QUERI

Computerized Cognitive Behavioral Therapy for Adults with Depressive or Anxiety Disorders

October 2013

Prepared for:
Department of Veterans Affairs
Veterans Health Administration
Quality Enhancement Research Initiative
Health Services Research & Development Service
Washington, D.C. 20420

Prepared by:
Evidence-based Synthesis Program (ESP) Center
Durham Veterans Affairs Healthcare System
Durham, N.C.
John W. Williams Jr., M.D., M.H.Sc., Director

Investigators:
Principal Investigator:
Eric Dedert, Ph.D.

Co-Investigators:
Jennifer R. McDuffie, Ph.D.
Cindy Swinkels, Ph.D.
Ryan Shaw, Ph.D.
Jessica Fulton, Ph.D.
Kelli D. Allen, Ph.D.
Santanu Datta, Ph.D.
John W. Williams Jr., M.D., M.H.Sc.

Research Associate:
Avishek Nagi, M.S.

Medical Editor:
Liz Wing, M.A.

VA HEALTH CARE Defining EXCELLENCE in the 21st Century

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.

Recommended citation: Dedert E, McDuffie JR, Swinkels C, Shaw R, Fulton J, Allen KD, Datta S, Williams JW. Computerized Cognitive Behavioral Therapy for Adults With Depressive or Anxiety Disorders. VA-ESP Project #09-010; 2013.

This report is based on research conducted by the Evidence-based Synthesis Program (ESP) Center located at the Durham VA Medical Center, Durham, NC, funded by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Health Services Research and Development. The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. No investigators have any affiliations or financial involvement (e.g., employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

TABLE OF CONTENTS

FIGURES

TABLES

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?

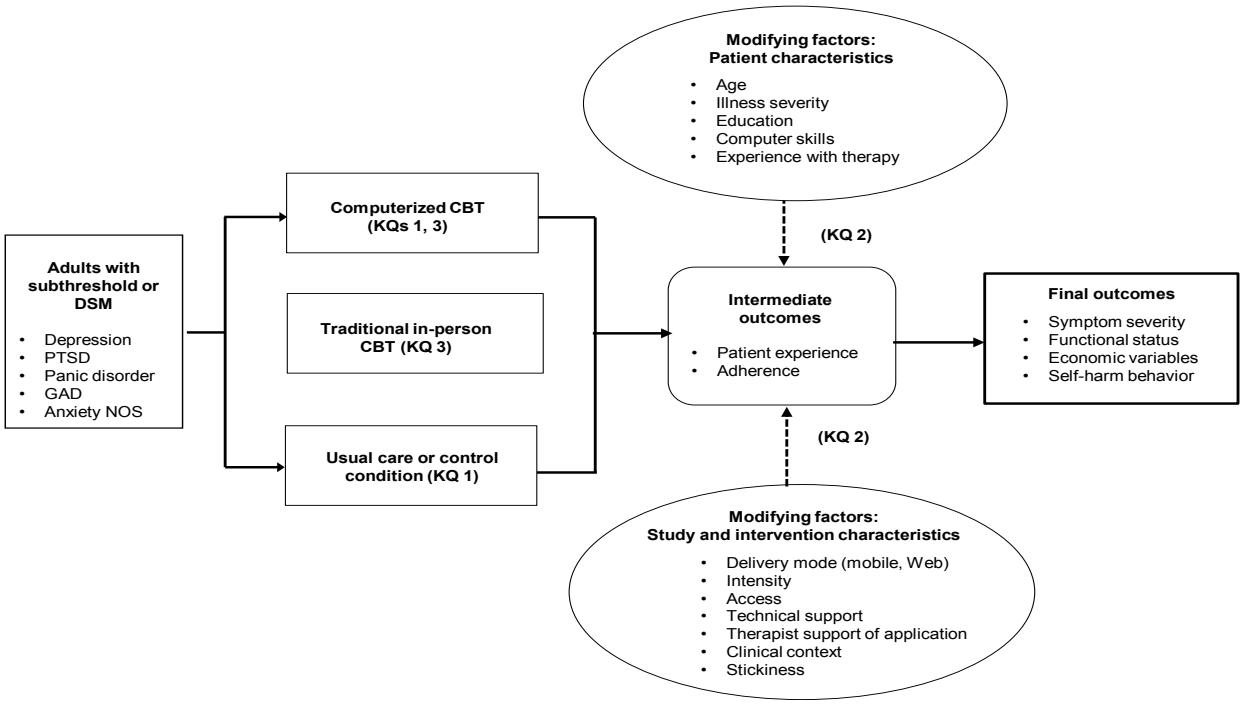
KQ 2: For cCBT interventions, what level, type, and modality of user support is provided (e.g., daily telephone calls, weekly email correspondence); who provides this support (e.g., therapist, graduate student, peer); what is the clinical context (primary intervention, adjunct); and how is this support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

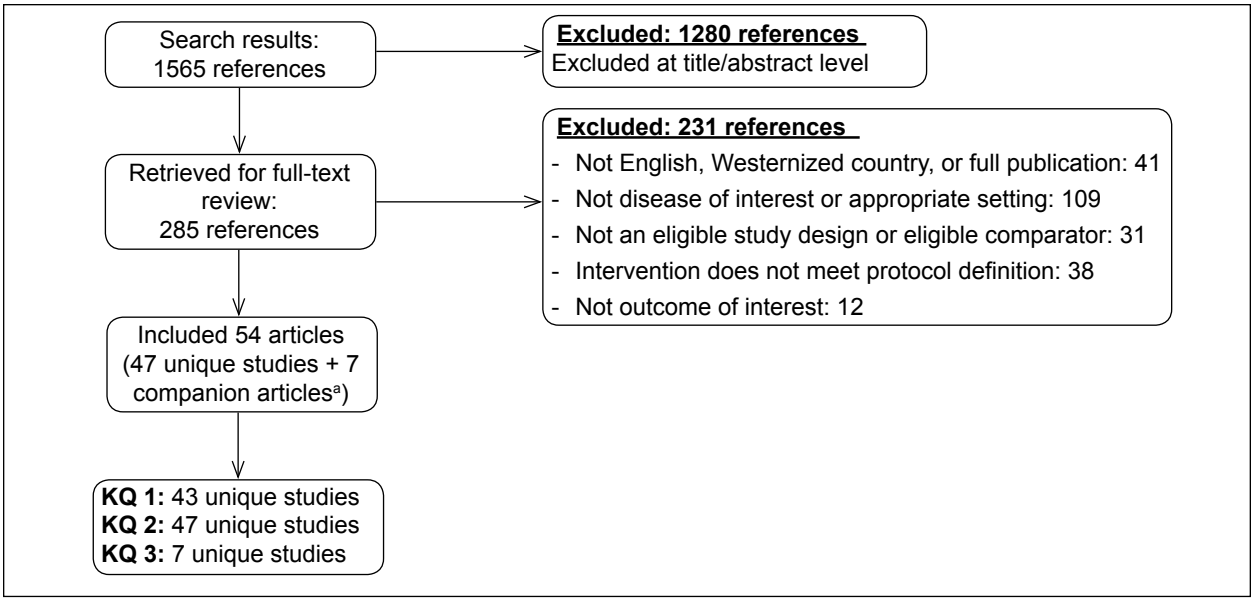
LITERATURE SEARCH

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.

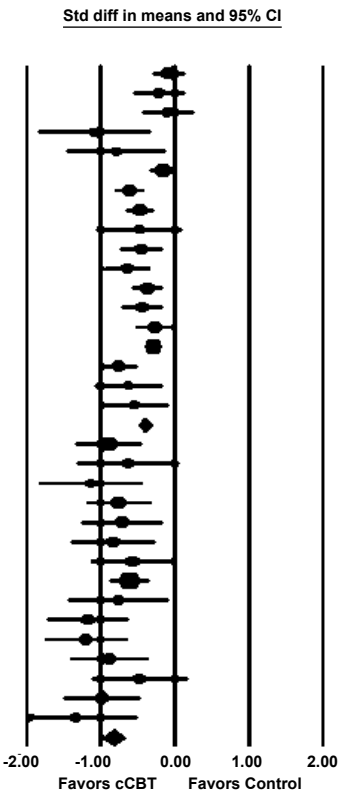
Effects of cCBT Interventions in Patients with Depressive Disorders and Symptom Thresholds

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

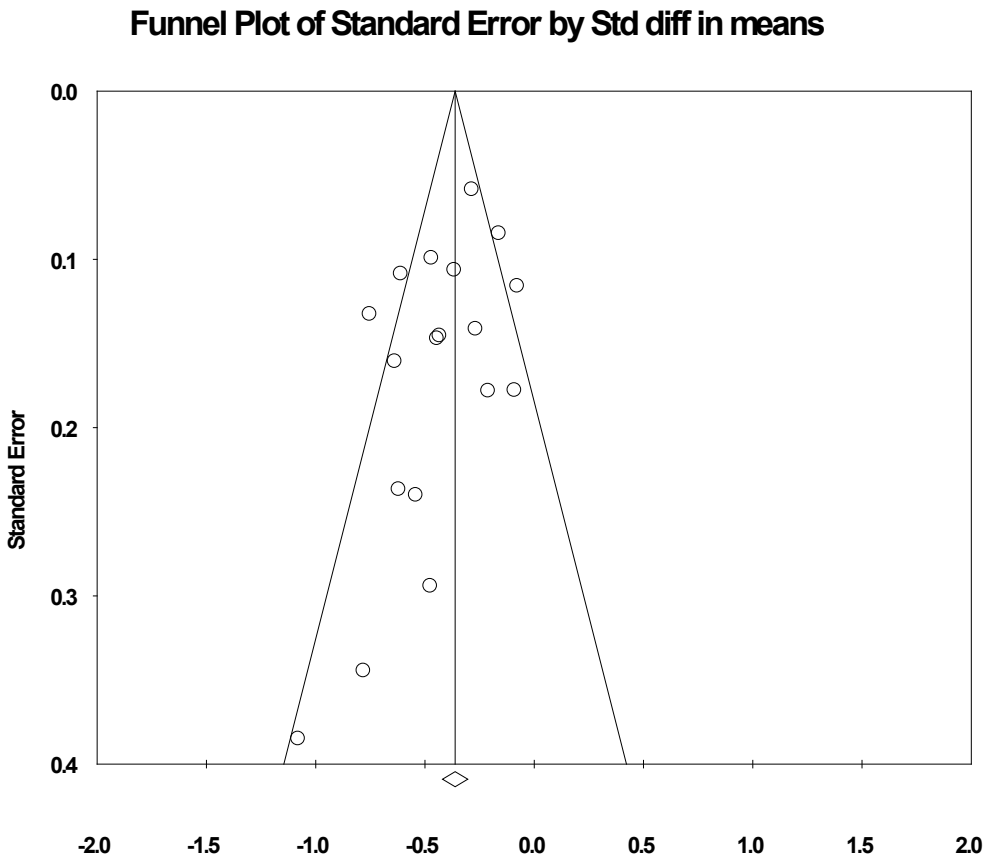
Group by: Disorder	Study name	Comparison	Outcome	Std diff in means	Lower limit	Upper limit	p-Value
Dep Sxs	Clarke 2002	cCBT v Control	Sx Severity	-0.08	-0.30	0.15	0.50
Dep Sxs	de Graaf 2009	cCBT1 v Control	Sx Severity	-0.21	-0.56	0.14	0.24
Dep Sxs	de Graaf 2009	cCBT2 v Control	Sx Severity	-0.09	-0.44	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).

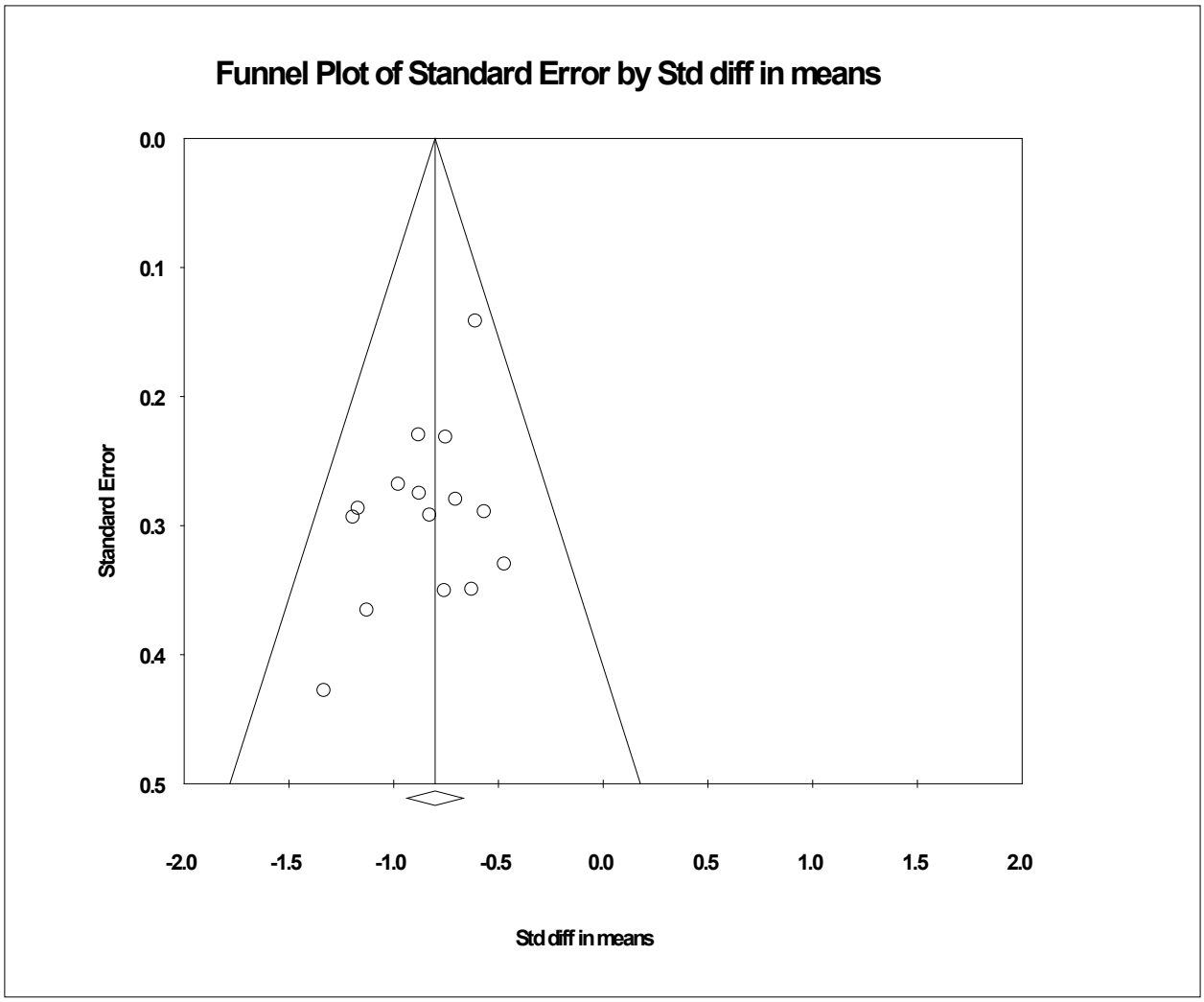
Figure 4. Funnel plot of studies conducted in patients with depressive symptoms



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

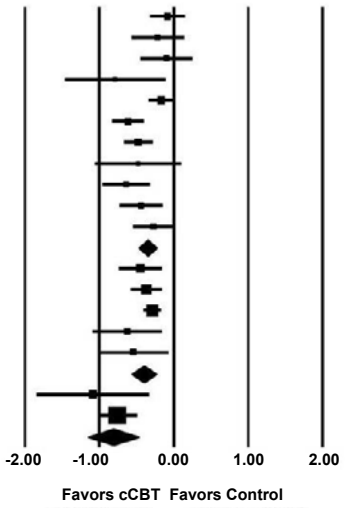
To examine treatment heterogeneity, we conducted mixed-treatment effects subgroup analyses for two prespecified factors: (1) level of cCBT support and (2) type of control group.

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

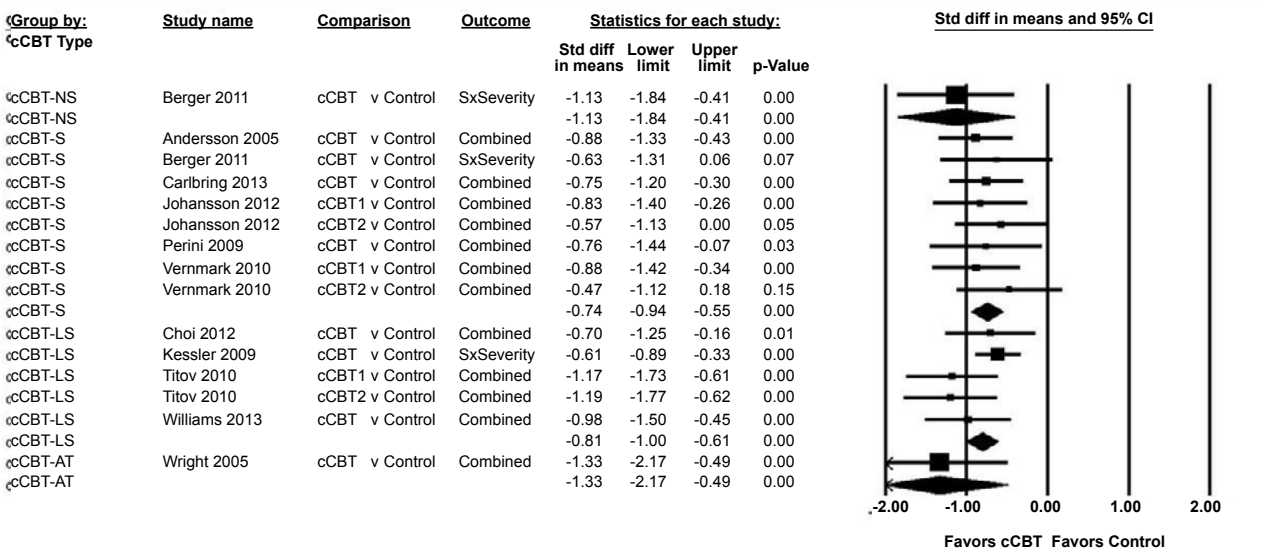


Abbreviations: CI=confidence interval; cCBT=computerized cognitive behavioral therapy; NS=no support; S=support; LS=live support; Sx=symptoms

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

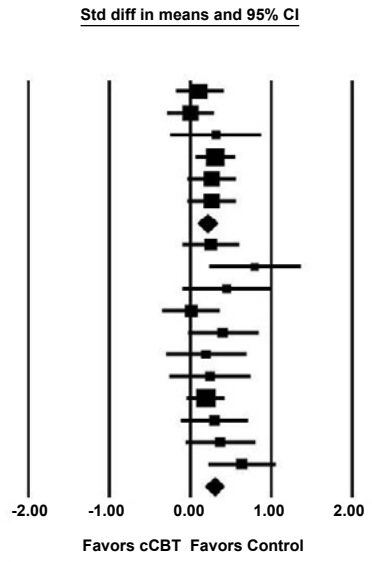
Twelve trials (17 comparisons) examining patients with depressive symptoms or major depressive disorder provided end-of-treatment data for HRQOL outcomes (Figure 8). Four trials (6 comparisons) were in patients with depressive symptoms, and 8 trials (11 comparisons) were in patients with diagnosed major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

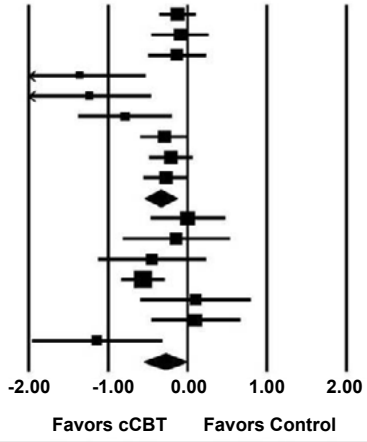
Long-Term Followup

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



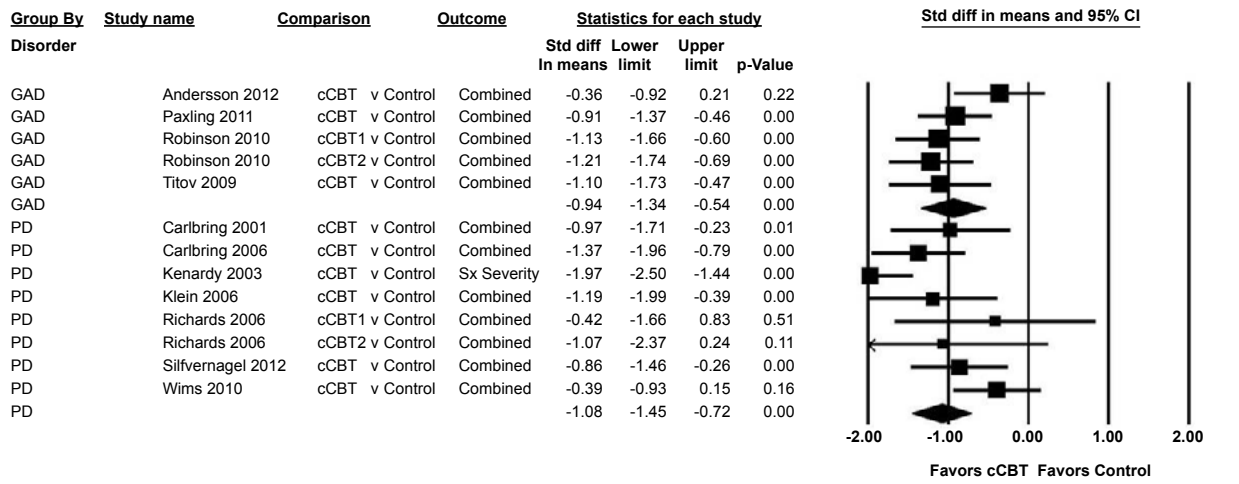
Abbreviations: cCBT=computerized cognitive behavioral therapy; CI=confidence interval; Dep Sxs=depressive symptoms; MDD=major depressive disorder; Sx=symptom

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.

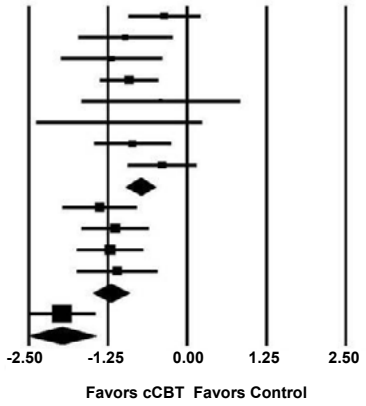
Level of cCBT Support

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.

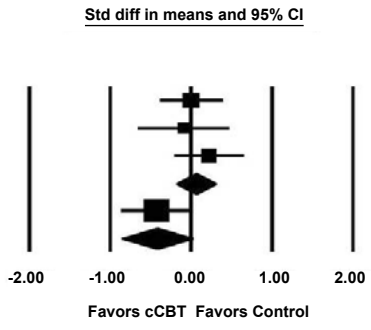
Effects of cCBT Interventions in Patients With Panic Disorder

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

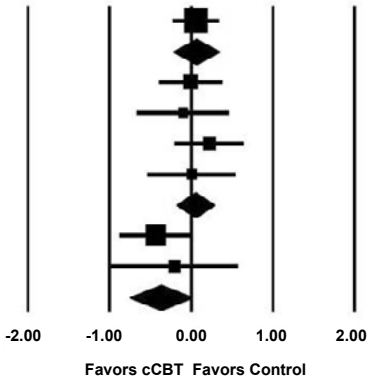
HRQOL outcome data were available for three comparisons across three trials of patients with panic disorder[50,59,66] but were not reported in the other trials. The cCBT intervention group was not found to be significantly better compared with the face-to-face therapy group (SMD -0.07; 95% CI, -0.34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

REFERENCES

1. Centers for Disease Control and Prevention. Mental Illness Surveillance Among Adults in the United States. MMWR 2011;60(Suppl). Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/su6003a1.htm?s_cid=su6003a1_w. Accessed August 2, 2013.

2. Kessler R, Aguilar-Gaxiola S, Alonso J, et al. The global burden of mental disorders: an update from the WHO World Mental Health (WMH) surveys. *Epidemiol Psichiatr Soc*. 2009;2009(1):23-33.

3. World Health Organization. The Global Burden of Disease: 2004 Update. Geneva, Switzerland: WHO Press, 2008. Available at: http://www.who.int/healthinfo/global_burden_disease/2004_report_update/en/. Accessed August 2, 2013.

4. Government Accountability Office. Number of Veterans Receiving Care, Barriers Faced, and Efforts to Increase Access, 2011. Available at: http://www.gao.gov/products/GAO-12-12. Accessed August 2, 2013.

5. Kessler RC, Chiu WT, Demler O, et al. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005;62(6):617-27.

6. Beck AT. Depression: Causes and treatment. Philadelphia, PA: University of Pennsylvania Press. 1967.

7. Beck AT, Rush AJ, Shaw BF, et al. Cognitive therapy of depression. New York, NY: Guilford Press. 1979.

8. Beck AT, Emery G. Anxiety disorders and phobias: A cognitive perspective. New York, NY: Basic Books. 1985.

9. Beck AT, Wright FD, Newman CF, et al. Cognitive therapy of substance abuse. New York, NY: Guilford Press. 1993.

10. Beck AT, Freeman A, Davis DD. Cognitive therapy for personality disorders (2nd Ed.). New York, NY: Guilford Press. 2004

11. Fairburn CG. Cognitive-behavioral therapy for bulimia nervosa. In F. Flach (Ed.), The Hatherleigh guide to psychiatric disorders, Part II. The Hatherleigh guide series (pp. 69–88). Long Island City, NY: The Hatherleigh Company. 2000.

12. Basco MR, Rush AJ. Cognitive-behavioral therapy for bipolar disorder. New York, NY: Guilford Press. 1996.

13. Beck AT, Rector NA, Stolar N, et al. Schizophrenia: Cognitive theory, research, and therapy. New York, NY: Guilford Press. 2009.

14. DeRubeis RJ, Hollon SD, Amsterdam JD. Cognitive therapy vs. medications in the treatment of moderate to severe depression. *Arch Gen Psychiatry*. 2005(62):409-416.

15. Elkin I, Shea MT, Watkins JT. National Institute of Mental Health Treatment of Depression Collaborative Research Program: General effectiveness of treatments. *Arch Gen Psychiatry*. 1989(46):971-982.

16. Hollon SD, Stewart MO, Strunk D. Enduring effects for cognitive behavior therapy in the treatment of depression and anxiety. *Annu Rev Psychol*. 2006(57):285-315.

17. Andrews G, Cuijpers P, Craske MG, et al. Computer therapy for the anxiety and depressive disorders is effective, acceptable and practical health care: a meta-analysis. *PLoS One*. 2010;5(10):e13196.

18. Griffiths KM, Farrer L, Christensen H. The efficacy of internet interventions for depression and anxiety disorders: a review of randomised controlled trials. *Med J Aust*. 2010;192(11 Suppl):S4-11.

19. Johansson R, Andersson G. Internet-based psychological treatments for depression. *Expert Rev Neurother*. 2012;12(7):861-9; quiz 870.

20. Farvolden P, Denisoff E, Selby P, et al. Usage and longitudinal effectiveness of a Web-based self-help cognitive behavioral therapy program for panic disorder. *J Med Internet Res*. 2005;7(1):e7.

21. Christensen H, Griffiths KM, Jorm AF. Delivering interventions for depression by using the internet: randomised controlled trial. *BMJ*. 2004;328(7434):265.

22. Christensen H, Griffiths KM, Korten AE, et al. A comparison of changes in anxiety and depression symptoms of spontaneous users and trial participants of a cognitive behavior therapy website. *J Med Internet Res*. 2004;6(4):e46.

23. Spek V, Cuijpers P, Nyklicek I, et al. Internet-based cognitive behaviour therapy for symptoms of depression and anxiety: a meta-analysis. *Psychol Med*. 2007;37(3):319-28.

24. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097.

25. Amstadter AB, Broman-Fulks J, Zinzow H, et al. Internet-based interventions for traumatic stress-related mental health problems: a review and suggestion for future research. *Clin Psychol Rev*. 2009;29(5):410-20.

26. Andersson G. Guided internet treatment for anxiety disorders. As effective as face-to-face therapies? *Stud Health Technol Inform*. 2012;181:3-7.

27. Andersson G, Cuijpers P. Internet-based and other computerized psychological treatments for adult depression: a meta-analysis. *Cogn Behav Ther*. 2009;38(4):196-205.

28. Cuijpers P, Marks IM, van Straten A, et al. Computer-aided psychotherapy for anxiety disorders: a meta-analytic review. *Cogn Behav Ther*. 2009;38(2):66-82.

29. Foroushani PS, Schneider J, Assareh N. Meta-review of the effectiveness of computerised CBT in treating depression. *BMC Psychiatry*. 2011;11:131.

30. Kaltenthaler E, Parry G, Beverley C, et al. Computerised cognitive-behavioural therapy for depression: systematic review. *Br J Psychiatry*. 2008;193(3):181-4.

31. Lewis C, Pearce J, Bisson JI. Efficacy, cost-effectiveness and acceptability of self-help interventions for anxiety disorders: systematic review. *Br J Psychiatry*. 2012;200(1):15-21.

32. Reger MA, Gahm GA. A meta-analysis of the effects of internet- and computer-based cognitive-behavioral treatments for anxiety. *J Clin Psychol*. 2009;65(1):53-75.

33. Tumur I, Kaltenthaler E, Ferriter M, et al. Computerised cognitive behaviour therapy for obsessive-compulsive disorder: A systematic review. *Psychother Psychosom*. 2007;76(4):196-202.

34. Agency for Healthcare Research and Quality. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville, MD: Agency for Healthcare Research and Quality. Available at: http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=318. Accessed August 5, 2013.

35. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-88.

36. Deeks JJ, Higgins JPT (editors). Chapter 9: Analysing data and undertaking meta-analysis. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org. Accessed August 5, 2013.

37. Cohen J. Statistical power analysis for the behavioral sciences.Second edition. Hillsdale, NJ: L. Erlbaum Associates. 1988.

38. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539-58.

39. Johansson R, Sjoberg E, Sjogren M, et al. Tailored vs. standardized internet-based cognitive behavior therapy for depression and comorbid symptoms: a randomized controlled trial. *PLoS One*. 2012;7(5):e36905.

40. Andersson G, Paxling B, Roch-Norlund P, et al. Internet-based psychodynamic versus cognitive behavioral guided self-help for generalized anxiety disorder: a randomized controlled trial. *Psychother Psychosom*. 2012;81(6):344-55.

41. Silfvernagel K, Carlbring P, Kabo J, et al. Individually tailored internet-based treatment for young adults and adults with panic attacks: randomized controlled trial. *J Med Internet Res*. 2012;14(3):e65.

42. van der Zanden R, Kramer J, Gerrits R, et al. Effectiveness of an online group course for depression in adolescents and young adults: a randomized trial. *J Med Internet Res*. 2012;14(3):e86.

43. Choi I, Zou J, Titov N, et al. Culturally attuned Internet treatment for depression amongst Chinese Australians: a randomised controlled trial. *J Affect Disord*. 2012;136(3):459-68.

44. Farrer L, Christensen H, Griffiths KM, et al. Internet-based CBT for depression with and without telephone tracking in a national helpline: randomised controlled trial. *PLoS One*. 2011;6(11):e28099.

45. Berger T, Hammerli K, Gubser N, et al. Internet-based treatment of depression: a randomized controlled trial comparing guided with unguided self-help. *Cogn Behav Ther*. 2011;40(4):251-66.

46. Paxling B, Almlov J, Dahlin M, et al. Guided internet-delivered cognitive behavior therapy for generalized anxiety disorder: a randomized controlled trial. *Cogn Behav Ther*. 2011;40(3):159-73.

47. Spence J, Titov N, Dear BF, et al. Randomized controlled trial of Internet-delivered cognitive behavioral therapy for posttraumatic stress disorder. *Depress Anxiety*. 2011;28(7):541-50.

48. van Bastelaar KM, Pouwer F, Cuijpers P, et al. Web-based depression treatment for type 1 and type 2 diabetic patients: a randomized, controlled trial. *Diabetes Care*. 2011;34(2):320-5.

49. Levin W, Campbell DR, McGovern KB, et al. A computer-assisted depression intervention in primary care. *Psychol Med*. 2011;41(7):1373-83.

50. Bergstrom J, Andersson G, Ljotsson B, et al. Internet-versus group-administered cognitive behaviour therapy for panic disorder in a psychiatric setting: a randomised trial. *BMC Psychiatry*. 2010;10:54.

51. Wims E, Titov N, Andrews G, et al. Clinician-assisted Internet-based treatment is effective for panic: A randomized controlled trial. *Aust N Z J Psychiatry*. 2010;44(7):599-607.

52. Titov N, Andrews G, Davies M, et al. Internet treatment for depression: a randomized controlled trial comparing clinician vs. technician assistance. *PLoS One*. 2010;5(6):e10939.

53. Robinson E, Titov N, Andrews G, et al. Internet treatment for generalized anxiety disorder: a randomized controlled trial comparing clinician vs. technician assistance. *PLoS One*. 2010;5(6):e10942.

54. Vernmark K, Lenndin J, Bjarehed J, et al. Internet administered guided self-help versus individualized e-mail therapy: A randomized trial of two versions of CBT for major depression. *Behav Res Ther*. 2010;48(5):368-76.

55. Kessler D, Lewis G, Kaur S, et al. Therapist-delivered Internet psychotherapy for depression in primary care: a randomised controlled trial. *Lancet*. 2009;374(9690):628-34.

56. de Graaf LE, Gerhards SA, Arntz A, et al. Clinical effectiveness of online computerised cognitive-behavioural therapy without support for depression in primary care: randomised trial. *Br J Psychiatry*. 2009;195(1):73-80.

57. Perini S, Titov N, Andrews G. Clinician-assisted Internet-based treatment is effective for depression: randomized controlled trial. *Aust N Z J Psychiatry*. 2009;43(6):571-8.

58. Warmerdam L, van Straten A, Twisk J, et al. Internet-based treatment for adults with depressive symptoms: randomized controlled trial. *J Med Internet Res*. 2008;10(4):e44.

59. Kiropoulos LA, Klein B, Austin DW, et al. Is internet-based CBT for panic disorder and agoraphobia as effective as face-to-face CBT? *J Anxiety Disord*. 2008;22(8):1273-84.

60. Mackinnon A, Griffiths KM, Christensen H. Comparative randomised trial of online cognitive-behavioural therapy and an information website for depression: 12-month outcomes. *Br J Psychiatry*. 2008;192(2):130-4.

61. Litz BT, Engel CC, Bryant RA, et al. A randomized, controlled proof-of-concept trial of an Internet-based, therapist-assisted self-management treatment for posttraumatic stress disorder. *Am J Psychiatry*. 2007;164(11):1676-83.

62. Spek V, Nyklicek I, Smits N, et al. Internet-based cognitive behavioural therapy for subthreshold depression in people over 50 years old: a randomized controlled clinical trial. *Psychol Med*. 2007;37(12):1797-806.

63. Carlbring P, Bohman S, Brunt S, et al. Remote treatment of panic disorder: a randomized trial of internet-based cognitive behavior therapy supplemented with telephone calls. *Am J Psychiatry*. 2006;163(12):2119-25.

64. Andersson G, Bergstrom J, Hollandare F, et al. Internet-based self-help for depression: randomised controlled trial. *Br J Psychiatry*. 2005;187:456-61.

65. Klein B, Richards JC, Austin DW. Efficacy of internet therapy for panic disorder. *J Behav Ther Exp Psychiatry*. 2006;37(3):213-38.

66. Carlbring P, Nilsson-Ihrfelt E, Waara J, et al. Treatment of panic disorder: live therapy vs. self-help via the Internet. *Behav Res Ther*. 2005;43(10):1321-33.

67. Wright JH, Wright AS, Albano AM, et al. Computer-assisted cognitive therapy for depression: maintaining efficacy while reducing therapist time. *Am J Psychiatry*. 2005;162(6):1158-64.

68. Proudfoot J, Ryden C, Everitt B, et al. Clinical efficacy of computerised cognitive-behavioural therapy for anxiety and depression in primary care: randomised controlled trial. *Br J Psychiatry*. 2004;185:46-54.

69. Kenardy JA, Dow MG, Johnston DW, et al. A comparison of delivery methods of cognitive-behavioral therapy for panic disorder: an international multicenter trial. *J Consult Clin Psychol*. 2003;71(6):1068-75.

70. Proudfoot J, Goldberg D, Mann A, et al. Computerized, interactive, multimedia cognitive-behavioural program for anxiety and depression in general practice. *Psychol Med*. 2003;33(2):217-27.

71. Clarke G, Reid E, Eubanks D, et al. Overcoming depression on the Internet (ODIN): a randomized controlled trial of an Internet depression skills intervention program. *J Med Internet Res*. 2002;4(3):E14.

72. Griffiths KM, Mackinnon AJ, Crisp DA, et al. The Effectiveness of an Online Support Group for Members of the Community with Depression: A Randomised Controlled Trial. *PLoS One*. 2012;7(12).

73. Titov N, Andrews G, Robinson E, et al. Clinician-assisted Internet-based treatment is effective for generalized anxiety disorder: Randomized controlled trial. *Aust N Z J Psychiatry*. 2009;43(10):905-912.

74. Carlbring P, Westling BE, Ljungstrand P, et al. Treatment of panic disorder via the Internet: A randomized trial of a self-help program. *Behav Ther*. 2001;32(4):751-764.

75. Richards JC, Klein B, Austin DW. Internet cognitive behavioural therapy for panic disorder: Does the inclusion of stress management information improve end-state functioning? *Clinical Psychologist*. 2006;10(1):2-15.

76. Kenardy J, McCafferty K, Rosa V. Internet-delivered indicated prevention for anxiety disorders: Six-month follow-up. *Clinical Psychologist*. 2006;10(1):39-42.

77. Ruwaard J, Broeksteeg J, Schrieken B, et al. Web-based therapist-assisted cognitive behavioral treatment of panic symptoms: a randomized controlled trial with a three-year follow-up. *J Anxiety Disord*; 2010:387-96.

78. Hickie IB, Davenport TA, Luscombe GM, et al. Practitioner-supported delivery of internet-based cognitive behaviour therapy: evaluation of the feasibility of conducting a cluster randomised trial. *Med J Aust*. 2010(11 Suppl):S31-5.

79. Wagner B, Horn AB, Andreas M. Internet-based versus face-to-face cognitive-behavioral intervention for depression: A randomized controlled non-inferiority trial. *J Affect Disord*. 2013.

80. Carlbring P, Hagglund M, Luthstrom A, et al. Internet-based behavioral activation and acceptance-based treatment for depression: a randomized controlled trial. *J Affect Disord*. 2013;148(2-3):331-7.

81. Williams AD, Blackwell SE, Mackenzie A, et al. Combining Imagination and Reason in the Treatment of Depression: A Randomized Controlled Trial of Internet-Based Cognitive-Bias Modification and Internet-CBT for Depression. *J Consult Clin Psychol*. 2013.

82. Glozier N, Christensen H, Naismith S, et al. Internet-Delivered Cognitive Behavioural Therapy for Adults with Mild to Moderate Depression and High Cardiovascular Disease Risks: A Randomised Attention-Controlled Trial. *PLoS One*. 2013;8:3 Article Number: e59139.

83. Lintvedt OK, Griffiths KM, Sorensen K, et al. Evaluating the effectiveness and efficacy of unguided internet-based self-help intervention for the prevention of depression: a randomized controlled trial. *Clin Psychol Psychother*. 2013;20(1):10-27.

84. Moritz S, Schilling L, Hauschildt M, et al. A randomized controlled trial of internet-based therapy in depression. *Behav Res Ther*. Vol. 50; 2012:513-21.

85. Newby JM, Mackenzie A, Williams AD, et al. Internet cognitive behavioural therapy for mixed anxiety and depression: a randomized controlled trial and evidence of effectiveness in primary care. *Psychol Med*. 2013:1-14.

86. Butler AC, Chapman JE, Forman EM, et al. The empirical status of cognitive-behavioral therapy: a review of meta-analyses. *Clin Psychol Rev*. 2006;26(1):17-31.

87. Ekers D, Richards D, Gilbody S. A meta-analysis of randomized trials of behavioural treatment of depression. *Psychol Med*. 2008;38(5):611-23.

88. Hunot V, Churchill R, Silva de Lima M, et al. Psychological therapies for generalised anxiety disorder. *Cochrane Database Syst Rev*. 2007(1):CD001848.

89. Karlin BE, Walser RD, Yesavage J, et al. Effectiveness of acceptance and commitment therapy for depression: comparison among older and younger veterans. *Aging Ment Health*. 2013;17(5):555-63.

90. Eftekhari A, Ruzek JI, Crowley JJ, et al. Effectiveness of national implementation of prolonged exposure therapy in veterans affairs care. *JAMA Psychiatry*. 2013;70(9):949-55.

91. Department of Veterans Affairs. Management of major depressive disorder (MDD). VA/DoD Clinical Practice Guidelines. 2009. Available at: http://www.healthquality.va.gov/Major_Depressive_Disorder_MDD_Clinical_Practice_Guideline.asp. Accessed August 2, 2013.

92. American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder. 3rd edition. Arlington, VA: American Psychiatric Association; 2010. Available at: http://www.psychiatry.org/practice/clinical-practice-guidelines. Accessed August 2, 2013.

93. Parikh SV, Segal ZV, Grigoriadis S, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. II. Psychotherapy alone or in combination with antidepressant medication. *J Affect Disord*. 2009;117 Suppl 1:S15-25.

94. National Institute for Health and Care Excellence. Depression: the treatment and management of depression in adults. NICE Clinical Guideline 90. October 2009. Available at: http://www.nice.org.uk/nicemedia/pdf/cg90niceguideline.pdf. Accessed August 3, 2013.

95. National Institute for Health and Care Excellence. Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults: management in primary, secondary and community care. NICE Clinical Guideline 113. January 2011. Available at: http://www.nice.org.uk/nicemedia/live/13314/52599/52599.pdf. Accessed August 12, 2013.

96. Hind D, O'Cathain A, Cooper CL, et al. The acceptability of computerised cognitive behavioural therapy for the treatment of depression in people with chronic physical disease: a qualitative study of people with multiple sclerosis. *Psychol Health*. 2010;25(6):699-712.

97. McMurchie W, Macleod F, Power K, et al. Computerised cognitive behavioural therapy for depression and anxiety with older people: a pilot study to examine patient acceptability and treatment outcome. *Int J Geriatr Psychiatry*. 2013.

98. Tsai J, Rosenheck RA. Use of the internet and an online personal health record system by US veterans: comparison of Veterans Affairs mental health service users and other veterans nationally. *J Am Med Inform Assoc*. 2012;19(6):1089-94.

99. Sarasohn-Kahn J. The online couch: mental health care on the web. California Healthcare Foundation. 2012. Available at: http://www.chcf.org/~/media/MEDIA%20LIBRARY%20Files/PDF/O/PDF%20OnlineCouchMentalHealthWeb.pdf. Accessed August 12, 2013.

100. Beating the Blues. Cognitive Behavioral Therapy. 2011. Available at: http://www.u2interactive.com/. Accessed August 3, 2013.

101. Robinson KA, Saldanha IJ, Mckoy NA. Frameworks for Determining Research Gaps During Systematic Reviews. Methods Future Research Needs Report No. 2. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. HHSA 290-2007-10061-I.) AHRQ Publication No. 11-EHC043-EF. Rockville, MD: Agency for Healthcare Research and Quality. June 2011. Available at: http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=735&pageaction=displayproduct Accessed April 8, 2012.