality of Life scale, 5 dimensions
GAD	generalized anxiety disorder
GAD-7	Generalized Anxiety Disorder scale, 7 items
GHQ-12	General Health Questionnaire, 12 items
GP	general practitioner
HADS	Hospital Anxiety and Depression Scale
HMO	Health Maintenance Organization
HRQOL	health-related quality of life
IC	information control
ISG	internet support group
K10	Kessler Psychological Distress Scale
MADRS	Montgomery-Asberg Depression Scale
MADRS-S	Montgomery-Asberg Depression Rating Scale (self-rating version)
MDD	major depressive disorder
MINI	Mini-International Neuropsychiatric Interview
NA	not applicable

Abbreviation	Term
NR	not reported
PAID	Problem Areas in Diabetes scale
PCL	Posttraumatic Stress Disorder Checklist
PD	panic disorder
PDSS	Panic Disorder Severity Scale
PHQ-9	Patient Health Questionnaire, 9 items
PROQSY	Programmable Questionnaire System
PST	problem-solving therapy
PSWQ	Penn State Worry Questionnaire
PTSD-SS	Posttraumatic Stress Disorder Symptom Scale
QOLI	Quality of Life Inventory
RCT	randomized controlled trial
SCID	Structured Clinical Interview for DSM Disorders
SCL	Symptom Checklist
SD	standard deviation
SDS	Sheehan Disability Scale
SF-12	Short Form Health Survey , 12 items
S-STAI	Short State-Trait Anxiety Inventory
TAU	treatment as usual
WHODAS	World Health Organization Disability Assessment Schedule
WHOQOL-BREF	World Health Organization Quality of Life, shorter version
WL	waitlist
WSAS	Work and Social Adjustment Scale

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APPENDIX E. GLOSSARY

Abstract screening

The stage in a systematic review during which titles and abstracts of articles identified in the literature search are screened for inclusion or exclusion based on established criteria. Articles that pass the abstract screening stage are promoted to the full-text review stage.

Attention control

A type of control group used in nonpharmaceutical intervention studies designed to mimic a placebo control. The nonintervention (control) group is subjected to a condition that does not include procedures or information pertinent to the study intervention but does have the same data collection procedures, number of clinic visits, amount of materials provided, level of contact with study staff or other professionals, etc. Keeping these aspects consistent across study arms controls for the effect of "attention" or therapeutic relationship.

ClinicalTrials.gov

A registry and results database of federally and privately supported clinical trials conducted in the United States and around the world. ClinicalTrials.gov provides information about a trial's purpose, location, and participant characteristics among other details.

Cochrane Database of Systematic Reviews

A bibliographic database of peer-reviewed systematic reviews and protocols prepared by the Cochrane Review Groups in The Cochrane Collaboration.

Cognitive behavioral therapy (CBT)

A short-term psychotherapy that focuses on how a person's thoughts and actions may be contributing to his or her depression.

Companion article

A publication from a trial that is not the article containing the main results of that trial. It may be a methods paper, a report of subgroup analyses, a report of combined analyses, or other auxiliary topic that adds information to the interpretation of the main publication.

Confidence interval (CI)

The range in which a particular result (such as a laboratory test) is likely to occur for everyone who has a disease. "Likely" usually means 95 percent of the time. Clinical research studies are conducted on only a certain number of people with a disease rather than all the people who have the disease. The study's results are true for the people who were in the study but not necessarily for everyone who has the disease. The CI is a statistical estimate of how much the study findings would vary if other different people participated in the study. A CI is defined by two numbers, one lower than the result found in the study and the other higher than the study's result. The size of the CI is the difference between these two numbers.

Data abstraction

The stage of a systematic review that involves a pair of trained researchers extracting reported findings specific to the research questions from the full-text articles that met the established inclusion criteria. These data form the basis of the evidence synthesis.

DistillerSR

An online application designed specifically for the screening and data extraction phases of a systematic review.

Embase

The Excerpta Medica database (EMBASE) produced by Elsevier, a major biomedical and pharmaceutical database indexing over 3500 international journals in the following fields: drug research, pharmacology, pharmaceutics, toxicology, clinical and experimental human medicine, health policy and management, public health, occupational health, environmental health, drug dependence and abuse, psychiatry, forensic medicine, and biomedical engineering or instrumentation. There is selective coverage for nursing, dentistry, veterinary medicine, psychology, and alternative medicine.

Exclusion criteria

The criteria, or standards, set out before a study or review. Exclusion criteria are used to determine whether a person should participate in a research study or whether an individual study should be excluded in a systematic review. Exclusion criteria may include age, previous treatments, and other medical conditions.

Full-text review

The stage of a systematic review in which a pair of trained researches evaluates the full-text of study articles for potential inclusion in the review.

GRADE

Grading of Recommendations Assessment, Development, and Evaluation (GRADE), a system of assessing the quality of medical evidence and evaluating the strength of recommendations based on the evidence.

Health-related quality of life (HRQOL)

A multidimensional concept that includes domains related to physical, mental, emotional, and social functioning. HRQOL goes beyond direct measures of population health, life expectancy, and causes of death, and focuses on the impact health status has on quality of life.

Inclusion criteria

The criteria, or standards, set out before the systematic review. Inclusion criteria are used to determine whether an individual study can be included in a systematic review. Inclusion criteria may include population, study design, sex, age, type of disease being treated, previous treatments, and other medical conditions.

Information control

A type of control group used in nonpharmaceutical intervention studies in which members of the control group are given access to equivalent quality information on a subject not directly related to the topic of the actual intervention. Similar to attention control, information control attempts to negate or nullify any positive effect from simply obtaining helpful information.

Optimal information size

The number of patients that need to be included in a pooled analysis (meta-analysis) to provide sufficient power to detect the smallest clinically important difference in treatment effect.

PRISMA

Preferred Reporting Items for Systematic Reviews and Meta-Analyses, an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses.

Publication bias

The tendency of researchers to publish experimental findings that have a positive result, while not publishing the findings when the results are negative or inconclusive. The effect of publication bias is that published studies may be misleading. When information that differs from that of the published study is not known, people are able to draw conclusions using only information from the published studies.

PubMed®

A database of citations for biomedical literature from MEDLINE®, life science journals, and online books in the fields of medicine, nursing, dentistry, veterinary medicine, the healthcare system, and preclinical sciences.

Randomized controlled trial (RCT)

A prospective, analytical, experimental study using primary data generated in the clinical environment. Individuals similar at the beginning of the trial are randomly allocated to two or more treatment groups and the outcomes the groups are compared after sufficient followup time. Properly executed, the RCT is the strongest evidence of the clinical efficacy of preventive and therapeutic procedures in the clinical setting.

Risk

A way of expressing the chance that something will happen. It is a measure of the association between exposure to something and what happens (the outcome). Risk is the same as probability, but it usually is used to describe the probability of an adverse event. It is the rate of events (such as breast cancer) in the total population of people who could have the event (such as women of a certain age).

Statistical significance

A mathematical technique to measure whether the results of a study are likely to be true. Statistical significance is calculated as the probability that an effect observed in a research study is occurring because of chance. Statistical significance is usually expressed as a P-value. The smaller the P-value, the less likely it is that the results are due to chance (and more likely that

the results are true). Researchers generally believe the results are probably true if the statistical significance is a P-value less than 0.05 ($p<.05$).

Strength of evidence (SOE)

A measure of how confident reviewers are about decisions that may be made based on a body of evidence. SOE is evaluated using one of four grades: (1) *High* confidence that the evidence reflects the true effect; further research is very unlikely to change reviewer confidence in the estimate of effect; (2) *moderate* confidence that the evidence reflects the true effect; further research may change the confidence in the estimate of effect and may change the estimate; (3) *low* confidence that the evidence reflects the true effect; further research is likely to change the confidence in the estimate of effect and is likely to change the estimate; and (4) *insufficient*; the evidence either is unavailable or does not permit a conclusion.

Systematic review

A summary of the clinical literature. A systematic review is a critical assessment and evaluation of all research studies that address a particular clinical issue. The researchers use an organized method of locating, assembling, and evaluating a body of literature on a particular topic using a set of specific criteria. A systematic review typically includes a description of the findings of the collection of research studies. The systematic review may also include a quantitative pooling of data, called a meta-analysis.

Waitlist control

A type of control group used in nonpharmaceutical intervention trials in which a group of participants included in an outcome study is assigned to a waiting list and receives the exact intervention at a later date, after the active treatment group has completed the study. This control group serves as a completely untreated comparison group during the study.