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SUMMARY WITH CRITICAL APPRAISAL

Internet-Delivered Cognitive Behavioural Therapy for Major Depression and Anxiety Disorders: A Review of Clinical Effectiveness

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Abbreviations

CAU	care as usual
CBT	cognitive behavioural therapy
DSM	Diagnostic and Statistical Manual of Mental Disorders
GAD	generalized anxiety disorder
HQO	Health Quality Ontario
HTA	health technology assessment
iCBT	internet-delivered cognitive behavioural therapy
iTAU	improved treatment as usual
MDD	major depressive disorder (major depression)
OCD	obsessive-compulsive disorder
PC	personal computer
PD	panic disorder
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTSD	post-traumatic stress disorder
RCT	randomized controlled trial
SAD	social anxiety disorder
SP	social phobia
TAU	treatment as usual

Context and Policy Issues

Major depression and anxiety disorders are common mental health conditions associated with disability, decreased quality of life, increased mortality, and economic burden on both individuals and health care systems.[1-5] Major depression is estimated to have a lifetime prevalence in Canadians of up to 11%.[6] Individuals with major depression may exhibit symptoms such as sadness, insomnia, loss of appetite, fatigue, irritability, feelings of hopelessness, loss of interest in hobbies, and suicidal thoughts.[7-9] The *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-V), classifies anxiety disorders into panic disorder, agoraphobia, social anxiety disorder, generalized anxiety disorder, specific phobias, separation anxiety disorder, selective mutism, and substance or medication-induced anxiety disorder.[8] Collectively, these anxiety disorders are estimated to have a lifetime prevalence of 28.8%.[10]

Treatment strategies for major depression and anxiety disorders often include clinical care with antidepressant or anxiolytic medication (or other pharmacotherapy), psychotherapy, or a combination of both approaches. Cognitive behavioural therapy (CBT) is the most frequently used evidence-based psychotherapy for the treatment of patients with depression or anxiety disorders.[1] By combining the principles of cognitive and behavioural therapies CBT aims to provide patients with the coping strategies and mechanisms to solve current problems and to change dysfunctional thoughts, behaviours, beliefs, and attitudes.[11] Traditionally delivered in face-to-face sessions between a patient and therapist, CBT is time consuming and is associated with barriers to treatment and barriers to accessing treatment. These barriers include high financial costs, perceived stigma, potentially poor access to treatment in rural areas, long wait times, privacy issues, and an overall lack of trained clinicians.[12,13]

Internet-delivered cognitive behavioural therapy (iCBT) has been introduced as a treatment option for major depression and anxiety disorders. This mode of delivery offers potential advantages when it comes to improving access to treatment, decreasing wait times, and

reducing costs when compared with traditional CBT, while remaining effective as a psychotherpy.[14] Although there are a wide variety of iCBT programs, they are typically comprised of a series of self-contained modules consisting of text, audio, and video files based on the principles of CBT that can be accessed using a computer or smartphone.[15] These programs can be offered without therapist assistance (usually classified as unguided or self-help) or with assistance from therapists, clinicians, or coaches by email, phone, video calls, or in-person (usually classified as guided).[16]

Health Quality Ontario (HQO) and CADTH have collaborated on a project entitled "Internet-Delivered Cognitive Behavioural Therapy for Major Depressive Disorder and Anxiety Disorders: A Health Technology Assessment".[17] The objective of this collaborative project was to provide a comprehensive review of the evidence on iCBT technologies and assess their potential value to the Canadian health care system. This Rapid Response report aims to serve as a supplement to the clinical review conducted as part of the health technology assessment. Evidence from primary studies that have been published more recently than the systematic reviews included in the full health technology assessment (HTA), as well as evidence on transdiagnostic interventions (i.e., programs that apply the same underlying treatment principles across multiple mental health conditions) will be examined in this review to provide decision-makers with additional information.

Research Question

What is the clinical effectiveness of internet-delivered cognitive behavioural therapy for patients with mild to moderate major depression or anxiety disorders?

Key Findings

Nine randomized controlled trials were identified regarding the clinical effectiveness of iCBT for patients with mild to moderate major depression or anxiety disorders. The studies were heterogeneous with respect to features of the iCBT programs (e.g., number of modules, duration, level of guidance, and frequency of support) and the scales used to assess patient outcomes.

Two randomized controlled trials included patients with mild to moderate major depression. One trial concluded that iCBT was non-inferior to care as usual, while the second study concluded that adding either unguided or therapist-guided iCBT as an adjunct to improved treatment as usual conferred a benefit over improved treatment as usual alone at 6- and 15-month follow-up assessments. The authors of the second study reported that there were no significant differences between unguided iCBT and low-intensity therapist-guided iCBT at any time in the trial.

One randomized controlled trial included patients with social anxiety disorder. Patients were randomized to wait list control or iCBT delivered using either a computer or a smartphone. The authors concluded that either mode of delivery offered benefits to patients in the form of symptom reduction compared to the wait list group.

Six randomized controlled trials included mixed patient populations with major depression, social anxiety disorder, generalized anxiety disorder, panic disorder with or without agoraphobia, or any combination of these. Five of these studies found iCBT to be more effective than care as usual alone or wait list control for reducing depression or anxiety

symptoms. The sixth study did not assess symptom severity, but it did report a high degree satisfaction with care in patients treated with iCBT.

Overall, the evidence base suggested that iCBT interventions are effective for mild to moderate major depression, generalized anxiety disorder, panic disorder with or without agoraphobia, and social anxiety disorder compared to wait list control, treatment as usual, or improved treatment as usual. However, the included studies from which these findings were summarized from have significant limitations that are detailed within this report. Due to the supplementary nature of this report, the evidence summarized here should not be interpreted without also considering the analysis conducted in the HQO and CADTH collaborative project entitled "Internet-Delivered Cognitive Behavioural Therapy for Major Depressive Disorder and Anxiety Disorders: A Health Technology Assessment".[17]

Methods

Literature Search Methods

A limited literature search was conducted on key resources including Medline, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to randomized controlled trials and non-randomized studies. The search was limited to English language documents published between January 1, 2008 and July 24, 2018.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults (aged 16 years and older) with a primary diagnosis of mild or moderate major depression or anxiety disorders (excluding OCD and PTSD) according to a validated diagnostic instrument (e.g., DSM-IV, DSM-V, ICD, CES-D, BDI, PHQ, Structured Diagnostic Interview Schedule) - Participants with a primary diagnosis of anxiety disorders or primary diagnosis of mild to moderate major depression coexisting with other mental health conditions (with the exception of severe depression, OCD, and PTSD) are included - Participants with concurrent pharmacotherapy use are included
Intervention	Internet-delivered CBT, including guided, unguided, transdiagnostic, and disorder-specific (Non-traditional CBT [e.g., mindfulness CBT], CBT that is delivered via bibliotherapy, and CBT that was described as computerized [e.g., delivered via CD-ROM] with no internet component were excluded)
Comparator	Face-to-face CBT; Usual care; Wait-list; Control group defined as a combination of usual care, wait list control
Outcomes	Clinical effectiveness (e.g., remission of depression or anxiety symptoms [acute phase], prevention of relapse following a successful acute treatment [maintenance phase], response to therapy [50% reduction in symptoms from baseline], improvement in social function or activities of daily living), time-to-event data (e.g., to response, remission, dropout), changes in use of pharmacotherapy, safety, quality of life, satisfaction with care, and patient adherence

Study Designs	Randomized controlled trials and non-randomized studies

BDI = Beck Depression Inventory; CES-D = Centre for Epidemiological Scale for Depression; DSM = Diagnostic and Statistical Manual of Mental Disorders; ICD = International Statistical Classification of Diseases and Related Health Problems; OCD = obsessive compulsive disorder; PHQ = Patient Health Questionnaire; PTSD = post-traumatic stress disorder.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2008. In addition, because this report was conducted as a supplement to "Internet-delivered Cognitive Behavioural Therapy (CBT): A Health Technology Assessment",[17] all primary studies included in the systematic reviews identified in the main report were excluded. All studies investigating transdiagnostic iCBT programs (published since 2008) were included in this report as transdiagnostic interventions were specifically excluded in the health technology assessment.

Critical Appraisal of Individual Studies

The included randomized controlled trials (RCT) were critically appraised using the Downs and Black checklist.[18] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

Summary of Evidence

Quantity of Research Available

A total of 1,480 citations were identified in the literature search. Following screening of titles and abstracts, 1,404 citations were excluded and 76 potentially relevant reports from the electronic search were retrieved for full-text review. Additionally, two potentially relevant publications were retrieved from the grey literature search. Of these 78 potentially relevant articles, 69 publications were excluded for various reasons, while nine publications met the inclusion criteria and were included in this report. Appendix 1 presents the PRISMA flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Detailed characteristics of the individual studies included in this report are provided in Appendix 2.

Study Design

Nine RCTs were identified and included in the review.[19-27] All nine recruited patients from multiple centers through general practitioner referral or using various advertising campaigns (e.g., internet, newspaper, television, flyers in universities, hospitals or primary care centers).[19-27] One study used a non-inferiority design.[19]

Year of Publication and Country of Origin

The included RCTs were conducted in Sweden,[19] Spain,[20] Switzerland,[21,22] New Zealand,[23,25] and Australia.[24,26,27] All studies were published between 2018 and 2011,[19-27] with one study published in 2018,[20] two in 2017,[19,22] one in 2016,[20] two in 2013,[23,24] one in 2012,[24] and one in 2011.[25]

Patient Population

Two RCTs included patients with mild to moderate major depression.[19,20] Eriksson et al.[19] recruited 90 adult patients (aged ≥18 years) with a diagnosis of major depression according to the DSM-IV. The average age of patients was 37 years and the sample was 70% female.[19] The Montero-Marin et al.[20] study included 296 patients who were diagnosed with mild to moderate major depression according to the Mini-International Neuropsychiatric Interview 5.0. Participants in the sample had an average age of 43 years and 76% were female.[20]

One RCT included patients with social anxiety disorder.[21] Stolz et al.[21] recruited 150 patients (aged ≥18 years) with a primary diagnosis of social anxiety disorder according to the DSM–IV. The average age of patients was 34.8 years and the sample was 63% female.

Six RCTs included mixed patient populations with major depression, social anxiety disorder, generalized anxiety disorder, panic disorder with or without agoraphobia, or any combination of these (detailed in Appendix 2 and 4).[22-27] Berger et al.[22] recruited 139 adults (aged ≥18 years) meeting the diagnostic criteria for social anxiety disorder, panic disorder with or without agoraphobia, or generalized anxiety disorder (according to Structured Clinical Interview for DSM–IV). Patients had an average age of 42 years and were 71% female.[22] The study by Carter et al.[23] included adults (aged 18 to 65 years) with a primary diagnosis of social phobia, panic disorder with or without agoraphobia, or generalized anxiety disorder according to the DSM–IV. Information on the age and gender of their sample was not reported.[23] The RCT by Newby et al.[24] included 99 adults (aged ≥18 years) that met the criteria for major depression or generalized anxiety disorder according to the Mini-International Neuropsychiatric Interview 5.0. The mean age of patients was 44.3 years and the sample was 78% female.[24] Bell et al.[25] recruited 83 patients aged between 18 and 65 years (mean age of 35.3 years, 67% female) with a current primary DSM-IV diagnosis of generalized anxiety disorder, panic disorder with or without agoraphobia, or social phobia. The study by Johnston et al.[26] included 131 patients (aged ≥18 years) meeting the DSM–IV diagnostic criteria for a principal diagnosis of generalized anxiety disorder, panic disorder with or without agoraphobia, or social phobia. Patients had an average age of 41.6 years and were 58.8% female.[26] Finally, Titov et al.[27] recruited 74 adult patients (mean age of 43.9, 73% female) meeting the diagnostic criteria for major depression, social phobia, panic disorder with or without agoraphobia, or generalized anxiety disorder (according to Mini-International Neuropsychiatric Interview 5.0).

All studies included patients that were 16 years of age or older and met the criteria for their primary diagnosis according to a validated diagnostic instrument.[19-27]

Interventions and Comparators

The intervention of interest for all studies was some form of iCBT.[19-27] One RCT[20,22] investigated unguided iCBT programs (self-help), seven RCTs[19-21,23-27] used iCBT programs with some form of guidance (therapist, clinician, coach, or research assistant support), and one RCT[19] examined both guided and unguided iCBT programs. The programs utilized, their level and type of support (or guidance), and the individual features of the program (e.g., number of modules, duration, target condition) varied between studies. With the exception of the Bell et al.[25] and Carter et al.[23] studies, none of the RCTs included examined the same iCBT programs.[19-22,24,26,27]

Unguided (self-help) iCBT

The study by Montero-Marin et al.[20] compared the effectiveness of improved treatment as usual (iTAU) plus either unguided iCBT or low-intensity therapist-guided iCBT against iTAU alone. This study used the Smiling is Fun program, a program consisting of 10 modules that focus on various psychological techniques to learn and practice adaptive ways to cope with depression and daily problems.[20] Improved treatment as usual was defined as care provided by general practitioners, who had received a 3-hour training program to update their knowledge on how to diagnose and treat depression in primary care according to the National Institute for Health and Care guidelines. This training primarily dealt with the appropriate use of antidepressants.[20] The study by Berger et al.[22] evaluated the unguided iCBT program Velibra plus care as usual (CAU) versus CAU alone. This program contains six treatment modules that are cognitive–behavioural in orientation and emphasize transdiagnostic principles.[22] Care as usual was not well-defined in the study by Berger et al.[22]

Guided (supported) iCBT

Eriksson et al.[19] examined the effectiveness of *Depressionshjalpen*, a therapist-guided iCBT program that consists of seven modules over the course of three months. Stolz et al.[21] utilized an eight module coach-guided iCBT program developed by the authors of the study (delivered using either a computer or smartphone) that targets both behavioral and cognitive maintaining factors. The studies by Carter et al.[23] and Bell et al.[25] investigated the guided iCBT program CLIMATE (developed by the Clinical Research Unit for Anxiety and Depression at St Vincent's Hospital, Sydney, Australia), which contains four to six sessions over a 12 week period. Newby et al.[24] used the Worry and Sadness Program, which is clinician-guided iCBT that contains six modules over a 10 week period. Johnston et al.[26] investigated the Anxiety Program, which is a guided transdiagnostic iCBT containing eight lessons to be completed over a 10 week period. Patients in this study received support from either a clinician or a coach.[26] Finally, the study by Titov et al.[27] used the Wellbeing Program, a therapist-guided, transdiagnostic iCBT program consists of eight lessons over a 10 week period. Additional details on how the individual studies defined guidance (i.e., what support or guidance was provided), the mode of communication (e.g., email, text-based messaging, phone calls), and the professionals providing support (e.g., their credentials and experience) are provided in Appendix 2.

As for the comparators in these seven RCTs, six studies used wait list control[21,23-27] and one RCT used treatment as usual.[19] The Eriksson et al.[19] study defined treatment as usual as including any scheduled contacts with general practitioners, nurses, or other medical professionals at the patient's primary care center. Treatments could include face-to-face psychotherapy, antidepressants, sick leave certification or any combinations of these treatments.[19]

Outcomes

The included studies primarily measured outcomes with several different scales that measure the severity of symptoms of depression and anxiety, disability, function, quality of life, and satisfaction with treatment (Appendix 2, Table 2). Studies that included participants with a variety of conditions used disease-specific scales for their primary diagnosis. A brief explanation of some of the commonly used scales is provided below.

(1) Beck Depression Inventory – II (BDI-II; used in six studies[19-22,24,25]): A 21-question multiple-choice self-report inventory used to evaluate the severity of

depressive symptoms. Each answer is scored on a value of 0 to 3. A total score is calculated: 0-13 (minimal depression), 14-19 (mild depression), 20-28 (moderate depression), and ≥29 (severe depression).

(2) Beck Anxiety Inventory (BAI; used in two studies[22,25]): A 21-question multiple-choice self-report inventory used to evaluate the severity of anxiety symptoms. The total score (sum of the 21 items) classifies anxiety severity: 0-9 (normal to minimal anxiety), 10-18 (mild to moderate anxiety), 19-29 (moderate to severe anxiety) and ≥30 (severe anxiety).[28]

(3) Generalized Anxiety Disorder 7 – Item Scale (GAD-7; used in three studies[24,26,27]): A self-report measure that measures symptoms and severity of generalized anxiety disorder using seven items on a scale of 0-3.[26] A total score is calculated (between 0 and 21), with higher scores representing more severe symptoms.

(4) Penn State Worry Questionnaire (PSWQ; used in five studies[22,24-27]): An instrument that assesses 16 items on a scale of 1-5 to measure excessive, generalized, and uncontrollable worry. A total score is calculated (between 16 and 80), with higher scores representing more severe symptoms. A score ≥45 indicates generalized anxiety disorder.[27]

(5) Patient Health Questionnaire – 9 (PHQ-9; used in three studies[24,26,27]): A nine-item measure of the symptoms and severity of major depressive disorder based on the DSM-IV criteria. Each question is scored on a value of 0 to 3, with higher scores indicating more severe symptoms. A total score of 10 on the PHQ-9 has been identified as an important threshold for identifying major depression that meets the DSM-IV criteria.[26]

(6) Sheehan Disability Scale (SDS; used in two studies[26,27]): A self-rated questionnaire designed to assess functional impairment in three inter-related domains: work/school, social activities, and family life.[26] Each domain is scored between 0 and 10 according to a visual analogue scale, with total scores ranging between 0 (unimpaired) and 30 (highly impaired).

(7) NEO-Five Factor Inventory-Neuroticism Subscale (NEO-FFI-N; used in two studies[24,27]): A 12 item measure of higher-order risk factor for anxiety and depression and is part of the NEO personality inventory (higher scores indicate higher severity).[27]

(8) Panic Disorder Severity Scale – Self Report (PDSS-SR; used in three studies[25-27]): An instrument that assesses seven items to measure panic disorder severity.[26] Items are individually scored between 0 (low severity) and 4 (high severity) to get a total raw score between 0 and 28.

(9) Social Phobia Scale (SPS; used in four studies[21,22,26,27]): A self-report instrument that assesses 20 items for fears of being judged by others during daily activities. Each question is scored on a value of 0 to 4 (total scores range between 0 and 80), with higher scores indicating more severe symptoms.

(10) Social Interaction Anxiety Scale (SIAS; used in four studies[21,22,26,27]): A self-report instrument that assesses 20 items for fears in social interactions. Each question is scored on a value of 0 to 4 (total scores range between 0 and 80), with higher scores indicating more severe symptoms

(11) 12-Item Short Form Survey (SF-12; used in three studies[20-22]): A multipurpose survey consisting of 12 questions that is used to evaluate mental and physical functioning and overall health-related quality of life.[21] Responses are weighted between 0 (lowest level of health) and 100 (highest level of health) and combined to yield a physical health composite score and a mental health composite score.

(12) Brief Symptom Inventory (BSI; used in two studies[21,22]): A 53 item self-report scale that evaluates psychological distress and psychiatric disorders. Answers are scores using the 5 point Likert scale (higher score indicates higher severity).

(13) Depression, Anxiety and Stress Scale – 21 Items (DASS-21; used in three studies[22,26,27]): A set of three self-report scales (each with seven items) designed to measure the emotional states of depression, anxiety, and stress. Items are scored on a scale of 0 (normal) to 3 (severe), which are then summed to give a total score between 0 and 63.

(14) Liebowitz Social Anxiety Scale – Self Report (LSAS-SR; used in one study[21]): An instrument that assesses symptoms of social anxiety using 24 items on a scale of 0-3 (total scores range between 0 and 72), separately for fear and avoidance.

(15) Fear Questionnaire (FQ; used in one study[25]): A questionnaire that measures general anxiety symptoms using 23 questions scored on a value of 0 to 8. Higher scores indicate a higher severity of fear.

(16) Body Sensations Questionnaire (BSQ; used in one study[22]): A questionnaire used to evaluate fear of body sensations on a 17-item scale.[22]Items are scored on a scale of 1 to 5, with a higher score indicating more severe worry or fear.

(17) EuroQol – Five Dimension, Visual Analogue Scale (EQ-5D, VAS; used in one study[20]): A scale used to measure health-related quality of life and functioning. The VAS is a vertical line on which patients rate their health states between 100 (best possible) and zero (worst possible).[20]

In addition to outcomes that were measured using various instruments and scales, the included RCTs evaluated a number of other outcomes. All nine RCTs[19-27] provided information on the number of dropouts or attritions rates in each treatment arm to various degrees. Five RCTs[21,22,24,26,27] assessed the number of patients meeting the diagnostic criteria for major depression, generalized anxiety disorder, social anxiety disorder, or panic disorder with or without agoraphobia following treatment. Two RCTs[19,20] monitored patients' use of medication as they progressed through treatment. Three studies[23,24,26] provided information on patient satisfaction with iCBT treatment. None of the included RCTs[19-27] measured or mentioned minimal clinically important differences (minimal clinically important score changes); however, the studies by Johnston et al.[26] and Titov et al.[27] monitored remission and recovery as defined by various cut-off values on symptom severity scales. Eriksson et al.[19] collected data on the number of patients who required sick leave prior to, during, and after treatment and the length of sick leave. Finally, one RCT[20] measured patients' use of mental health services and other health care services (e.g., general practitioner visits).

Summary of Critical Appraisal

The critical appraisal of the nine RCTs are summarized below and detailed in Appendix 3.

The nine identified RCTs[19-27] were generally well-conducted but had some important limitations, based on the assessment using the Downs and Black Checklist.[18] Most of the studies shared similar strengths and limitations in the design of their trials and reporting of their results. All studies included in this review had well-described objectives, methodology, patient inclusion and exclusion criteria, and generally provided a clear description of the intervention and comparator. One exception to this was the study by Berger et al.,[22] where the comparator (care as usual) was not described. All nine studies[19-27] reported appropriate estimates of random variability (standard errors, standard deviations), confidence intervals, and actual probability values (*P*-values), increasing the strength of reporting by the study authors. Limited data was reported on adverse events experienced by patients that may have been a result of iCBT treatment in eight RCTs.[19-26] One study[27] made specific mention of patients who had deteriorated according to DASS-21 scores. A final consideration to make regarding the reporting by study authors is their disclosure of potential conflicts of interest and source of funding. The authors of six studies[19,20,23,25,26] indicated they had no conflicts of interest and provided their source of funding, two studies[21,27] did not discuss any conflicts of interest, one study[24] did not provide a source of funding, and the author of one study[22] disclosed that they were employed as a research director at the company that developed, owns, and operates the iCBT program investigated in the trial.

Although there was some variation in the methods used to randomize patients between the nine studies,[19-27] randomization seems to have been done appropriately by individuals not otherwise involved in the study or by computer randomization software and therefore could not bias the allocation process (selection bias). Sample size calculations were conducted in eight studies[19-22,24-27] to determine the number of patients needed to recruit; however, in two of these studies[19,22] recruitment did not meet the number of patients predicted. One study[23] did not conduct sample size calculations, potentially decreasing the power and value of its findings. In all nine studies[19-27] the participants were aware of their allocation to treatment arms (open-label), creating a serious risk of bias. Additionally, outcome assessors were aware of the treatment the patient received in eight studies.[19,21-27] The remaining study[20] used personnel blind to the participants' allocation to assess outcome. Participant and outcome assessor knowledge of treatment allocation could potentially influence responses to the scales, prescription of medications, and discontinuation decisions, which could introduce bias in either direction, depending on the expectations of those involved. In eight studies[19-22,24-27] the baseline patient characteristics, which included age, sex, education, income, number of co-morbid diagnoses, use of antidepressants or other medication, and baseline symptom severity scores were well-balanced between treatment and control groups and any differences were documented. This balance between groups increases confidence in the randomization process. The Carter et al.[23] study did not provide information regarding baseline patient characterises beyond their primary diagnosis, so baseline imbalance could not be assessed. As for the validity of the outcomes for these nine RCTs,[19-27] the scales and tools used as primary outcomes are generally well-studied in the literature and are valid for symptom measurement. The study by Stoltz et al.[21] used a composite score (a combination of scores on the Social Phobia Scale, the Social Interaction Anxiety Scale, and the Liebowitz Social Anxiety Scale—Self Report) as their primary outcome, and although the individual components of this composite are validated scales the appropriateness of combining the scores is unclear. The Carter et al.[23] study used a series of telephone questions that were created by the authors of the study to assess patient treatment satisfaction. The applicability of their findings based on responses to these non-validated questions to other populations is unclear.[23]

Due to the nature of iCBT as internet software, patient compliance with the intervention can be monitored by the number of lessons each patient completed throughout the course of the program. All nine studies[19-27] provided information on these patients in the form of attrition or dropout rates, which were reported to be high (>10% dropout rate) in all studies (see Appendix 2 and 3 for details). Eight of the included RCTs[19-26] lost at least 15% of their participants prior to their final follow-up, which is a serious risk of bias. The dropout rates were considered in the results of six studies,[20-22,24,26,27] where an intention-to-treat analysis was used. However, the large number of dropouts may still have had an unclear effect on the conclusions made in these studies (e.g., using a last observation carried forward intention-to-treat analysis is going to underestimate disease severity if patients drop out because of worsening disease). Patient and assessor knowledge of the intervention may have influenced results given the subjective nature of the outcomes measured in these studies.

As for external validity, the study participants (patients clinically diagnosed with major depression and/or anxiety disorders), care providers (general practitioners or specialists involved in mental health care), and health care setting in all included studies[19-27] appear to be relevant to the "real-world". However, it is important to consider that all patients included in these studies met the clinical diagnosis for their primary condition, and many patients that seek help for depression or anxiety symptoms in a generalized setting may not meet the same threshold. In addition, five studies[21,22,24,26,27] relied on individuals to reach out to study investigators after seeing advertisements in newspapers, websites, university campuses, hospitals, or primary care centers. This method of recruitment may have represented a motivated subset of people with depression or anxiety disorders that are more likely to complete iCBT programs and to apply their learning in their lives, thus potentially overestimating the treatment effect of iCBT. Additionally, the authors of one study[22] noted that their participant population had a higher level of education than the general population, which may have also influenced the treatment effect.

Summary of Findings

The overall findings of the included literature are summarized below. A detailed summary of the main findings are available in Appendix 4.

What is the clinical effectiveness of internet-delivered cognitive behavioural therapy for patients with mild to moderate major depressive disorder or anxiety disorders?

Major Depression

Symptom Severity

Two RCTs[19,20] reported on the effectiveness of iCBT for patients with major depression. One study[19] concluded that both the iCBT and TAU groups experienced significant reduction of depression symptoms from pre-treatment (according to BDI-II scores; iCBT: Cohen's *d* = 1.17, Cohen's *d* = 1.23 and Cohen's *d* = 1.42 at 3, 6 and 12 months, respectively; TAU: Cohen's *d* = 1.31, Cohen's *d* = 1.43 and Cohen's *d* = 1.29 at 3, 6 and 12 months, respectively); however, neither treatment was statistically superior to the other (Cohen's *d* = 0.09, Cohen's *d* = 0.18 and Cohen's *d* = 0.09 at 3, 6 and 12 months, respectively). The second study[20] observed no difference between iTAU plus either low-intensity therapist-guided iCBT or unguided iCBT compared to iTAU alone at 3 months (as assessed with BDI-II scores, the primary outcome measure), but showed statistically significant improvement in depressive symptoms at 6- and 15-month follow-ups for both

iCBT groups over the iTAU alone group. There were no significant differences between unguided iCBT and guided iCBT at any time.[20]

Use of Pharmacotherapy

One RCT[19] reported a significant decrease in the number of patients taking antidepressants at the 3-month follow-up in the iCBT group compared to the TAU group (p = 0.020). This difference was not maintained at 6- and 12-month follow-ups. A second RCT[20] indicated that patients treated with unguided iCBT or guided iCBT had decreased use of medication at follow-up compared to improved TAU.

Safety

No studies provided information on the safety or rate of adverse event rates associated with the use of iCBT in patients with major depression.

Quality of Life

The study by Eriksson et al.[19] reported improvement in quality of life (EQ-5D) in both the iCBT and TAU groups (compared to baseline scores).

Satisfaction with Care

No studies provided information on the satisfaction with iCBT treatment in patients with major depression.

Patient Adherence and Dropout

One RCT[19] provided the number of dropouts in the iCBT and TAU groups but did not provide additional analysis. The Montero-Marin et al.[20] study reported attrition rates for all three groups (self-guided iCBT: 37.8%; therapist-guided iCBT: 29.2%; improved TAU: 27.5%), which were not statistically different from each other.

Social Anxiety Disorder

Symptom Severity

One RCT[21] reported on the effectiveness of iCBT for patients with social anxiety disorder. According to their composite score (a combination of scores on the Social Phobia Scale, the Social Interaction Anxiety Scale, and the Liebowitz Social Anxiety Scale—Self Report), both the computer-delivered iCBT and smartphone-delivered iCBT groups outperformed the wait list control for symptom reduction (computer iCBT vs. wait list: Cohen's d = 0.75 [95% CI: 0.22–1.25]; smartphone iCBT vs. wait list: Cohen's d = 0.89 [95% CI: 0.35–1.41]).[21] The study also reported a significant ($p \leq 0.05$) number of people no longer met the diagnostic criteria for social anxiety disorder in both iCBT groups (computer-delivered iCBT: N =14/37 [37.8%]; smartphone-delivered iCBT: N = 9/34 [26.5%] compared to the wait list control (N = 0/21 [0.0%]) following treatment.[21]

Use of Pharmacotherapy

No studies provided information on the use of pharmacotherapy following treatment with iCBT in patients with social anxiety disorder.

Safety

Reliable deterioration rates were reported in one study.[21] A total of three deteriorations, defined as an increase in primary outcome measures according to the reliable change index,[29] were reported (one in computer-delivered iCBT, one in smartphone-delivered iCBT, and one in the wait list control group).

Quality of Life

No studies provided information on the quality of life following treatment with iCBT in patients with social anxiety disorder.

Satisfaction with Care

No studies provided information on the satisfaction with iCBT treatment in patients with social anxiety disorder.

Patient Adherence and Dropout

One RCT[21] provided information on the number of dropouts in their iCBT groups and in their control group. The dropout rate was not statistically significant between iCBT delivered with computers (23.3%), smartphones (30.0%), and the wait list group (23.3%).

Mixed Population

Symptom Severity

Five RCTs[22,24-27] reported on the effectiveness of iCBT for patients with major depression, anxiety disorders, or comorbid diagnoses. All five reported that patients treated with iCBT showed improvement in symptoms (as assessed by various scales) compared to patients receiving care as usual[22] or in a wait list control group.[24-27] The magnitude of improvement and tools used to asses symptom severity varied, but details are included in Appendix 4. In addition, two studies[22,26] monitored the diagnostic status of patients as they completed their treatment. Both reported that a larger number of patients no longer meeting the diagnostic criteria for their primary diagnosis following iCBT treatment compared to CAU[22] or wait list control.[26] The RCTs by Johnston et al.[26] and Titov et al.[27] reported on the percentage of patients on iCBT that entered remission and recovery (according to various symptom measure scales), which was shown to be significant when compared to the wait list control group.[26] Two studies[26,27] presented their results by diagnostic group, allowing for comparisons of the effectiveness of iCBT by patient population (e.g., those with major depression, generalized anxiety disorder, panic disorder, or social phobia). One study[26] concluded that participants with a principal diagnosis of generalized anxiety disorder, panic disorder, or social phobia achieved large within-group effect sizes on the corresponding disorder-specific measures. The second study[27] stated that their sample size was insufficient to reliably detect differences based on principal diagnosis (i.e., depression vs. anxiety). The remaining three studies[22,24,25] only reported results by treatment group (i.e., iCBT or control), making the effectiveness of iCBT in each of their diagnostic subgroups unclear.

Use of Pharmacotherapy

No studies provided information on the use of pharmacotherapy following treatment with iCBT in patients with mixed depression or anxiety disorders.

Safety

One study monitored deterioration rates (defined as more than a 15% deterioration on DASS-21 scores between pre-treatment and follow-up) throughout the trial. One patient (3%) had deteriorated at post-treatment with a total of four deteriorating by 3-month follow-up (12%).

Quality of Life

One RCT[22] reported an improvement in the quality of life (according to SF-12 scores) for patients receiving iCBT compared to CAU.

Satisfaction with Care

Five RCTs[22-24,26,27] reported on satisfaction of care with iCBT for patients with major depression, anxiety disorders, or comorbid diagnoses. The Berger et al.[22] study indicated that patients on iCBT reported a high level of satisfaction with their iCBT treatment. Carter et al.[23] concluded that iCBT was typically rated favourably by patients referred to a secondary care service as assessed by a series of questionnaires. This study[23] reported no significant differences between diagnostic groups on ratings of treatment satisfaction or treatment acceptability ($p > 0.05$). The authors of the Newby et al.[24] study suggested that patients who completed their iCBT program were highly satisfied. Finally, 93% and 84% of patients that completed a post-treatment questionnaire indicated that they were very or mostly satisfied with iCBT treatment in the Titov et al.[27] and Johnston et al.[26] studies, respectively.

Patient Adherence and Dropout

Six RCTs[22-27] reported on patient adherence and dropout with iCBT in patients with major depression, anxiety disorders, or comorbid diagnoses. Information on the number of dropouts, attrition rates, and the number of iCBT modules completed by patients was reported by study authors. The percentage of patients completing all iCBT modules ranged from 45% in the Bell et al. study[25] to 89% in the Newby et al.[24] study. One RCT[22] was able to conduct post-treatment questionnaires in 57 (81%) iCBT patients versus 63 (91%) in the CAU group. The Carter et al.[23] and Bell et al.[25] studies collected post-treatment information from 30 (75%) patients in the iCBT group and 38 (88%) in the wait list control. The remaining three RCTs[24,26,27] reported that post-treatment questionnaires were completed by 88% (43/49),[24] 87% (81/93),[26] and 90% (34/39)[27] of patients in the iCBT groups and 83% (50/60),[24] 89% (41/46)[26] and 92% (35/38)[27] of patients in the wait list control groups, respectively.

Limitations

A number of limitations were identified in the critical appraisal (Appendix 3), however, additional limitations exist.

Although a relatively large number of RCTs were examined, this review was restricted to literature published since 2008 and not included in the systematic reviews summarized in the clinical section of the HQO and CADTH collaborative project entitled “Internet-Delivered Cognitive Behavioural Therapy for Major Depressive Disorder and Anxiety Disorders: A Health Technology Assessment”.[17] Therefore, the evidence summarized here should not be interpreted without also considering the analysis in that report.

While all studies investigated iCBT, there were eight unique programs included in this review.[19-27] The interventions were heterogeneous with respect to program content, number of modules, duration, level of guidance (e.g., therapist, clinician, coach, unguided), and frequency of support (e.g., daily, weekly, only when requested by the patient). Patients may respond differently to various iCBT programs depending on the individual characteristics. As an example, some patient subgroups may respond better to treatment programs that offer a high level of therapist-support, while others may find unguided iCBT to be more useful. The appropriateness of combining such heterogeneous studies is unclear.

One potentially major limitation in the design of the included studies was that patient and outcome assessor blinding was not possible due to the nature of iCBT as an intervention. Given that a large number of outcomes reported in these trials were based on subjective questionnaires this may have had an effect on the reliability of the results. Additionally, the differences in baseline use of pharmaceutical agents (e.g., antidepressants, anxiolytics) between treatment groups were often documented but not controlled for. One study[19] instructed all physicians in the trial to not increase the dosage of medications that patients received in both the iCBT and care as usual groups (decreases were permitted). The authors of two studies[26,27] stated in their inclusion criteria that only patients who did not intend to change the dose of their medication during the course of the program were included. These risks of bias may have confounded the treatment effects of iCBT.

All studies[19-27] included in this review aimed to find statistically significant differences between treatment with iCBT and control groups (e.g., wait list control or treatment as usual) on various scales that measure symptom severity, quality of life, or satisfaction with care. It should be noted that a statistically significant difference in scores on these scales does not necessarily indicate a clinically significant improvement in symptoms, quality of life, or treatment satisfaction. Although there is literature that seeks to determine what the minimal clinically important difference on these scales is, it was not discussed in detail within the studies included in this review.

Another limitation that should be considered is that these studies only examined patients that met clinical threshold for diagnosis (of either major depression or anxiety disorders). Although this was part of our inclusion criteria, it is important to note that mental health conditions are complex and that many patients that may seek help for symptoms of depression or anxiety may be of sub-clinical threshold; however, the effectiveness of iCBT in these populations is outside of the scope of this report. Additionally, recruitment of patients into five of the included studies[21,22,24,26,27] relied on individuals to reach out to study investigators after seeing advertisements in newspapers, websites, university campuses, hospitals, or primary care centers. This method of recruitment through self-selection may have represented a motivated subset of people with depression or anxiety disorders that are more likely to complete iCBT programs and to apply their learning in their lives.

No data was available comparing iCBT to traditional face-to-face CBT (individual or group format). Additionally, evidence comparing guided CBT to unguided CBT was only available in one trial.[20] Adverse events resulting from treatment with iCBT were not well-documented in the included studies; therefore, the safety of iCBT is unclear.[19-27]

The nine included RCTs were not conducted in Canada or North America; hence the results of these studies may not be generalizable for the Canadian setting. The majority of participants in all studies were female (patient populations ranged from 59%[26] to 76%[20] female), although this may be a result of the higher prevalence of both major depression and anxiety disorders in that group.[30,31] The findings presented in this review are specific to

major depression and anxiety disorders as classified by the DSM-V. Therefore, these results are not generalizable to patients with postpartum depression, bipolar disorder, dysthymia, seasonal affective disorder, psychotic disorders, drug or alcohol dependence related depression and anxiety, obsessive compulsive disorder, post-traumatic stress disorder, and major depression or anxiety resulting from physical disorders (e.g., cancer, stroke, diabetes, or acute coronary syndrome).

Conclusions and Implications for Decision or Policy Making

Nine randomized controlled trials were identified regarding the clinical effectiveness of iCBT for patients with mild to moderate major depression or anxiety disorders.[19-27]

Evidence from the included studies showed that treatment with iCBT may lead to a larger reduction of symptom severity in adult patients with major depression and anxiety disorders than wait list, CAU alone, or iTAU alone.[20-27] The exception to this was the Eriksson et al.[19] study, where iCBT demonstrated non-inferiority to TAU. Additional clinical outcomes, including use of pharmacotherapy, quality of life, satisfaction with treatment, and remission and recovery rates also generally favoured iCBT groups.[19-27] Information on how iCBT compared to face-to-face CBT was not identified in this review.

The applicability of the evidence base to Canadian settings is unclear as all studies were conducted outside of North America, however there is no strong evidence suggesting that the results would not generalize to Canadians with depression or anxiety. The reviewed iCBT interventions appeared to be quite heterogeneous in program content and it is unclear which features may be most beneficial to patients (e.g., number of modules, duration of program, frequency and type of support).

The limitations of the included studies and of the report should be considered when interpreting the results. Additionally, due to the supplementary nature of this report, the evidence summarized here should not be interpreted without also considering the analysis conducted in the HQO and CADTH collaborative project entitled “Internet-Delivered Cognitive Behavioural Therapy for Major Depressive Disorder and Anxiety Disorders: A Health Technology Assessment”.[17] Further research investigating the effectiveness of iCBT compared to face-to-face CBT, the effect of guided versus unguided iCBT, and the association between use of iCBT and adverse events would diminish uncertainty.

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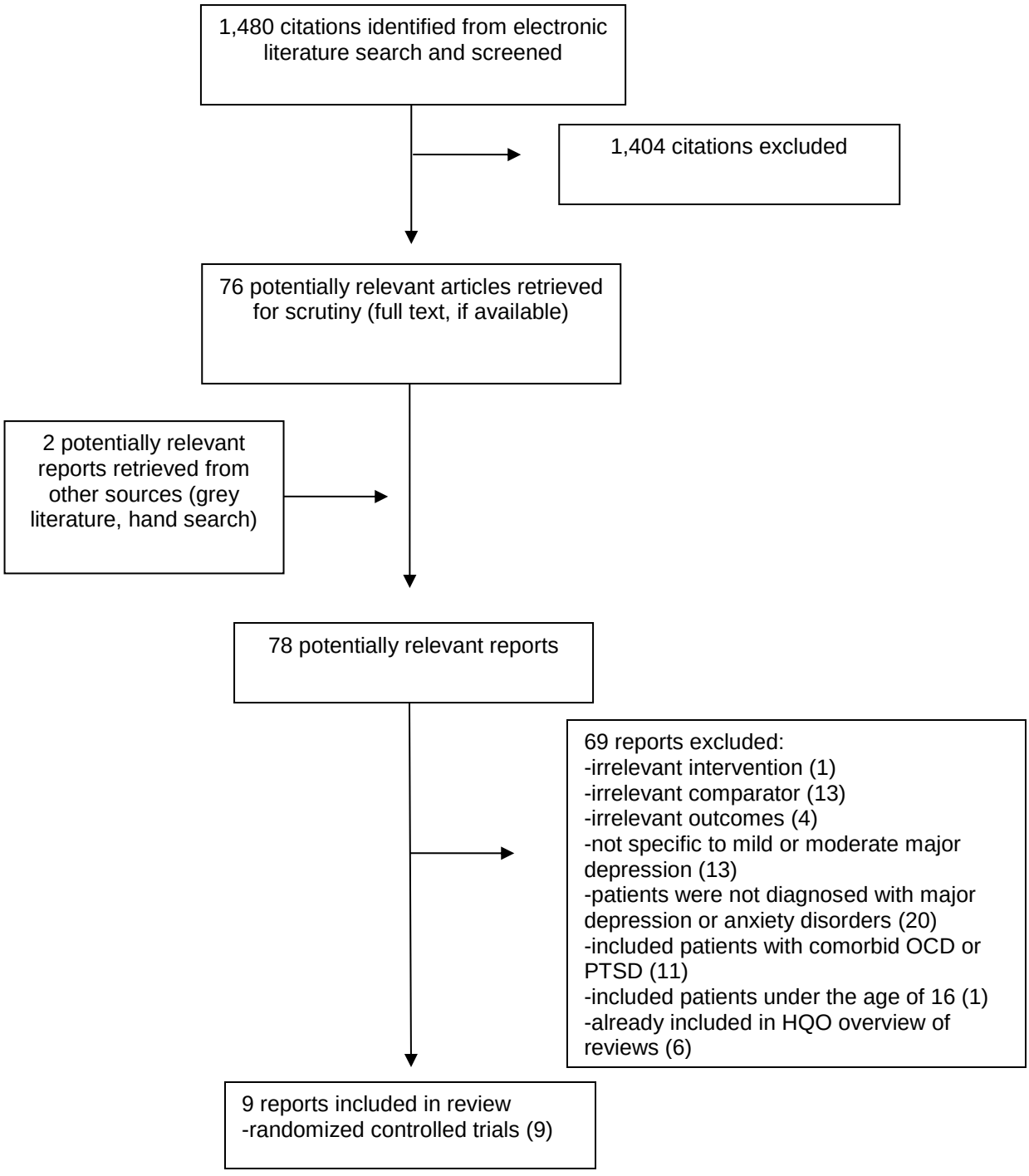
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Primary Studies

First Author, Publication Year, Country	Study Design and Objective	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
Major Depression					
Eriksson, 2017[19] Sweden	RCT, multi-center, open-label, non-inferiority trial To evaluate the long-term effects (6 and 12 months) of iCBT for treatment of mild and moderate depression compared to TAU in PCCs in Sweden.	Adults (aged ≥18 years) with confirmed diagnosis of depression (according to DSM-IV), MADRS-S score < 35 and accessibility to internet. N= 90 (52 iCBT group and 38 in TAU group) Sex: 63 female participants, 27 male participants Age (mean): 37 years	Therapist-guided iCBT (Depressionshjalpen 7 modules, 3 month treatment period). Guidance, which consisted of telephone and email support, was provided by licensed psychologists or psychotherapists, except for two psychologists under supervision to be licensed. All were trained in CBT and had experience in treating depression *"…based on a structured CBT approach, with strong emphasis on behavioral activation and components of acceptance and commitment therapy"* (page 129)	TAU *"This could include scheduled contacts with [general practitioners], nurses and other personnel at the [primary care center], face-to-face psychotherapy, antidepressants, sick leave certification and combinations of these treatments."* (page 129)	Primary outcomes: - Reduction in depressive symptoms (BDI-II questionnaires) Secondary outcomes : - Psychological distress (GHQ-12) - Quality of life (EQ-5D) - Use of medications (antidepressants and sedative) - Number of patients on sick leave and numbers of sick days taken Follow-up: 3, 6, 12 months
Montero-Marin, 2016[20] Spain	RCT, multi-center, open-label, parallel, 1:1:1 ratio "*Our aim was to compare the effectiveness of a low-intensity therapist-guided internet-based*	Adults (aged 18-65 years), understand Spanish, mild or moderate symptoms of depression (BDI-II) lasting longer than 2 weeks. N= 296 (98 in no guidance group, 96 in	iTAU + iCBT (Smiling is Fun: 10 modules expected to be completed over 10 weeks) with either low-intensity therapist-guidance or no guidance. Low-intensity guidance was provided by trained psychotherapists using email to offer help with	iTAU *"This treatment was provided by their [general practitioners], who had previously received a 3-hour training program to update their*	Primary outcomes: - Measure of depression severity (BDI-II) Secondary outcomes: - Quality of life (ED-5D, VAS and SF-12) - Use of medication, mental health services, and other health services

Table 2: Characteristics of Included Primary Studies

First Author, Publication Year, Country	Study Design and Objective	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
	program and a completely self-guided internet-based program with improved treatment as usual (iTAU) care for depression." (page 1)	low-intensity therapist-guided group, and 102 in iTAU group) Sex: 224 female participants, 72 male participants Age (mean): 43 years	any difficulties or problems encountered when using the program. Participants could also ask clinical questions or ask for advice via email (maximum of three contacts over the treatment period). Both treatment groups could reach out to a technician for technical problems. The modules are oriented to work on different psychological techniques to provide the patient with the opportunity to learn and practice adaptive ways to cope with depression and daily problems	*knowledge on how to diagnose and treat depression in primary care, based on the National Institute for Health and Care guidelines."* (page 3)	- Attrition rates Follow-up: 15 months
Social Anxiety Disorder					
Stolz, 2018[21] Switzerland	RCT, open-label, parallel, 2:2:1 ratio To compare the efficacy of guided iCBT for conventional computers and smartphones with a wait list control group.	Adults (aged ≥18 years) with a primary diagnosis of SAD according to *DSM–IV* without a history of psychotic or bipolar disorders or active suicidal plans. N = 150 (60 in conventional computer group, 60 in smartphone group, and 30 in wait list control group) Age (mean): 34.8 (34.6 in conventional	Coach-guided iCBT delivered using either a conventional computer or a smartphone (8 modules to be completed over 12 weeks). Guidance was provided by the primary author and advanced master's students in clinical psychology via a text-based messaging system. Feedback and encouragement to engage in the program was provided on a weekly basis. Patients could also	Wait list control	Primary outcomes (composite): - Symptoms of SAD (SPS, SIAS, and LSAS-SR) - Diagnostic status (SCID-I) Secondary outcomes: - Depression (BDI-II) - General symptomatology (BSI) - Interpersonal problems (IIP-64) - Quality of life (SF-12 Health Survey) - Number of patients meeting criteria for

Table 2: Characteristics of Included Primary Studies

First Author, Publication Year, Country	Study Design and Objective	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
		computer group, 34.7 in smartphone group, and 35.2 in wait list control group) Sex: 56 male participants, 94 female participants	reach out with specific questions. *"The treatment targets both behavioral and cognitive maintaining factors, such as self-focused attention, negative automatic thoughts, experiential avoidance, processing of self as an object under social evaluation, ruminative post event processing of social situations, safety behaviors and biased perception of somatic and cognitive anxiety symptoms."* (page 295)		diagnostic status at post-treatment - Number of dropouts Follow-up: 12 weeks, 6 months
Mixed Disorders					
Berger, 2017[22] Switzerland	RCT, multi-center, open-label, 1:1 ratio To compare the effectiveness of transdiagnostic, unguided iCBT and CAU with CAU alone.	Adults (aged ≥18 years), seen an MD/GP and received approval, confirmed diagnosis of SAD, PDA and/or GAD (according to DSM-IV) with no medical or objections to the patients participation and internet accessibility N = 139 (70 in iCBT plus CAU group, 69 in CAU group) Age (mean): 42.0 years for both groups	Transdiagnostic, unguided iCBT (Velibra: 6 treatment modules over a 9 week period) plus CAU *"The six treatment modules are cognitive–behavioural in orientation and emphasize transdiagnostic principles, such as anxiety as an evolutionary adaptive emotion, the 'false alarm' model of anxiety, experiential avoidance, and the role of approach v. avoidance motivation."*	CAU (no additional information on what CAU consisted of was provided)	Primary outcomes: - Self-help report measure (pre/post-treatment and follow-up) through internet - Disorder unspecific measures (assessed using DASS-21, BAI, BDI-II, BSI, GSI, and SF-12) - Number of patients meeting criteria for diagnostic status at post-treatment Secondary outcomes: - Disorder-specific measures (SPS and SIAS) - Cognition measures

Table 2: Characteristics of Included Primary Studies

First Author, Publication Year, Country	Study Design and Objective	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
		Sex: 98 female participants,41 male participants Psychotherapy: 51 participants were currently in psychotherapy and 47 participants were taking prescribed medication	(page 71)		(ACQ) - Body sensation measures (BSQ) - Agoraphobia measures (MIA/MIB) - Pathological worry measure (PSWQ-16) - Patient satisfaction (CSQ-8) Follow-up: 6 months
Carter, 2013[23] New Zealand	RCT, multi-center, open-label, 1:1 ratio *"To evaluate the suitability and acceptability of computerised cognitive behaviour therapy."* (page 1)	Adults (aged 18-65 years), primary diagnosis of GAD, panic disorder with or without agoraphobia, or social phobia (according to DSM-IV). N = 88 (40 in iCBT group, 48 in wait list group) This participant population appears to be the same as the one in the Bell, 2012[25] study	Guided iCBT (CLIMATE program: 4 to 6 sessions over a 12 week period). Guidance came in the form of minimal contact from research assistants (who were not clinicians) every two weeks to ensure participants were not having any technical difficulties and to encourage participation. *"…utilises cognitive behavioural principles that have been shown to be effective in the treatment of anxiety disorders."* (page 144)	Wait list control (also received phone calls every 2 weeks)	No clinical outcomes. Data collected on recruitment and retention of patients by diagnosis, treatment ratings, satisfaction, treatment accessibility and telephone support Follow-up: 12 weeks (end of assessment), 24 weeks
Newby, 2013[24] Australia	RCT, multi-center, open-label, 1:1 ratio To assess the effectiveness of iCBT compared to WLC in patients	Adults (aged ≥18 years) meeting the DSM-IV criteria for GAD and/or MDD with stable dosage of medication for at least 2 months prior to study. N = 99 (46 in iCBT	Clinician-guided transdiagnostic iCBT (Worry and Sadness Program: 6 modules completed over a 10 week period). Guidance was defined as regular email and/or telephone support	Wait list control	Primary outcomes: - Measure depression severity (PHQ-9) - Generalized anxiety (GAD-7) - Non- psychological distress (K-10)

Table 2: Characteristics of Included Primary Studies

First Author, Publication Year, Country	Study Design and Objective	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
	diagnosed with MDD and GAD (co-morbidity) in a primary setting	group, 53 in WLC group) Sex: 77 female participants and 22 male participants Age (mean): 44.3 years	provided by a Ph.D. clinical psychologist or by a research support officer under their supervision. After lesson two, support was provided by patient request or if there was deterioration in the K-10 or PHQ-9 scores. *"Lesson content is presented in the form of an illustrated story about two fictional characters who experience anxiety and depression, and gain mastery over their symptoms using CBT techniques (e.g. activity scheduling)."* (page 2638)		Secondary outcomes: - Measure of disability (WHODAS-II) - Psychometric properties (BDI-II) - Worry (PSWQ) - Personality dimension of neuroticism (NEO-FFI-N) - Number of patients meeting diagnostic criteria for GAD or MDD - Treatment satisfaction scores Follow-up: 3 months
Bell, 2012[25] New Zealand	RCT, open-label, 1:1 ratio To compare the effectiveness of iCBT with wait list control for treatment of patients with anxiety disorder (social phobia, panic disorder, GAD).	Adults (aged 18-65 years), diagnosis of GAD, panic disorder or social phobia (according to DSM-IV), computer access, English proficiency. N= 83 (40 in iCBT group, 43 in WLC group) Age (mean): 35.3 years (33.6 years in iCBT group and 36.9 years in WLC group) Sex: 56 female participants,27 male	Guided CRUfAD iCBT program (4 to 6 sessions over a 12 week period). Guidance came in the form of minimal contact from research assistants (who were not clinicians) every two weeks to ensure participants were not having any technical difficulties and to encourage participation. *"The lessons provided education about the symptoms and treatment of the particular disorder, gave instructions about developing an exposure*	Wait list control (also received phone calls every 2 weeks)	Primary outcomes: - Self-report scores (WSAS) - Measure of anxiety (PGI) Secondary outcomes: - Anxiety symptom and panic disorder specific measures (GADI, PSWQ, PDSS-SR, LSAS, FNE, FQ, BAI) Tertiary outcomes: - Depression rating scores (BDI-II) - Self-report scores (Likert scale) Other outcomes:

Table 2: Characteristics of Included Primary Studies

First Author, Publication Year, Country	Study Design and Objective	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
		participants This participant population appears to be the same as the one in the Carter, 2013[23] study.	*hierarchy and practising graded exposure, demonstrated principles of cognitive restructuring and concluded with information about relapse prevention."* (page 632)		- Completion rates by diagnosis Follow-up: 12, 24 weeks
Johnston, 2011[26] Australia	RCT, parallel, multi-center, open-label, 1:1:1 ratio To determine whether transdiagnostic iCBT is effective and results in change for specific disorders when a coach is consulted rather than a clinician.	Adults (aged ≥18 years) diagnosed with GAD, panic disorder or social phobia (according to DSM-IV) who are not currently participating in CBT, not using illicit drugs or consuming more than three drinks a day, not experiencing psychotic mental illness, and have a consistent dose of medication for more than a month. N = 131 (42 in WLC group, 46 in clinician group and 43 in coach group) Age (mean): 41.6 years (39 years for coach group, 44 years for clinician group, and 42 years for WLC group) Sex: 54 female participants, 77 male participants	Transdiagnostic iCBT (Anxiety Program: 8 lessons over a 10 week period) with either clinician support or coach support. Clinician support was provided by a clinical psychologist who had previous experience with iCBT. The clinician was able to provide clinical advice and to expand on the information provided by the program. The coach support was provided by a registered psychologist without specialist post-graduate training, who was employed as a Research Assistant. The coach was not permitted to provide clinical advice or to add to the information or skill provided in the program *"Each Lesson began with a restatement of the key skills described in previous lessons, an introduction to skills described in the current*	Wait list control	Outcomes: - Symptom severity (MINI, GAD-7, DASS-21, PSWQ) - Rates of remission (GAD-7 total score ≥8) and recovery (a reduction of 50% of pre-treatment GAD-7) - Social anxiety measure (SIAS-6/SPS-6) - Panic disorder severity (PDSS-SR) - Severity of depression (PHQ-9) - Psychosocial functioning measure (SDS) - Number of patients meeting diagnostic criteria following treatment - Treatment satisfaction Follow-up: 3 months

Table 2: Characteristics of Included Primary Studies

First Author, Publication Year, Country	Study Design and Objective	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
			lesson, illustrated examples about people with each of the target disorders practicing those skills, and a summary of the main points." (page 4)		
Titov, 2011[27] Australia	RCT, multi-center, open-label, 1:1 ratio To determine the efficacy of iCBT compared to WLC to treat depression as well as three anxiety disorders (GAD, social phobia, PDA).	Adults (aged ≥18 years) diagnosed with MDD, GAD, panic disorder and/or social phobia (according to DSM-IV) who are not currently participating in CBT, not using illicit drugs or consuming more than three drinks a day, not experiencing psychotic mental illness, and have a consistent dose of medication for more than a month. N = 74 (37 in iCBT group and 37 in WLC group) Sex: 54 female participants, 30 male participants Age (mean): 43.9 years (44.8 years in iCBT group and 42.9 years in WLC group)	Therapist-guided transdiagnostic iCBT (the Wellbeing Program: 8 online lessons over a 10 week period). Guidance was provided in the form of weekly telephone calls or instant messaging with patients by a clinical psychologist. These contacts aimed to reinforce progress, provide a summary of key skills learned in the weekly lesson, normalize difficulties with treatment, encourage participation, and to answer participants' questions. *"Each Lesson began with a summary of the key skills described up to that point in the program, an introduction to the skills to be described in that Lesson, illustrated examples about people with depression and/or anxiety practicing those skills, and a summary of the main points."* (page 446)	Wait list control	Primary outcomes: - Diagnostic measure (MINI) - Generic outcome measure (DASS-21) - Disorder-specific measure (PHQ-9, PSWQ, SP-12, PDSS-SR) Secondary outcomes: - Anxiety measure (GAD-7, NEO-FFI-N) - Psychosocial measure (SDS) - Number of patients meeting diagnostic criteria following treatment - Rates of remission and recovery (measured using DASS-21, PHQ-9, and GAD-7 scores) - Deterioration rates Follow-up: 3 months

ACQ = Anticipatory Cognitions Questionnaire; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; BSI = Brief Symptom Inventory; BSQ = Body Sensations Questionnaire; CAU = case as usual; CBT = cognitive behavioural therapy; CRUfAD = Clinical Research Unit for Anxiety and Depression; CSQ = Client Satisfaction Questionnaire; DASS = Depression and Anxiety Stress Scale; DSM = Diagnostic and Statistical Manual of Mental Disorders; EQ-5D = EuroQol – Five Dimension; FNE = Fear of Negative Evaluation; FQ = Fear Questionnaire; GAD = generalized anxiety disorder; GADI = Generalised Anxiety Disorder Assessment Inventory; GHQ-12 = General Health Questionnaire; iCBT = internet-delivered cognitive behavioural therapy; IIP = Inventory of Interpersonal Problems; iTAU = improved treatment as usual; K-10 = Kessler 10-item Psychological Distress scale; LSAS-SR = Liebowitz Social Anxiety Scale-Self-Report; MADRS-S = Montgomery–Åsberg Depression Rating Scale – self rating; MDD = major depressive disorder; MIA/MIB = Mobility Inventory for Agoraphobia; MINI = Mini International Neuropsychiatric Interview; NEO-FFI-N = NEO-Five Factor Inventory – Neuroticism Subscale; PCC = primary care centers; PDA = panic disorder with or without agoraphobia; PDSS-SR = Panic Disorder Severity Scale for social phobia; PGI = Patients Global Impression ; PHQ-9 = Patient Health Questionnaire; PSWQ = Penn State Worry Questionnaire; RCT = randomized controlled trial; SAD = social anxiety disorder; SCID = Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders; SDS = Sheehan Disability Scales; SF-12 = Short form health survey; SIAS = Social Interaction Anxiety Scale; SPS = Social Phobia Scale; TAU = treatment as usual; VAS = Visual Analog Scale; WHODAS-II = World Health Organization Disability Assessment Scale; WLC = wait list control; WSAS = Work and Social Adjustment Scale.

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Primary Studies using Downs and Black Checklist

Strengths	Limitations
Major Depression	
Eriksson, 2017[19]	
• The objectives, interventions, controls, and main outcomes are clearly described • Patients were consecutively randomized by an independent research unit (concealed from investigators) • Dropouts were relatively balanced between treatment and control groups and data on these patients were discussed • Treatment groups were overall balanced in baseline patient characteristics and any differences were well-documented (current use of sedatives was the only characteristic to reach statistical significance) • Study participants, care providers, and setting appear to be representative of the population and care setting of interest (although the authors noted that the sample's mean age of 36 was younger than the assumed mean age of all the patients of a typical primary care clinic) • Actual probability values (*P*-values) were reported • The authors declared they had no conflicts of interest and the source of funding was provided (grants from a Swedish Social Insurance Agency and Region Västra Götaland)	• It is unclear if there were any adverse events resulting from the intervention • Due to the nature of the intervention, patients and assessors were not blinded to treatment assignment • Although sample size calculations were undertaken, the number of patients recruited did not meet the number estimated by the calculations (142 estimated vs. 90 randomized) • Intention-to-treat analysis was not conducted
Montero-Marin, 2016[20]	
• The objectives, interventions, controls, and main outcomes are clearly described • Detailed methodology on patient recruitment and assessment of inclusion/exclusion criteria is included • Study participants were individually randomized using block randomization to the three treatment groups. Blocks were created using a computer-generated random number sequence and allocation was done by an individual not otherwise involved in the study • Sample size calculations were undertaken and the appropriate number of patients recruited (300 estimated vs. 296 randomized) • Treatment and control groups were overall balanced in baseline patient characteristics • Intention-to-treat analysis was conducted • Study participants, care providers, and setting appear to be representative of the population and care setting of interest • Outcome assessors were blind to the treatment received • Length of follow-up was consistent between the three groups • Characteristics of dropouts were discussed (no differences in baseline characteristics for sociodemographic and primary or secondary outcomes were observed between completers and non-completers). No significant difference in	• It is unclear if there were any adverse events resulting from the intervention • Due to the nature of the intervention, patients were not blinded to treatment assignment

Table 3: Strengths and Limitations of Primary Studies using Downs and Black Checklist

Strengths	Limitations
dropout rates between groups • Estimates of random variability (standard errors) and actual probability values (*P*-values) were reported • The authors declared they had no conflicts of interest and the source of funding was provided (grants from the Instituto de Salud Carlos III of the Ministry of Economy and Competitiveness and the European Union)	
Social Anxiety Disorder	
Stolz, 2018[21]	
• The objectives, interventions, controls, and main outcomes are clearly described • Detailed methodology on patient recruitment and assessment of inclusion/exclusion criteria is included • Randomization was performed using a computerized random number generator with allocation concealed from investigators • Sample size calculations were undertaken and the appropriate number of patients recruited • Treatment groups were overall balanced in baseline patient characteristics and any differences were well-documented • Intention-to-treat analysis was conducted • Dropouts were relatively balanced between treatment and control groups and data on these patients were discussed • Length of follow-up was consistent between the three groups • Estimates of random variability (standard errors/deviations) and actual probability values (*P*-values) provided • Study participants, care providers, and setting appear to be representative of the population and care setting of interest	• It is unclear if there were any adverse events resulting from the intervention • Blinding of assessors was compromised because some participants disclosed information about treatment during interviews • Although a source of funding was provided (Swiss National Science Foundation Grant), potential conflicts of interest were not disclosed
Mixed Disorders	
Berger, 2017[22]	
• The objectives, interventions, controls, and main outcomes are clearly described • Detailed methodology on patient recruitment and assessment of inclusion/exclusion criteria is included • Randomization was performed using a random number generator with allocation concealed from investigators and patients • Stratified randomization was conducted to ensure a balanced distribution of primary diagnosis, medication and concurrent psychotherapy between groups • Intention-to-treat analysis was conducted • Time to post-treatment assessment was consistent between groups (3 months) • Estimates of random variability (standard errors/deviations) and actual probability values (*P*-values) provided • Study participants, care providers, and setting appear to be	• It is unclear if there were any adverse events resulting from the intervention • Due to the nature of the intervention, patients and assessors were not blinded to treatment assignment • The dropout rate in the treatment group was relatively high (19% compared to 9% in the control group at post-treatment; 37% at 6-month follow-up) • One author disclosed that they were employed as a research director the company that developed, owns and operates the internet intervention investigated in this trial • Although sample size calculations were undertaken, the number of patients recruited did not meet the number estimated by the calculations to detect a small to medium effect (176 estimated vs. 139 randomized)

Table 3: Strengths and Limitations of Primary Studies using Downs and Black Checklist

Strengths	Limitations
representative of the population and care setting of interest (although the authors noted that the sample had a higher level of education than the general population) • The trial's source of funding was provided (Swiss National Science Foundation Grant)	
Carter, 2013[23]	
• The objectives, interventions, controls, and main outcomes are clearly described • Detailed methodology on patient recruitment and assessment of inclusion/exclusion criteria is included • Randomization was done using a stratified block design for the primary diagnosis (GAD, social phobia or panic disorder) by the clinical research unit coordinator who was not directly involved in the implementation of the study (clinicians and the study coordinator were not involved in allocation) • Characteristics of patients who were lost to follow-up were discussed • Estimates of random variability (standard deviations) and actual probability values provided • Study participants, care providers, and setting appear to be representative of the population and care setting of interest • The trial's source of funding was provided (the Canterbury District Health Board, the Canterbury Medical Research Foundation, and New Zealand Lottery Grants Board) • The authors stated that they had no conflicts of interest	• Details on baseline patient characteristics other than their primary diagnosis are lacking (e.g., there was no mention of age or sex) • It is unclear if there were any adverse events resulting from the intervention • Intention-to-treat analysis was not conducted • Due to the nature of the intervention, patients and assessors were not blinded to treatment assignment • A large number of patients randomized to the treatment group (14/40, 35%) did not complete treatment • Sample size calculations were not conducted • Outcomes were not compared between the iCBT group and the wait list group, but were discussed between diagnostic groups within the iCBT group
Newby, 2013[24]	
• The objectives, interventions, controls, and main outcomes are clearly described • Detailed methodology on patient recruitment and assessment of inclusion/exclusion criteria is included • Randomization was done using a random number service by a team member that was not involved in the study • Sample size calculations were undertaken and the appropriate number of patients recruited • Treatment and control groups were overall balanced in baseline patient characteristics and any differences were well-documented (disability on the WHODAS-II was the only characteristic to reach statistical significance) • Length of follow-up was consistent between the treatment and control groups • Intention-to-treat analysis was conducted • Estimates of random variability (standard deviations) and actual probability values provided • Dropouts were relatively balanced between treatment and control groups and data on these patients were discussed • Study participants, care providers, and setting appear to be representative of the population and care setting of interest • The authors stated that they had no conflicts of interest	• It is unclear if there were any adverse events resulting from the intervention • Patients and assessors were not blinded to treatment assignment • Source of funding was not disclosed

Table 3: Strengths and Limitations of Primary Studies using Downs and Black Checklist

Strengths	Limitations
Bell, 2012[25]	
• The objectives, interventions, controls, and main outcomes are clearly described • Detailed methodology on patient recruitment and assessment of inclusion/exclusion criteria is included • Randomization was done using a stratified block design for the primary diagnosis (GAD, social phobia or panic disorder) by the clinical research unit coordinator who was not directly involved in the implementation of the study (clinicians and the research assistant were not involved in allocation) • Treatment and control groups were overall balanced in baseline patient characteristics • Sample size calculations were undertaken and the appropriate number of patients recruited (80 estimated vs. 83 randomized) • Study participants, care providers, and setting appear to be representative of the population and care setting of interest • Length of follow-up was consistent between the treatment and control groups (12 and 24 weeks) • Estimates of random variability (standard errors) and actual probability values (*P*-values) provided • The authors declared they had no conflicts of interest and the source of funding was provided (financed by the Canterbury Medical Research Foundation and the New Zealand Lottery Grants Board)	• It is unclear if there were any adverse events resulting from the intervention • It is unclear if patient or outcome assessors were blinded to the treatment assignment (it is likely they were not) • The dropout rate in the treatment group was relatively high (35% of patients randomized to iCBT did not complete treatment). Differences in drop-outs between diagnostic groups were not significant • Intention-to-treat analysis was not conducted
Johnston, 2011[26]	
• The objectives, interventions, controls, and main outcomes are clearly described • Detailed methodology on patient recruitment and assessment of inclusion/exclusion criteria is included • Sample size calculations were undertaken and the appropriate number of patients recruited (108 estimated vs. 139 randomized) • Treatment groups were overall balanced in baseline patient characteristics and any differences were well-documented • Study participants, care providers, and setting appear to be representative of the population and care setting of interest • Length of follow-up was consistent between the treatment and control groups (3 months) • Estimates of random variability (standard deviations) and actual probability values (*P*-values) provided • Intention-to-treat analysis was conducted (baseline observations were carried forward) • The authors declared they had no conflicts of interest and the source of funding was provided (the National Health and Medical Research Council of Australia, the New South Wales Institute of Psychiatry, and the Australian Rotary Health Research Fund)	• It is unclear if there were any adverse events resulting from the intervention • Patients and assessors were not blinded to treatment assignment • The dropout rates in the treatment groups were relatively high (26% and 24% of patients did not complete all lessons in the coach-supported and clinician-supported groups, respectively)

Table 3: Strengths and Limitations of Primary Studies using Downs and Black Checklist

Strengths	Limitations
Titov, 2011[27]	
• The objectives, interventions, controls, and main outcomes are clearly described • Detailed methodology on patient recruitment and assessment of inclusion/exclusion criteria is included • Treatment groups were overall balanced in baseline patient characteristics and any differences were well-documented (the iCBT group had significantly higher PDSS-SR scores and marginally higher DASS-21 scores pre-treatment) • Study participants, care providers, and setting appear to be representative of the population and care setting of interest • Sample size calculations were undertaken and the appropriate number of patients recruited (72 estimated vs. 77 randomized) • Estimates of random variability (standard deviations) and actual probability values (*P*-values) provided • Intention-to-treat analysis was conducted (baseline observations were carried forward) • Dropouts were relatively balanced between treatment and control groups • Information on patients who deteriorated (according to DASS-21 scores) was provided	• Follow-up (at 3 months) was only conducted for the treatment group • Patients and assessors were not blinded to treatment assignment • Although a source of funding was provided (Australian National Health and Medical Research Council), potential conflicts of interest were not disclosed

ACOG = American College of Obstetricians and Gynaecologists; DASS-21 = Depression Anxiety Stress Scales-21 item; EBM = Evidence-Based Medicine; GRADE = Grading of Recommendations, Assessment, Development and Evaluations; NICE = National Institute for Health and Care Excellence; PDSS-SR = Panic Disorder Severity Scale-Self Rating; QCG = Queensland Clinical Guidelines; RANZCOG = the Royal Australian and New Zealand College of Obstetricians and Gynaecologists; RCT = randomized controlled trial; SOGC = Society of Obstetricians and Gynaecologists Canada.

Appendix 4: Main Study Findings and Author's Conclusions

Table 4: Summary of Findings of Included Studies

<table>
<tr><th>Main Study Findings</th><th>Author's Conclusion</th></tr>
<tr><td colspan="2">Major Depression</td></tr>
<tr><td colspan="2">Eriksson, 2017[19]</td></tr>
<tr><td>
Randomized controlled trial comparing the effectiveness of a therapist-supported iCBT program (Depressionshjalpen, N = 52) compared to treatment as usual (N = 38) for the treatment of patients with major depression.

Comparison of iCBT and treatment as usual control (TAU) with respect to several outcomes
<table>
<tr><th rowspan="3">Measure</th><th colspan="2">Mean score</th></tr>
<tr><th colspan="2">Treatment group</th></tr>
<tr><th>iCBT (N = 52[a], 36[b], 39[c], or 38[d])</th><th>TAU (N = 38[a], 28[b], 31[c], or 30[d])</th></tr>
<tr><td>BDI-II*</td><td></td><td></td></tr>
<tr><td>Pre-treatment[a]</td><td>26</td><td>26</td></tr>
<tr><td>3 month follow-up[b]</td><td>13</td><td>12</td></tr>
<tr><td>6 month follow-up[c]</td><td>13</td><td>11</td></tr>
<tr><td>12 month follow-up[d]</td><td>11</td><td>12</td></tr>
<tr><td>GHQ-12</td><td></td><td></td></tr>
<tr><td>Pre-treatment[a]</td><td>20.9</td><td>20.1</td></tr>
<tr><td>3 month follow-up[b]</td><td>13.2</td><td>12.3</td></tr>
<tr><td>6 month follow-up[c]</td><td>12.0</td><td>11.6</td></tr>
<tr><td>12 month follow-up[d]</td><td>11.5</td><td>13.0</td></tr>
<tr><td>EQ-5D</td><td></td><td></td></tr>
<tr><td>Pre-treatment[a]</td><td>0.65</td><td>0.62</td></tr>
<tr><td>3 month follow-up[b]</td><td>0.75</td><td>0.76</td></tr>
<tr><td>6 month follow-up[c]</td><td>0.79</td><td>0.83</td></tr>
<tr><td>12 month follow-up[d]</td><td>0.79</td><td>0.82</td></tr>
</table>
Notes: confidence intervals for these mean scores were available in the paper; however, they could not be extracted as they were presented in graphical form.
*Primary outcome. P-values were non-significant ($p > 0.05$) at all time intervals.
BDI = Beck Depression Inventory; EQ-5D = EuroQol; SD = standard deviation; GHQ = General Health Questionnaire.

Comparison of iCBT and treatment as usual control (TAU) with respect to use of medication and sick leave
<table>
<tr><th rowspan="3">Outcome</th><th colspan="2">Number of patients (% of total)</th><th rowspan="3">P-value</th></tr>
<tr><th colspan="2">Treatment group</th></tr>
<tr><th>iCBT (N = 52[a], 36[b], 39[c], or 38[d])</th><th>TAU (N = 38[a], 28[b], 31[c], or 30[d])</th></tr>
<tr><td>Taking antidepressants</td><td></td><td></td><td></td></tr>
<tr><td>Pre-treatment[a]</td><td>13 (25%)</td><td>8 (21%)</td><td>NS</td></tr>
<tr><td>3 month follow-up[b]</td><td>8 (22%)</td><td>14 (50%)</td><td>0.020</td></tr>
<tr><td>6 month follow-up[c]</td><td>14 (36%)</td><td>13 (42%)</td><td>NS</td></tr>
<tr><td>12 month follow-up[d]</td><td>15 (40%)</td><td>13 (43%)</td><td>NS</td></tr>
<tr><td>Taking sedatives</td><td></td><td></td><td></td></tr>
<tr><td>Pre-treatment[a]</td><td>5 (10%)</td><td>0 (0%)</td><td>0.049</td></tr>
<tr><td>3 month follow-up[b]</td><td>3 (8%)</td><td>1 (4%)</td><td>NS</td></tr>
<tr><td>6 month follow-up[c]</td><td>2 (5%)</td><td>0 (0%)</td><td>NS</td></tr>
</table>
</td><td>
"The main results in this randomized controlled study with follow-ups until 1 year after treatment start were that no significant differences in reduction of self-reported depressive symptoms were found between ICBT and TAU, either not directly after treatment or at the 1-year follow-up. Furthermore, there were no differences concerning perception of psychological distress, sick leave frequency or total days of sick leave during the 12-month study period. There was a significant difference concerning antidepressant medication; ICBT patients dropped the medication during the 3-month treatment period, but resumed medication during the following months, and the use of antidepressants was almost the same in both groups at the 6- and 12-month follow-ups. No remarkable differences concerning perception of quality of life could be seen during the 12-month period. Therapist contacts were, as expected, significantly more in the TAU group, but there was no increase in other care contacts with the PCCs during the 3-month treatment period. These findings provide support for ICBT as an equally effective treatment as TAU also in the primary care context for patients accepting ICBT treatment." (pages 132 to 133)

"The results of this trial suggests that ICBT with weekly minimal therapist support is non-inferior to the usual treatments in primary care and a treatment alternative also in the long-term perspective for patients with depression in primary care." (page134)
</td></tr>
</table>

Main Study Findings	Author's Conclusion

12 month follow-up[d]	2 (5%)	2 (7%)	NS
On sick leave			
Before inclusion[a]	25 (48%)	15 (40%)	NR
During months 0-3[b]	15 (29%)	12 (32%)	NR
During months 4-6[c]	10 (19%)	9 (24%)	NR
During months 7-12[d]	7 (13%)	6 (16%)	NR

NR = not reported; NS = non-significant.

Montero-Marin, 2016[20]

Randomized controlled trial comparing the effectiveness of low-intensity therapist-guided iCBT (N = 96), a completely self-guided (CSG) iCBT (N = 98), and an improved treatment as usual control group (N = 102) for the treatment of patients with major depression.

Comparison of low-intensity therapist-guided iCBT (LITG), completely self-guided iCBT (CSG), and improved treatment as usual (iTAU) with respect to primary outcomes

	Mean score (SD)		
	Treatment group		
Measure	LITG (N=64[a], 78[b], 69[c], 68[d])	CSG (N=98[a], 75[b], 64[c], 61[d])	iTAU (N=102[a], 86[b], 77[c], 74[d])
BDI-II			
Pre-treatment[a]	21.73 (4.83)	22.59 (4.78)	21.76 (5.39)
Follow-up (3 month)[b]	17.08 (10.24)	16.59 (10.60)	17.91 (11.06)
Follow-up (6 month)[c]	13.56 (11.56)	14.27 (10.00)	18.12 (12.15)
Follow-up (15 month)[d]*	11.39 (10.96)	11.53 (10.72)	16.72 (10.97)

*LITG vs. iTAU: p = 0.01; CSG vs. iTAU: p = 0.001; LITG vs. CSG: p = 0.48. BDI-II scores were used as the primary outcome.
BDI = Beck Depression Inventory; SD = standard deviation.

Comparison of low-intensity therapist-guided iCBT (LITG), completely self-guided iCBT (CSG), and improved treatment as usual (iTAU) with respect to secondary outcomes

	Mean score (SD)		
	Treatment group		
Measure	LITG (N = 64[a], 65[b])	CGS (N = 55[a], 57[b])	iTAU (N = 64[a], 66[b])
Mental SF-12[a]			
Pre-treatment	27.95 (8.78)	28.59 (8.90)	29.13 (11.18)
Follow-up (3 month)	36.97 (12.57)	34.72 (12.46)	35.41 (12.19)
Follow-up (6 month)	42.22 (13.24)	42.35 (11.03)	36.05 (12.38)
Follow-up (15 month)	43.65 (13.41)	43.44 (11.66)	36.35 (12.12)
Physical SF-12[a]			
Pre-treatment[a]	47.98 (10.87)	47.83 (12.29)	48.74 (11.67)
Follow-up (3 month)	49.20 (10.58)	48.84 (11.89)	47.91 (10.31)
Follow-up (6 month)	46.87 (10.79)	47.42 (12.18)	47.56 (10.74)
Follow-up (15 month)	48.05 (9.85)	47.65 (11.89)	47.53 (11.78)
EQ-5D VAS[b]			
Pre-treatment	57.46 (18.23)	53.56 (20.05)	57.80 (15.81)
Follow-up (3 month)	65.85 (21.34)	63.11 (21.61)	62.12 (18.12)
Follow-up (6 month)	69.83 (20.21)	65.81 (21.44)	62.33 (20.83)
Follow-up (15 month)	72.45 (15.93)	68.89 (22.79)	62.59 (20.37)

EQ-5D VAS = visual analogue scale of the EuroQol; SD = standard deviation; SF-12 = Short Form Health Survey .

"There were no clear differences between either CSG or LITG compared with iTAU at Time 1 (Table 2). However, there were differences between iTAU versus CSG, and iTAU versus LITG at Time 2 and at Time 3, with both computerized interventions performing better than usual care. There were no significant differences between CSG and LITG at any time." (page 6)

"This trial compared two Internet-based interventions, with and without psychotherapeutic support, with usual care. We observed differences in the medium and long term in favor of psychotherapy, but not in the short term. This was somewhat consistent with previous studies on depression when comparing face-to-face psychotherapy (alone or plus usual care), with usual care based on medication treatments." (page 10)

"A Spanish-language Internet-based intervention for the treatment of depression (Smiling is Fun) added to usual care proved to be more effective than treatment as usual alone at follow-up assessments. Pending cost-effectiveness analysis, these results suggest that it might be worth investing in this program for PC clinics in Spain, and possibly in other Spanish-speaking settings. The kind of low-intensity support offered in the program did not show additional improvement on the effectiveness of the computerized intervention. It remains to be seen whether or not any other forms of online/telephone support might yield further gains." (page 10)

Main Study Findings	Author's Conclusion

Comparison of low-intensity therapist-guided iCBT (LITG), completely self-guided iCBT (CSG), and improved treatment as usual (iTAU) with respect to other outcomes

Outcome	% of patients, Treatment group: LITG	CGS	iTAU	*P*-value
Attrition rate	33.3%	41.8%	34.3%	0.812
Use of medication				
Pre-treatment	91.7%	85.7%	89.2%	
Post-treatment	67.6%	68.3%	80.6%	0.160
Use of mental health services				
Post-treatment	18.8%	19.7%	29.9%	0.214

Social Anxiety Disorder

Stolz, 2018[21]

Randomized controlled trial comparing the effectiveness of guided self-help iCBT delivered using either a computer (N = 60) or a smartphone application (N = 60) to a wait list control (N = 30) for the treatment of patients with social anxiety disorder.

Comparison of computer-based iCBT (PC), smartphone-based iCBT (App), and wait list control (WL) with respect to several outcomes

Measure	Mean score (SD for observed values; SE for estimated values), Treatment group: PC (N = 60[a], 46[b])	App (N = 60[a], 42[b])	WL (N = 30[a], 23[b])
Composite (SPS, SIAS, LSAS; primary outcome)			
Pre-treatment (observed)[a]	−0.08 (0.9)	0.14 (0.7)	−0.13 (0.9)
Post-treatment (observed)[b]	−1.26 (1.0)	−1.37 (0.9)	−0.45 (1.0)
Post-treatment (estimated)[b]*	−1.28 (0.1)	−1.35 (0.1)	−0.53 (0.2)
Follow-up (estimated)	−1.36 (0.1)	−1.41 (0.1)	
SPS			
Pre-treatment (observed)[a]	37.1 (13.2)	41.1 (13.8)	38.9 (12.4)
Post-treatment (observed)[b]	22.0 (12.9)	22.0 (11.7)	34.7 (11.9)
Post-treatment (estimated)[b]	21.7 (1.8)	22.6 (1.9)	33.5 (2.6)
Follow-up (estimated)	19.6 (1.9)	20.6 (2.0)	
SIAS			
Pre-treatment (observed)[a]	51.3 (15.0)	52.3 (10.4)	46.6 (13.9)
Post-treatment (observed)[b]	36.2 (16.9)	33.2 (14.3)	43.3 (14.6)
Post-treatment (estimated)[b]	36.0 (2.0)	33.0 (2.1)	41.6 (2.8)
Follow-up (estimated)	34.1 (2.1)	31.3 (2.2)	
LSAS			
Pre-treatment (observed)[a]	81.5 (22.1)	87.3 (19.6)	82.6 (20.7)
Post-treatment (observed)[b]	54.8 (12.3)	52.7 (13.9)	74.4 (0.5)
Post-treatment (estimated)[b]	54.6 (3.2)	53.5 (3.3)	74.0 (4.5)
Follow-up (estimated)	51.3 (3.5)	51.1 (3.6)	
BDI			
Pre-treatment (observed)[a]	17.2 (9.2)	19.6 (11.6)	17.4 (12.3)
Post-treatment (observed)[b]	10.3 (8.1)	12.7 (12.3)	18.2 (13.9)

"In the present study, both treatment formats were effective in reducing symptoms of SAD and increasing psychological well-being after 12 weeks of treatment." (page 501)

"Despite these limitations, the present study extends the existing knowledge on iCBT by systematically testing a novel delivery option. Besides easier integration in daily life and routine, mobile CBT could have promise for low and middle-income countries due to a large unmet need for mental health services (Saraceno et al., 2007), in which the coverage of smartphones with an Internet subscription is much higher than those of online desktop computers might ever be (Aranda-Jan, Mohutsiwa-Dibe, & Loukanova, 2014). In conclusion, this study provides evidence that SAD can be effectively treated with mobile self-help applications, with treatment gains being maintained 6 months after randomization." (page 502)

Main Study Findings			Author's Conclusion
Post-treatment (estimated)[b]	10.2 (1.5)	13.3 (1.6)	17.0 (2.2)
Follow-up (estimated)	9.9 (1.6)	13.7 (1.6)	
GSI			
Pre-treatment (observed)[a]	1.2 (0.5)	1.5 (0.6)	1.3 (0.6)
Post-treatment (observed)[b]	0.8 (0.5)	0.8 (0.6)	1.1 (0.6)
Post-treatment (estimated)[b]	0.7 (0.1)	0.8 (0.1)	1.0 (0.1)
Follow-up (estimated)	0.7 (0.1)	0.8 (0.1)	
IIP			
Pre-treatment (observed)[a]	1.8 (0.5)	1.8 (0.4)	1.8 (0.5)
Post-treatment (observed)[b]	1.5 (0.5)	1.4 (0.5)	1.8 (0.6)
Post-treatment (estimated)[b]	1.4 (0.1)	1.4 (0.1)	1.7 (0.1)
Follow-up (estimated)	1.3 (0.1)	1.3 (0.1)	
SF-12			
Pre-treatment (observed)[a]	34.0 (10.2)	31.4 (8.7)	34.9 (10.4)
Post-treatment (observed)[b]	41.8 (11.3)	40.0 (10.4)	35.9 (10.1)
Post-treatment (estimated)[b]*	41.4 (1.4)	40.3 (1.5)	36.8 (2.0)
Follow-up (estimated)	41.8 (1.6)	41.8 (1.7)	

*PC vs. WL: *d* = 0.74 [95% CI: 0.22–1.25]; App vs. WL: *d* = 0.89 [95% CI: 0.35–1.41]; BDI = Beck Depression Inventory; Composite = composite score across SPS, SIAS, and LSAS; GSI = Global Severity Index; IIP = Inventory of Interpersonal Problems; LSAS = Liebowitz Social Anxiety Scale; SD = standard deviation; SE = standard error; SIAS = Social Interaction Anxiety Scale; SF-12 = Short Form-12 health survey, mental subscale; SPS = Social Phobia Scale.

Comparison of computer-based iCBT (PC), smartphone-based iCBT (App), and wait list control (WL) with respect to other outcomes

Outcome	Number of patients (% of total) Treatment group PC (N = 37[a], 60[b])	App (N = 34[a], 60[b])	WL (N= 23[a], 30[b])	*P*-values
Meeting criteria for diagnostic status at post-treatment Completers only[a]	14 (37.8%)	9 (26.5%)	23 (100%)	<0.05
Number of patients lost to follow-up Post-treatment[b]	14 (23.3%)	18 (30.0%)	7 (23.3%)	NS

NS = non-significant.

Mixed Population

Berger, 2017[22]

Randomized controlled trial investigating the effectiveness of a transdiagnostic, unguided iCBT program (velibra) plus care as usual (N = 70) compared to care as usual alone (N = 69) for the treatment of patients with social anxiety disorder (N = 40), panic disorder with or without agoraphobia (N = 63), and/or generalized anxiety disorder (N = 39).

Comparison of iCBT plus care as usual (iCBT + CAU) versus care as usual (CAU) alone with respect to outcomes measured with scales

	Mean score (SD for observed values; SE for estimated values) Treatment group iCBT + CAU (N = 70[a], 57[b],	CAU (N = 69[a],	Between-group effect sizes (Cohen's *d*

"CAU plus unguided ICBT was more effective than CAU at post-treatment, with small to medium between-group effect sizes on primary (Cohen's d = 0.41–0.47) and secondary (Cohen's d = 0.16–0.61) outcomes. Treatment gains were maintained at follow-up." (page 67)

"Among participants who fulfilled the diagnostic criteria for SAD at pretreatment (n = 82), 11/39 (28.2%) of the participants in the treatment group and 2/43 (4.7%) in the control group no longer met diagnostic criteria for SAD (χ^2_1 = 8.5, p < 0.01). Among

Main Study Findings			
Measure	70[c], 44[d])	63[b], 69[c])	[95% CI])
DASS-21			
Pre-treatment (observed)[a]	58.2 (24.4)	55.8 (21.3)	
Post-treatment (observed)[b]	40.9 (25.7)	52.7 (24.7)	
Post-treatment (estimated)[c]	40.8 (3.09)	52.6 (3.00)	0.47 (0.13–0.81)
Follow-up (observed)[d]	41.9 (30.0)		
BAI			
Pre-treatment (observed)[a]	34.9 (9.1)	33.3 (10.3)	
Post-treatment (observed)[b]	27.8 (9.1)	31.4 (10.0)	
Post-treatment (estimated)[c]	27.5 (1.22)	31.5 (1.19	0.41 (0.07–0.74)
Follow-up (observed)[d]	26.6 (9.4)		
BDI-II			
Pre-treatment (observed)[a]	22.6 (10.6)	22.0 (11.0)	
Post-treatment (observed)[b]	15.8 (12.4)	22.9 (12.6)	
Post-treatment (estimated)[c]	15.3 (1.54)	22.9 (1.52)	0.61 (0.27–0.95)
Follow-up (observed)[d]	16.3 (13.7)		
BSI			
Pre-treatment (observed)[a]	1.34 (0.56)	1.27 (0.57)	
Post-treatment (observed)[b]	0.94 (0.63)	1.18 (0.71)	
Post-treatment (estimated)[c]	0.90 (0.09)	1.18 (0.08)	0.42 (0.08–0.75)
Follow-up (observed)[d]	0.97 (0.77)		
SF-12 MH			
Pre-treatment (observed)[a]	31.2 (8.8)	33.2 (9.5)	
Post-treatment (observed)[b]	37.5 (11.8)	33.0 (9.2)	
Post-treatment (estimated)[c]	37.9 (1.30)	32.7 (1.27)	0.49 (0.15–0.83)
Follow-up (observed)[d]	39.9 (12.2)		
SF-12 PH			
Pre-treatment (observed)[a]	48.5 (11.2)	48.3 (10.8)	
Post-treatment (observed)[b]	48.3 (11.4)	47.2 (9.5)	
Post-treatment (estimated)[c]	48.7 (1.29)	47.0 (1.27)	0.16 (−0.17 to 0.50)
Follow-up (observed)[d]	48.6 (11.1)		
PSWQ			
Pre-treatment (observed)[a]	62.7 (9.3)	60.4 (11.0)	
Post-treatment (observed)[b]	58.4 (11.1)	60.0 (13.5)	
Post-treatment (estimated)[c]	57.4 (1.62)	59.5 (1.57)	0.17 (−0.16 to 0.50)
Follow-up (observed)[d]	58.0 (10.9)		
SPS			
Pre-treatment (observed)[a]	29.1 (17.2)	28.7 (17.5)	
Post-treatment (observed)[b]	20.9 (13.4)	27.1 (18.0)	
Post-treatment (estimated)[c]	20.9 (1.97)	27.0 (1.94)	0.38 (0.05–0.72)
Follow-up (observed)[d]	20.0 (16.2)		
SIAS			
Pre-treatment (observed)[a]	37.5 (17.3)	37.0 (16.2)	
Post-treatment (observed)[b]	28.2 (15.0)	36.0 (17.5)	
Post-treatment (estimated)[c]	28.5 (1.98)	36.0 (1.97)	0.46 (0.12–0.80)
Follow-up (observed)[d]	29.1 (15.2)		
ACQ			
Pre-treatment (observed)[a]	2.13 (0.62)	2.06 (0.61)	
Post-treatment (observed)[b]	1.81 (0.64)	1.97 (0.61)	
Post-treatment (estimated)[c]	1.76 (0.07)	1.98 (0.08)	0.35 (0.02–0.69)
Follow-up (observed)[d]	1.69 (0.57)		
BSQ			
Pre-treatment (observed)[a]	2.64 (0.86)	2.47 (0.78)	
Post-treatment (observed)[b]	2.23 (0.77)	2.36 (0.80)	
Post-treatment (estimated)[c]	2.20 (0.10)	2.39 (0.10)	0.24 (−0.09 to

Author's Conclusion
participants who met the diagnostic criteria for PDA at pre-treatment (n = 88), 18/47 (38.3%) in the treatment group and 4/41 (9.8%) in the control group no longer fulfilled the criteria for PDA at post-treatment (χ_1^2 = 9.5, p < 0.01). Among participants with a GAD diagnosis at pre-treatment (n = 58), 13/29 (44.8%) recovered in the treatment group, and 0/29 (0%) in the control group (χ_1^2 = 16.8, p < 0.001)." (page 74) *"The findings indicate that this unguided ICBT – velibra – when delivered in this way is effective in reducing symptomatology and in increasing psychological wellbeing assessed as early as 9 weeks after treatment initiation."* (page 74)

Main Study Findings	Author's Conclusion

Follow-up (observed)[d]	2.01 (0.86)		0.58)

ACQ = Agoraphobic Cognitions Questionnaire; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; BSI = Brief Symptom Inventory; BSQ = Body Sensations Questionnaire; CI = confidence interval; DASS-21 = Depression Anxiety Stress Scales; PSWQ = Penn State Worry Questionnaire; SD = standard deviation; SE = standard error; SIAS = Social Interaction Anxiety Scale; SF-12 MH = Short Form Health Survey mental health subscale; SF-12 PH = Short Form Health Survey physical health subscale; SPS = Social Phobia Scale.

Comparison of iCBT plus care as usual (iCBT + CAU) versus care as usual (CAU) alone with respect to patient meeting diagnostic criteria

	Number of patients (% of total)		
	Treatment group		
Outcome	iCBT + CAU	CAU	*P*-value
No longer meet the diagnostic criteria for SAD Post-treatment	11 (28.2%)	2 (4.7%)	<0.01
No longer meet the diagnostic criteria for PDA Post-treatment	18 (38.3%)	4 (9.8%)	<0.01
No longer meet the diagnostic criteria for GAD Post-treatment	13 (44.8%)	0 (0%)	<0.001

Carter, 2013[23]

Randomized controlled trial evaluating the suitability and acceptability of a transdiagnostic iCBT program (CLIMATE) for the treatment of patients with generalized anxiety disorder (N=5), panic disorder with or without agoraphobia (N = 12), and/or social phobia (N = 12).

At the end assessment participants were asked to answer the following questions on an anchored Likert scale ranging from 0 (not at all) to 8 (extremely). Results are presented by diagnostic group and represent the mean score (standard deviation).

Treatment satisfaction (N = 29):

- **How satisfied were you with this treatment?**
  - Generalized anxiety disorder: 6.5 (1.3)
  - Panic disorder: 5.2 (1.7)
  - Social phobia: 5.8 (1.4)
  - Groups combined: 5.6 (1.5)
- **How effective do you think this treatment was?**
  - Generalized anxiety disorder: 6.3 (1.7)
  - Panic disorder: 5.2 (1.4)
  - Social phobia: 5.2 (1.3)
  - Groups combined: 5.4 (1.4)
- **Would you recommend this treatment to somebody else?**
  - Generalized anxiety disorder: 5.7 (1.5)
  - Panic disorder: 6.2 (1.7)
  - Social phobia: 7.0 (1.4)
  - Groups combined: 6.5 (1.6)

Treatment acceptability (N = 29):

- **How acceptable did you find it to receive treatment via a computer?**

"Overall, the mean treatment ratings were favourable on all of the treatment scales. No significant differences were found between the diagnostic groups on ratings of treatment credibility, treatment satisfaction, treatment acceptability or telephone support (p > 0.05, using one-way analysis of variance)." (page 148)

"Encouragingly, patient ratings of treatment were typically favourable. This suggests that for patients who were randomised to treatment, computerised treatment was viewed positively and that the treatment itself is acceptable to patients. These findings are consistent with other studies which have found that participants' perceptions of CCBT are generally positive." (page 151)

"In conclusion, CCBT was typically rated favourably by patients referred to a secondary care service and randomised to treatment. However, only a small minority of patients was eligible and consenting for the trial. Therefore, while CCBT may be an acceptable treatment, its suitability for secondary care settings remains unclear." (page 151)

Main Study Findings	Author's Conclusion

- Generalized anxiety disorder: 6.0 (0.7)
- Panic disorder: 6.1 (2.2)
- Social phobia: 5.7 (1.7)
- Groups combined: 5.9 (1.8)

- **How much of this treatment did you complete?**
  - Generalized anxiety disorder: 4.2 (2.4)
  - Panic disorder: 5.6 (2.7)
  - Social phobia: 5.4 (1.9)
  - Groups combined: 5.3 (2.3)
- **How enjoyable did you find this program?**
  - Generalized anxiety disorder: 5.2 (1.8)
  - Panic disorder: 5.1 (1.6)
  - Social phobia: 5.6 (1.3)
  - Groups combined: 5.3 (1.5)
- **How applicable was this program to your particular anxiety disorder?**
  - Generalized anxiety disorder: 6.4 (1.3)
  - Panic disorder: 5.3 (1.5)
  - Social phobia: 6.4 (1.6)
  - Groups combined: 6.0 (1.6)

Patient treatment completion rates of iCBT by diagnostic group

Outcome	Diagnostic group			Groups combined (N = 40)
	GAD (N = 7)	Panic (N = 16)	Social phobia (N = 17)	
Treatment completion rate (% of patients randomized that completed treatment)	5 (71%)	9 (56%)	12 (71%)	26 (65%)

GAD = generalize anxiety disorder.

Newby, 2013[24]

Randomized controlled trial investigating the effectiveness of a transdiagnostic, clinician assisted iCBT program (Worry and Sadness Program) (N = 46) compared to wait list control (N = 53) for the treatment of patients with major depression (N = 15), generalized anxiety disorder (N = 37), or comorbid major depression and generalized anxiety disorder (N = 47).

Comparison of iCBT versus wait list control with respect to several outcomes

Measure	Mean score (SD)		Between-group effect sizes (Hedges' *g* [95% CI])
	Treatment group		
	iCBT (N = 46[a], 43[b], 39[c])	WLC (N = 54[a], 53[b])	
PHQ-9*			
Pre-treatment[a]	10.39 (3.90)	11.62 (4.80)	
Post-treatment[b]	5.76 (4.24)	10.41 (4.88)	1.00 (0.59–1.40)
Follow-up (3 month)[c]	4.05 (3.79)		
GAD-7*			
Pre-treatment[a]	10.37 (3.74)	10.43 (5.00)	
Post-treatment[b]	5.93 (4.28)	9.92 (4.90)	0.85 (0.43–1.27)
Follow-up (3 month)[c]	4.39 (3.71)		
K-10*			
Pre-treatment[a]	25.43 (5.14)	26.51 (6.30)	

"A total of 49 individuals were randomized into the treatment group. Of these, 46 completed pre-treatment questionnaires and were eligible for analysis, and 41/46 completed the total six lessons (89% adherence)." (page 2640)

"This study compared a six-lesson clinician-assisted iCBT programme for mixed depression and anxiety with a WLC group. Adherence was high (89%), and the iCBT programme was more efficacious than WLC on all primary and secondary measures of depression, generalized anxiety and functional impairment. Between 40 and 45% of participants in the treatment group showed reliable improvements immediately following treatment. Importantly, gains were maintained at 3-month follow-up for the treatment group, with evidence of further improvements (albeit small effects) in GAD symptoms and general distress between post-treatment and follow-up. Approximately

Main Study Findings				Author's Conclusion
Post-treatment[b] Follow-up (3 month)[c]	18.78 (5.74) 15.46 (7.59)	27.51 (6.64)	1.40 (0.99–1.80)	*70% of participants no longer met diagnostic criteria on structured interview at 3-month follow-up."* (page 2643) *"In summary, our findings suggest that we have an effective and accessible iCBT programme that reduces symptoms of co-morbid depression and anxiety."* (page 2646)
BDI-II Pre-treatment[a] Post-treatment[b]	 21.24 (6.98) 10.48 (8.30)	 22.41 (9.17) 21.24 (10.56)	 1.13 (0.72–1.53)	
PSWQ Pre-treatment[a] Post-treatment[b]	 64.22 (8.67) 57.00 (10.98)	 63.11 (11.77) 62.96 (9.99)	 0.56 (0.15–0.96)	
WHODAS-II Pre-treatment[a] Post-treatment[b]	 24.35 (6.38) 20.17 (6.47)	 27.89 (8.27) 25.66 (7.82)	 0.76 (0.34–1.18)	
NEO-FFI-N Pre-treatment[a] Post-treatment[b]	 31.28 (5.38) 26.17 (7.44)	 32.11 (6.03) 32.09 (7.07)	 0.80 (0.39–1.20)	

*Primary outcome measures
BDI-II = Beck Depression Inventory – Second Edition; CI = confidence interval; GAD-7 = Generalized Anxiety Disorder seven-item scale; K-10 = Kessler 10-item Psychological Distress scale; NEO-FFI-N = NEO-Five Factor Inventory – neuroticism subscale; PHQ-9 = Patient Health Questionnaire nine-item scale; SD = standard deviation; WHODAS-II = 12-item World Health Organization Disability Assessment Schedule II; WLC = wait list control.

Bell, 2012[25]

Randomized controlled trial investigating the effectiveness of an iCBT program (CRUfAD) (N = 40) compared to wait list control (N = 43) for the treatment of patients with social phobia (N = 37), panic disorder with or without agoraphobia (N = 32), or generalized anxiety disorder (N = 14).

Symptom severity was measured pre-treatment and at two follow-ups (at 12 and 24 weeks) using various scales. Results are presented by treatment group and represent the mean scores (standard error).

Primary outcomes:

- **Work and Social Adjustment Scale (WSAS)**
  - Pre-treatment (iCBT: N = 36; WLC: N = 43)
    - iCBT: 18.1 (1.27)
    - WLC: 14.7 (1.12)
  - Follow-up (12 weeks) (iCBT: N = 30; WLC: N = 38)
    - iCBT: 11.5 (1.19)
    - WLC: 16.4 (1.07)
    - Between-group effect sizes (Cohen's *d*): 0.85
  - Follow-up (24 weeks) (iCBT: N = 29; WLC: N = 38)
    - iCBT: 12.0 (2.2)
    - WLC: 19.7 (1.96)
- **Patients Global Impression (PGI) scale**
  - Pre-treatment (iCBT: N = 36; WLC: N = 43)
    - iCBT: 5.0 (0.2)
    - WLC: 4.4 (0.18)
  - Follow-up (12 weeks) (iCBT: N = 30; WLC: N = 38)
    - iCBT: 4.1 (0.25)
    - WLC: 4.3 (0.23)
    - Between-group effect sizes (Cohen's *d*): 0.20
  - Follow-up (24 weeks) (iCBT: N = 29; WLC: N = 38)
    - iCBT: 3.8 (0.22)
    - WLC: 4.3 (0.2)

Secondary outcomes:

"Compared with WLC, the CCBT group improved significantly on approximately half of the self-report primary (the Work and Social Adjustment Scale) and approximately half of the secondary measures at both 12 and 24 weeks (the Liebowitz Social Anxiety Scale, the Penn State Worry Questionnaire, the Generalised Anxiety inventory and the Fear Questionnaire). Effect sizes in this study were moderate." (page 630)

"This is one of the few studies to investigate CCBT for anxiety disorders in patients in a secondary care service. The results show that CCBT in this secondary care setting has the potential to be beneficial and confirms and extends the findings from previous studies of self-referral or primary care settings." (page 639)

Main Study Findings	Author's Conclusion

• **Generalized Anxiety Disorder Inventory (GADI)**
  ○ Pre-treatment (iCBT: N = 36; WLC: N = 43)
  ▪ iCBT: 33.4 (2.02)
  ▪ WLC: 27.5 (1.79)
  ○ Follow-up (12 weeks) (iCBT: N = 30; WLC: N = 38)
  ▪ iCBT: 21.2 (2.01)
  ▪ WLC: 28.0 (1.83)
  ▪ Between-group effect sizes (Cohen's *d*): 0.69
  ○ Follow-up (24 weeks) (iCBT: N = 29; WLC: N = 38)
  ▪ iCBT: 20.8 (2.02)
  ▪ WLC: 26.4 (1.81)
• **Penn State Worry Questionnaire (PSWQ)**
  ○ Pre-treatment (iCBT: N = 36; WLC: N = 43)
  ▪ iCBT: 63.4 (2.1)
  ▪ WLC: 60.8 (1.86)
  ○ Follow-up (12 weeks) (iCBT: N = 30; WLC: N = 38)
  ▪ iCBT: 56.0 (1.75)
  ▪ WLC: 62.6 (1.59)
  ▪ Between-group effect sizes (Cohen's *d*): 0.76
  ○ Follow-up (24 weeks) (iCBT: N = 29; WLC: N = 38)
  ▪ iCBT: 53.2 (1.8)
  ▪ WLC: 60.8 (1.6)
• **Panic Disorder Severity Scale (PDSS)**
  ○ Pre-treatment (iCBT: N = 36; WLC: N = 43)
  ▪ iCBT: 10.8 (0.97)
  ▪ WLC: 7.4 (0.76)
  ○ Follow-up (12 weeks) (iCBT: N = 30; WLC: N = 38)
  ▪ iCBT: 7.3 (0.97)
  ▪ WLC: 8.4 (0.89)
  ▪ Between-group effect sizes (Cohen's *d*): 0.22
  ○ Follow-up (24 weeks) (iCBT: N = 29; WLC: N = 38)
  ▪ iCBT: 6.9 (1.07)
  ▪ WLC: 7.5 (0.96)
• **Fear of Negative Evaluation (FNE)**
  ○ Pre-treatment (iCBT: N = 36; WLC: N = 43)
  ▪ iCBT: 22.4 (1.35)
  ▪ WLC: 24.0 (1.2)
  ○ Follow-up (12 weeks) (iCBT: N = 30; WLC: N = 38)
  ▪ iCBT: 22.1 (0.89)
  ▪ WLC: 22.4 (0.81)
  ▪ Between-group effect sizes (Cohen's *d*): 0.07
  ○ Follow-up (24 weeks) (iCBT: N = 29; WLC: N = 38)
  ▪ iCBT: 19.0 (1.17)
  ▪ WLC: 22.3 (1.06)
• **Liebowitz Social Anxiety Scale (LSAS)**
  ○ Pre-treatment (iCBT: N = 36; WLC: N = 43)
  ▪ iCBT: 78.3 (5.23)
  ▪ WLC: 70.1 (4.65)
  ○ Follow-up (12 weeks) (iCBT: N = 30; WLC: N = 38)
  ▪ iCBT: 67.0 (3.28)
  ▪ WLC: 76.7 (3.02)
  ▪ Between-group effect sizes (Cohen's *d*): 0.59
  ○ Follow-up (24 weeks) (iCBT: N = 29; WLC: N = 38)
  ▪ iCBT: 61.8 (4.38)
  ▪ WLC: 75.7 (3.97)	

Main Study Findings	Author's Conclusion

• **Fear Questionnaire (FQ)**
  ○ Pre-treatment (iCBT: N = 36; WLC: N = 43)
  ▪ iCBT: 52.9 (18.1)
  ▪ WLC: 50.6 (17.2)
  ○ Follow-up (12 weeks) (iCBT: N = 30; WLC: N = 38)
  ▪ iCBT: 45.7 (2.49)
  ▪ WLC: 52.48 (2.4)
  ▪ Between-group effect sizes (Cohen's *d*): 0.54
  ○ Follow-up (24 weeks) (iCBT: N = 29; WLC: N = 38)
  ▪ iCBT: 46.0 (2.86)
  ▪ WLC: 54.0 (2.62)
• **Beck Anxiety Inventory (BAI)**
  ○ Pre-treatment (iCBT: N = 36; WLC: N = 43)
  ▪ iCBT: 24.0 (1.91)
  ▪ WLC: 18.3 (1.72)
  ○ Follow-up (12 weeks) (iCBT: N = 30; WLC: N = 38)
  ▪ iCBT: 17.8 (2.04)
  ▪ WLC: 17.9 (1.97)
  ▪ Between-group effect sizes (Cohen's *d*): 0.01
  ○ Follow-up (24 weeks) (iCBT: N = 29; WLC: N = 38)
  ▪ iCBT: 16.1 (2.1)
  ▪ WLC: 16.1 (1.89)
 	
<u>Tertiary outcomes:</u>
• **Beck Depression Inventory – Second Edition (BDI-II)**
  ○ Pre-treatment (iCBT: N = 36; WLC: N = 43)
  ▪ iCBT: 21.9 (2.09)
  ▪ WLC: 16.9 (1.85)
  ○ Follow-up (12 weeks) (iCBT: N = 30; WLC: N = 38)
  ▪ iCBT: 14.3 (1.73)
  ▪ WLC: 18.0 (1.57)
  ▪ Between-group effect sizes (Cohen's *d*): 0.43
  ○ Follow-up (24 weeks) (iCBT: N = 29; WLC: N = 38)
  ▪ iCBT: 14.8 (1.73)
  ▪ WLC: 19.3 (1.55)
 	
Patient treatment completion rates of iCBT by diagnostic group
<table><tr><td></td><td colspan="3">Diagnostic group</td><td rowspan="2">Groups combined (N = 40)</td></tr><tr><td>Outcome</td><td>GAD (N = 7)</td><td>Panic (N = 16)</td><td>Social phobia (N = 17)</td></tr><tr><td>**Treatment completion rate (% of patients randomized that completed treatment)**</td><td>4 (57%)</td><td>5 (31%)</td><td>9 (53%)</td><td>18 (45%)</td></tr></table>GAD = generalize anxiety disorder.	

Johnston, 2011[26]	
Randomized controlled trial comparing the effectiveness of a transdiagnostic iCBT program supported by either a clinician (N = 43) or a coach (N = 46) to a wait list control (N = 42) for the treatment of patients with social phobia (N = 45), panic disorder with or without agoraphobia (N = 27), or generalized anxiety disorder (N = 59). Comparison of iCBT (including both coach-supported and clinician supported)	*"Outcomes for the pooled treatment groups (CL+CO) were superior to the Control group on measures of anxiety, depression and disability, were associated with medium to large effect sizes (Cohen's d = .76 – 1.44) (response rate = 89–100%), and were maintained at follow-up. Significant*

Main Study Findings	Author's Conclusion

versus wait list control (WLC) with respect to several outcomes

Measure	Mean score (SD) Treatment group: iCBT (N = 89[a], 81[b], 73[c])	Mean score (SD) Treatment group: WLC (N = 42[a], 41[b], 34[c])	Between-group effect sizes (Cohen's *d* [95% CI])
GAD-7			
Pre-treatment[a]	11.71 (4.34)	12.50 (4.80)	
Post-treatment[b]	6.17 (4.38)	11.79 (4.60)	1.44 (0.05 – 2.31)
Follow-up (3 month)[c]	6.61 (5.54)	5.70 (3.53)	
DASS-21			
Pre-treatment[a]	50.70 (21.75)	52.57 (20.86)	
Post-treatment[b]	28.67 (21.71)	48.48 (20.41)	0.94 (−5.24 – 5.45)
Follow-up (3 month)[c]	27.35 (25.14)	24.25 (16.54)	
PSWQ			
Pre-treatment[a]	63.63 (11.01)	61.29 (12.66)	
Post-treatment[b]	52.07 (10.70)	61.50 (12.74)	0.83 (−3.02 – 3.06)
Follow-up (3 month)[c]	52.06 (13.37)	50.05 (11.23)	
SIAS-6/SPS-6			
Pre-treatment[a]	20.31 (11.45)	22.17 (13.59)	
Post-treatment[b]	12.56 (9.03)	22.05 (13.83)	0.89 (−3.30 – 2.76)
Follow-up (3 month)[c]	13.26 (10.53)	14.53 (11.10)	
PDSS-SR			
Pre-treatment[a]	10.20 (6.89)	10.74 (6.44)	
Post-treatment[b]	5.71 (5.80)	10.50 (6.35)	0.81 (−1.11 – 2.01)
Follow-up (3 month)[c]	5.97 (7.31)	5.58 (5.03)	
PHQ-9			
Pre-treatment[a]	11.46 (5.57)	11.71 (6.31)	
Post-treatment[b]	6.88 (5.21)	11.29 (5.28)	0.85 (−0.75 – 1.93)
Follow-up (3 month)[c]	6.76 (6.00)	11.29 (5.28)	
SDS			
Pre-treatment[a]	17.17 (7.06)	16.43 (7.74)	
Post-treatment[b]	10.15 (7.54)	15.88 (7.75)	0.76 (−1.58 –2.33)
Follow-up (3 month)[c]	9.27 (8.82)	9.40 (7.71)	

CI = confidence interval; DASS-21 = Depression Anxiety Stress Scales-21 item; GAD-7 = Generalized Anxiety Disorder 7-Item; PDSS-SR - Panic Disorder Severity Scale – Self Rating; PSWQ = Penn State Worry Questionnaire; SD = standard deviation; SDS = Sheehan Disability Scale; SIAS-6/SPS-6 = Social Interaction Scale and Social Phobia Scale Short Form; WLC = wait list control.

Comparison of coach-supported iCBT (CO) versus clinician-supported iCBT (CL) with respect to several outcomes

Measure	Mean score (SD) Treatment group: CO (N = 43[a], 39[b], 40[c])	Mean score (SD) Treatment group: CL (N = 46[a], 42[b], 34[c])	Between-group effect sizes (Cohen's *d* [95% CI])
GAD-7			
Pre-treatment[a]	11.28 (5.18)	11.63 (5.96)	
Post-treatment[b]	6.16 (4.59)	7.54 (5.70)	0.27 (−1.38 – 1.64)
Follow-up (3 month)[c]	5.37 (4.98)	8.07 (6.61)	0.46 (−1.45 – 1.95)
DASS-21			
Pre-treatment[a]	45.30 (19.54)	55.74 (22.69)	
Post-treatment[b]	22.05 (16.90)	34.87 (23.95)	0.62 (−6.30 – 5.67)
Follow-up (3 month)[c]	21.16 (22.27)	33.13 (26.49)	0.49 (−7.16 – 7.15)
PSWQ			
Pre-treatment[a]	62.81 (11.35)	64.39 (10.75)	
Post-treatment[b]	50.28 (10.34)	53.74 (10.86)	0.52 (−2.62 – 3.65)

reductions were found on disorder-specific outcomes for each of the target diagnoses, and were associated with large effect sizes. CO participants achieved similar outcomes to CL participants at post-treatment, yet had significantly lower symptom severity scores on general anxiety, panic-disorder, depression and disability at follow-up (d = .45 – .46). Seventy-four percent of CO and 76% of CL participants completed the program. Less than 70 minutes of Clinician or Coach time was required per participant during the program." (page 1)

"This randomized controlled trial revealed overall outcomes that were superior for the treatment groups relative to a waitlist control condition and which were stable over a 3 month follow up period and satisfactory to participants. Outcomes by principal diagnosis appeared consistent with those obtained in disorder-specific iCBT programs, and allowed participants to generalise gains beyond symptoms of their principal complaint. Coach assisted iCBT was as effective as Clinician assisted iCBT. Further studies need to explore questions about the role of comorbidity, consumer attitudes, to investigate clinical and coaching support roles and the relative efficacy of transdiagnostic and disorder-specific iCBT." (page 11)

Main Study Findings	Author's Conclusion

Follow-up (3 month)[c]	49.86 (12.00)	54.19 (14.37)	0.33 (−3.82 – 3.96)
SIAS-6/SPS-6			
Pre-treatment[a]	19.95 (12.84)	20.65 (10.12)	
Post-treatment[b]	10.95 (8.98)	14.07 (8.90)	0.35 (−2.22 – 3.04)
Follow-up (3 month)[c]	11.65 (9.64)	14.76 (11.20)	0.30 (−2.94 – 3.18)
PDSS-SR			
Pre-treatment[a]	9.72 (6.89)	10.65 (6.93)	
Post-treatment[b]	4.95 (4.99)	6.41 (6.44)	0.26 (−1.61 – 1.75)
Follow-up (3 month)[c]	4.30 (6.68)	7.52 (7.59)	0.45 (−1.74 – 2.45)
PHQ-9			
Pre-treatment[a]	11.28 (5.18)	11.63 (5.96)	
Post-treatment[b]	6.16 (4.59)	7.54 (5.70)	0.27 (−1.38 – 1.64)
Follow-up (3 month)[c]	5.37 (4.98)	8.07 (6.61)	0.46 (−1.45 – 1.95)
SDS			
Pre-treatment[a]	16.23 (6.37)	18.04 (7.62)	
Post-treatment[b]	8.35 (6.72)	11.83 (7.93)	0.48 (−1.81 – 2.51)
Follow-up (3 month)[c]	6.84 (7.56)	11.54 (9.37)	0.56 (−2.15 – 2.84)

CI = confidence interval; DASS-21 = Depression Anxiety Stress Scales-21 item; GAD-7 = Generalized Anxiety Disorder 7-Item; PDSS-SR - Panic Disorder Severity Scale – Self Rating; PSWQ = Penn State Worry Questionnaire; SD = standard deviation; SDS = Sheehan Disability Scale; SIAS-6/SPS-6 = Social Interaction Scale and Social Phobia Scale Short Form; WLC = wait list control.

Comparison of iCBT (including both coach-supported and clinician supported) versus wait list control (WLC) with respect to several outcomes

Measure	Number of patients (% of total) iCBT (N = 89)	95% CI
Remission		
Post-treatment	46 (65%)	53–75%
Follow-up (3 month)	45 (63%)	52–74%
Recovery		
Post-treatment	36 (51%)	39–62%
Follow-up (3 month)	37 (52%)	70–87%
Met diagnostic criteria GAD, SP, or PDA		
Follow-up (3 month)	46 (52%)	41–62%

CI = confidence interval;

Titov, 2011[27]

Randomized controlled trial investigating the effectiveness of a transdiagnostic, therapist-supported iCBT program (Wellbeing program) (N = 37) compared to wait list control (N = 37) for the treatment of patients with major depression (N = 38), social phobia (N = 8), panic disorder with or without agoraphobia (N =7), or generalized anxiety disorder (N = 21).

Comparison of iCBT versus wait list control (WLC) with respect to several outcomes

Measure	Mean score (SD) Treatment group: iCBT (N = 37[a], 34[b], 32[c])	Mean score (SD) Treatment group: WLC (N = 37[a], 35[b])	Between-group effect sizes (Cohen's *d* [95% CI])
DASS-21			
Pre-treatment[a]	58.48 (21.47)	48.00 (22.80)	
Post-treatment[b]	32.80 (22.90)	44.86 (20.87)	0.56 (−6.17 to 7.94)
Follow-up (3 month)[c]	35.02 (25.74)		

"Chi-squared analyses indicated significant differences between groups at post treatment for both remission and recovery on the DASS-21, PHQ-9, and GAD-7 (range =4.5-9.32, all ps< .05), which were generally maintained in the Treatment group at follow-up (Table 7). At 3-month follow-up, 23/37 (62%) of Treatment group participants no longer met diagnostic criteria for their original principal diagnosis (Table 3), 54% no longer meet diagnostic criteria for any of the four disorders, and the number with a co-morbid diagnosis reduced from 87% to 32% (Table 2)." (page 448)

Main Study Findings

PHQ-9			
Pre-treatment[a]	13.48 (5.36)	12.56 (5.81)	
Post-treatment[b]	8.13 (5.98)	11.32 (5.10)	0.58 (−1.06 to 2.51)
Follow-up (3 month)[c]	8.54 (6.98)		
PSWQ			
Pre-treatment[a]	60.78 (10.24)	57.54 (9.90)	
Post-treatment[b]	53.32 (11.80)	58.37 (10.13)	0.47 (−2.80 to 4.27)
Follow-up (3 month)[c]	53.45 (13.04)		
PDSS-SR			
Pre-treatment[a]	8.45 (8.03)	4.89 (4.19)	
Post-treatment[b]	5.29 (7.30)	5.13 (5.19)	−0.03 (−1.70 to 2.33)
Follow-up (3 month)[c]	5.72 (7.38)		
SP-12			
Pre-treatment[a]	14.75 (10.58)	15.05 (9.96)	
Post-treatment[b]	11.83 (8.97)	14.00 (10.58)	0.22 (−3.18 to 3.11)
Follow-up (3 month)[c]	10.78 (9.67)		

CI = confidence interval; DASS-21 = Depression Anxiety Stress Scales-21 item; PDSS-SR - Panic Disorder Severity Scale – Self Rating; PHQ-9 = Patient Health Questionnaire-9 item; PSWQ = Penn State Worry Questionnaire; SD = standard deviation; WLC = wait list control.

Comparison of iCBT versus wait list control (WLC) with respect to remission and recovery outcomes

Measure	Number of patients (% of total) Treatment group: iCBT (N = 37[a], 34[b], 32[c])	Number of patients (% of total) Treatment group: WLC (N = 37[a], 35[b])	*P*-value
DASS-21			
Pre-treatment score ≥35[a]	30 (81%)	25 (68%)	0.14
Pre-treatment score <35[a]	7 (19%)	12 (32%)	
Post-treatment score ≥35 (non-remission)[b]	11 (30%)	19 (51%)	0.004
Post-treatment score <35 (remission)[b]	19 (51%)	6 (16%)	
Post-treatment score ≤50% pre-treatment (recovery)[b]	19 (51%)	8 (22%)	0.007
Follow-up score ≥35 (non-remission)[c]	14 (38%)		
Follow-up score <35 (remission)[c]	16 (43%)		
Follow-up score ≤50% pre-treatment (recovery)[c]	17 (46%)		
PHQ-9			
Pre-treatment score ≥10[a]	27 (73%)	22 (59%)	0.16
Pre-treatment score <10 [a]	10 (27%)	15 (41%)	
Post-treatment score ≥10 (non-remission)[b]	10 (27%)	15 (41%)	0.03
Post-treatment score <10 (remission)[b]	17 (46%)	7 (19%)	
Post-treatment score ≤50% pre-treatment (recovery)[b]	17 (46%)	5 (14%)	0.002
Follow-up score ≥10 (non-remission)[c]	13 (35%)		
Follow-up score <10 (remission)[c]	14 (38%)		
Follow-up score ≤50%	16 (43%)		

Author's Conclusion

"These findings provide preliminary support for the efficacy of a transdiagnostic iCBT protocol in the treatment of depression and anxiety disorders. Overall outcomes in the Treatment group were superior to those in the Control group, satisfaction with the protocol was high, and a modest amount of therapist time was required. Replication is required with larger samples and direct comparisons with disorder-specific programs are necessary to determine the relative benefits of each approach, with particular regard for the effect of co-morbid diagnoses. Treatment programs that can effectively treat more than one disorder and that may also reduce barriers to treatment have considerable potential." (page 451)

Main Study Findings				Author's Conclusion
pre-treatment (recovery)[c]				
GAD-7				
Pre-treatment score ≥8[a]	29 (78%)	26 (70%)	0.30	
Pre-treatment score <8[a]	8 (22%)	11 (30%)		
Post-treatment score ≥8 (non-remission)[b]	13 (35%)	9 (51%)	0.03	
Post-treatment score <8 (remission)[b]	16 (43%)	7 (19%)		
Post-treatment score ≤50% pre-treatment (recovery)[b]	18 (49%)	6 (14%)	0.003	
Follow-up score ≥8 (non-remission)[c]	12 (32%)			
Follow-up score <8 (remission)[c]	17 (46%)			
Follow-up score ≤50% pre-treatment (recovery)[c]	15 (41%)			

DASS-21 = Depression Anxiety Stress Scales-21 item; GAD-7 = Generalized Anxiety Disorder 7-Item; PHQ-9 = Patient Health Questionnaire-9 item; WLC = wait list control.

CAU = care as usual; CRUfAD = Clinical Research Unit for Anxiety and Depression; GAD = generalized anxiety disorder; PCC = primary care center; PDA = panic disorder with or without agoraphobia; SAD = social anxiety disorder.

Appendix 5: Additional References of Potential Interest

Previous CADTH Reports

e-Therapy interventions for the treatment of anxiety: clinical evidence. *(CADTH Rapid response report: summary with critical appraisal)*. Ottawa (ON): CADTH; 2018: https://www.cadth.ca/sites/default/files/pdf/htis/2018/RC0984%20e-Therapy%20Anxiety%20Final.pdf. Accessed 2018 Aug 31.

e-Therapy interventions for the treatments of patients with depression: a review of clinical effectiveness. *(CADTH Rapid response report: summary with critical appraisal)*. Ottawa (ON): CADTH; 2018: https://www.cadth.ca/sites/default/files/pdf/htis/2018/RC0983%20-%20E%20therapy%20for%20depression%20Final.pdf. Accessed 2018 Aug 31.

Self-directed cognitive behavioural therapy for adults with diagnosis of depression: systematic review of clinical effectiveness, cost-effectiveness, and guidelines. *(CADTH Health technology assessment rapid review)*. Ottawa (ON): CADTH; 2010: https://www.cadth.ca/sites/default/files/pdf/M0014_CBT_for_Depression_L3_e.pdf. Accessed 2018 Aug 31.

Randomized Controlled Trials

Study Protocols

Justicia A, Elices M, Cebria AI, et al. Rationale and methods of the iFightDepression study: a double-blind, randomized controlled trial evaluating the efficacy of an Internet-based self-management tool for moderate to mild depression. *BMC Psychiatry*. 2017 Apr 19;17(1):143. PubMed: PM28420367

BACKGROUND: During the last decade online interventions have emerged as a promising approach for patients with mild/moderate depressive symptoms, reaching at large populations and representing cost-effective alternatives. The main objective of this double-blind, randomized controlled trial is to examine the efficacy of an internet-based self-management tool (iFightDepression) for mild to moderate depression as an add-on to treatment as usual (TAU) versus internet-based psychoeducation plus TAU. METHODS: A total of 310 participants with major depression disorder (MDD) will be recruited at four different mental-health facilities in Spain. Participants will be randomly allocated to one of two study arms: iFightDepression (iFD) tool + TAU vs. internet-based psychoeducation + TAU. Both interventions last for 8 weeks and there is a 12 weeks follow up. The primary outcome measure is changes in depressive symptoms assessed with the Hamilton Depression Rating Scale. Additionally, pre-post interventions assessments will include socio-demographic data, a brief medical and clinical history and self-reported measures of depressive symptoms, quality of life, functional impairments and satisfaction with the iFD tool. DISCUSSION: iFightDepression is an easy-prescribed tool that could increase the efficacy of conventional treatment and potentially reach untreated patients, shortening waiting lists to receive psychological treatment. Confirming the efficacy of the iFD internet-based self-management tool as an add-on treatment for individuals with mild to moderate depression will be clinically-relevant. TRIAL REGISTRATION: Registration number NCT02312583. Clinicaltrials.gov. December 4, 2014.