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SUMMARY WITH CRITICAL APPRAISAL

e-Therapy Interventions for the Treatment of Anxiety: Clinical Evidence

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Context and Policy Issues

Generalized anxiety disorder is the most common mental disorder seen in primary care and is characterized by excessive worry and symptoms of anxiety that are difficult to control, cause significant distress and impairment, and that occur on more days than not for at least six months.[1] Other symptoms include restlessness, fatigue, trouble concentrating, irritability, muscle tension, and sleep problems.[1] In the 2012 Canadian Community Health Survey (CCHS), 2.5% of respondents (700,000 individuals) 15 years of age or older reported symptoms of generalized anxiety in the previous 12 months and 8.7% (2.4 million) reported symptoms over a lifetime.[2] Panic disorder and social anxiety disorder are other common anxieties that may occur alongside generalized anxiety disorder and cause significant impairment in functioning and quality of life.[1]

The choice of treatment for anxiety disorders is determined by the severity of the condition and patient preference. Evidence for effectiveness is available for cognitive behavioural therapy (CBT) and pharmacotherapy, used individually or in combination.[3,4] The choice to implement pharmacotherapy and/or CBT is based on treatment availability and patient preference.[3] In meta-analyses, the treatment effects of serotonergic antidepressants and CBT were similar.[3] In patients who have experienced a partial response with pharmacotherapy, clinical trials have shown that the addition of CBT may lead to further reduction in symptoms.[3] Cognitive behavioural therapy develops cognitive skills, evidence-based thinking, problem-solving and coping strategies, and behavioural skills for effective decision-making and time management.[4] The delivery of such therapeutic programs over online platforms, known as e-therapy, has the potential to increase access to mental health treatment within a confidential and safe environment.

Research Question

What is the clinical effectiveness of e-therapy interventions for the treatment of anxiety?

Key Findings

In this review, ten studies were evaluated of which three were systematic reviews/meta-analyses of randomized controlled trials (RCTs) and seven were individual RCTs not included in the three systematic reviews. All studies included therapist-guided e-therapy interventions for generalized anxiety disorder, panic disorder, or social anxiety disorder. The studies were heterogeneous with respect to the specific intervention implemented, the type of therapist-guidance provided, the qualifications and expertise level of therapists, and measurement tools used to assess outcomes. Participants self-selected into studies and may have represented people with anxiety disorders who were more motivated.

Two meta-analyses and one RCT focused specifically on generalized anxiety disorder. In all three studies, statistically significant effects were observed in favour of therapist-guided e-therapy interventions compared with waitlist, care as usual, information, or other psychological placebos, on several validated instruments. Two meta-analyses and two RCTs included participants with panic disorder. Therapist-guided e-therapy interventions

were superior to the same controls, across several measurement instruments in all but one study that had 39 participants with panic disorder. Three meta-analyses and three RCTs examined the effect of e-therapy interventions in people with social anxiety disorder. All studies demonstrated benefits of interventions compared with passive or active controls. One study examined individual and group therapist-guided e-therapy for social anxiety disorder and found that both were superior to waitlist. One meta-analysis and two RCTs (in older adults 60 years of age or over) with mixed anxiety disorders were identified. All three studies found benefits of therapist-guided e-therapy interventions compared with waitlist or general weekly email support. No data were available for generalized anxiety disorder, panic disorder, or social anxiety disorder for the following subgroups of interest: military, para-military, and veteran populations.

Most studies found that treatment responses were maintained at follow-ups of three to 24 months, although this data must be interpreted with caution as controls were not available and participants may have started other treatments during the follow-up period.

Three studies reported large number of losses to follow-up, of 25% to 33%. Losses were similar among intervention and control groups in most studies. In one study of older adults, a larger percentage in the e-therapy intervention group was lost to follow-up compared with general weekly email support (33% vs. 3%).

The evidence base suggested that therapist-supported e-therapy interventions are effective for generalized anxiety disorder, panic disorder, and social anxiety disorder compared with waitlist and active controls, but may have similar effects as face-to-face CBT.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including Medline via OVID, PsycINFO via OVID, PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, and randomized controlled trials (RCTs). The search was also limited to English language documents published between Jan 1, 2015 and May 2, 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	Adult patients with diagnosed anxiety disorder[a] with or without co-morbid mental health conditions. Subgroups of interest: military, para-military (e.g. police, RCMP, EMT), and veteran populations.
Intervention	e-Therapy interventions that include therapist contact: • Online or mobile based therapy
Comparator	In person treatment Videochat or videoconference therapy Telehealth Wait list Treatment as Usual
Outcomes	Improvements in symptoms (based on psychometric scales, self-report, and clinician report) Reductions in symptoms, improved functioning Drop-out/attrition rates
Study Designs	Health Technology Assessments, systematic reviews, meta-analyses randomized controlled trials

EMT = emergency medical technician; RCMP = Royal Canadian Mounted Police

[a] Primary diagnosis of anxiety (generalized anxiety disorder, panic disorder, or social anxiety disorder): studies of patients with a diagnosis of anxiety secondary to a chronic physical health condition were excluded.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, were published prior to 2015, or were included in one of the selected systematic reviews or meta-analyses. Interventions that were solely videochat or telephone were excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using the AMSTAR II checklist[5] and the RCTs were critically appraised using the Cochrane Risk of Bias Tool.[6] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 552 citations were identified in the literature search. Following screening of titles and abstracts, 472 citations were excluded and 80 potentially relevant reports from the electronic search were retrieved for full-text review. No relevant publications were identified from the grey literature search. Of these potentially relevant articles, 70 publications were excluded for various reasons, while 10 publications (three systematic reviews/meta-analyses and seven RCTs) met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references of potential interest are in Appendix 5.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

The systematic reviews/meta-analyses were published between 2015 and 2018.[7-9] All reviews included RCTs and quantitative synthesis of results. Andrews et al.[7] searched for RCTs until September 2016 and included 32 studies that were relevant to one of the populations of interest to this rapid review (i.e. generalized anxiety disorder, panic disorder, or social anxiety disorder). Kampmann et al.[8] searched for RCTs from 1985 to June 2015 and included 18 studies. Olthuis et al.[9] searched for RCTs from 1950 to September 2014 and included 23 studies in the specific populations of interest and five studies in populations with mixed anxiety disorder (i.e. generalized anxiety disorder, panic disorder with or without agoraphobia, social phobia, post-traumatic stress disorder, or specific phobia).

The additional seven RCTs, which were not included in the included systematic reviews, were published between 2015 and 2017.[10-16]

Country of Origin

The countries of origin for the first authors of the systematic reviews were Australia,[7] the Netherlands[8], and Canada[9].

The RCTs were conducted in Sweden,[10,11,13,14] Switzerland, Austria, and Germany,[15] Australia,[16] and Romania.[12]

Patient Population

The review by Andrews et al.[7] included adults 18 years of age or older with generalized anxiety disorder, panic disorder (with or without agoraphobia), or social anxiety disorder as the primary diagnosis. Kampmann et al.[8] included studies in adults 18 years of age or older with social anxiety disorder. Olthuis et al.[9] included studies in adults over 18 years of age with generalized anxiety disorder, panic disorder, social anxiety disorder, or mixed anxiety disorders.

The RCTs were categorized into those that focused on: (a) generalized anxiety disorder, (b) panic disorder, (c) social anxiety disorder, and (d) mixed anxiety disorders (Appendix 2).

One RCT included participants with generalized anxiety disorder.[11] Dahlin et al.[11] recruited adults 18 years of age or older (average: 39.5 years) with a diagnosis of generalized anxiety disorder based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). In this study population, 24% also had major depression.[11] Diagnostic telephone interviews were conducted with potential participants prior to randomization.

Two RCTs included participants with panic disorder.[12,13] Ciuca et al.[12] recruited adult participants 18 to 65 years of age (average: 35.2 years) who met diagnostic criteria for panic disorder based on the Psychiatric Diagnostic Screening Questionnaire (PDSQ). Comorbid diagnoses were agoraphobia (52%), major depression (22%), generalized anxiety disorder (18%), social phobia (5%), obsessive-compulsive disorder (3%), specific phobia (2%), and bulimia (1%).[12] Ivanova et al.[13] recruited adults 18 years of age or older (average: 35.3 years) who met the DSM-IV diagnostic criteria for panic disorder. Diagnosis was conducted via telephone[12,13] or Skype.[12]

Three RCTs included participants 18 years of age or older (average: 42.9, 35.3, and 35.4 years) with social anxiety disorder, according to the diagnostic criteria of DSM-IV.[13-15] Comorbidities were common: in Johansson et al.,[14] 29% had depression, 25% agoraphobia, and 21% generalized anxiety disorder; and in Schulz et al.,[15] about 48% had one or more comorbid disorder, such as specific phobias (16%) and current major depressive episode (15%). In all three RCTs, diagnostic telephone interviews were conducted.

Two RCTs included older participants, 60 years of age or over, with mixed anxiety disorders, as determined from a diagnostic telephone interview.[10,16] Silfvernagel et al.[10] recruited older adults over 60 years of age (average: 66.1 years) with recurring symptoms of anxiety. The majority (53%) of participants in this study were diagnosed with generalized anxiety disorder.[10] Participants were also included if they had comorbid major depression (32%), but not as the primary diagnosis.[10] Other diagnoses were panic disorder (17%), panic disorder with agoraphobia (6%), social phobia (9%), and post-traumatic stress disorder (6%).[10] In Dear et al.,[16] participants 60 years of age or older (average: 65.4 years) with anxiety were included. Many participants (34%) fulfilled the criteria for three diagnoses, however 18% were not diagnosed with any condition. The most common diagnosis was generalized anxiety disorder (55%), followed by major depressive episode (45%), panic disorder or agoraphobia (32%), social phobia (28%), obsessive compulsive disorder (5%), and post- traumatic stress disorder (4%).[16]

Interventions and Comparators

Among the systematic reviews, Andrews et al.[7] compared internet-supported cognitive behaviour therapy (iCBT) with care as usual, waitlist, information, or placebo. Several of the included trials incorporated therapist support with iCBT, however further details of the type of support were not provided. Kampmannn et al.[8] conducted a subgroup analysis of iCBT that had a therapist-guided component, compared with either a passive control (i.e. waitlist) or an active control (i.e. CBT without internet support). Details of the guidance provided by therapists were not provided in the review. Olthuis et al.[9] examined therapist-support iCBT compared with waitlist, unguided CBT, and face-to-face CBT. This review specified that a therapist-supported iCBT intervention must have been delivered over the Internet through web pages and/or email and included interaction with a therapist through email or telephone, but not face-to-face.[9]

In the RCT of generalized anxiety disorder,[11] a therapist-guided acceptance-based iCBT program, that also included an audio compact disc and workbook, was compared with waitlist. The iCBT intervention was an online, commercially available Swedish program (*"Oroshjalpen"*) that consisted of seven modules and the central components of mindfulness, acceptance, and valued action. The modules were arranged in a specific order, however the user had access to the full program from the start and could navigate between modules. Participants were advised to complete one module per week in the recommended order and were given a total of nine weeks to complete the full program. Guidance was provided by four clinical psychologist graduate students, who interacted with participants through a secure messaging system, and were advised to spend a total of 15 minutes per participant per week to monitor activity, respond to messages, and provide feedback. On average, 9.3 minutes were spent on each participant per week. A licensed psychologist supervised the clinical psychologist graduate students weekly.

For panic disorder, Ciuca et al.[12] compared therapist-guided iCBT with unguided iCBT and a waitlist control. The iCBT program was called PAXonline Program for Panic Disorder

(PAXPD) and consisted of 16 modules that were completed over a 12-week time frame. The modules addressed education of the disorder and interventions, techniques for decreasing neurophysiological hyperarousal, exposure to feared somatic sensations, situational exposures, training in positive emotions and problem-solving, behavioural activation and cognitive restructuring exercises, and prevention of relapses. Participants had access to all modules from the start, however they were recommended to work through them in consecutive order. Guidance was provided by three licensed therapists with formal training in CBT and at least three years clinical experience, in regular weekly (or upon module completion) 15 to 45 minute video sessions (synchronous contact). During the video sessions, the therapist checked completion, understanding of module material, homework, and how the participant was feeling, answered questions, and assisted with the recommended exercises. The average total time spent by therapists per participant was 247.2 minutes, over an average of 7.8 sessions.

Ivanova et al.[13] compared guided internet-delivered acceptance and commitment therapy (iACT) for panic disorder and social anxiety disorder, with unguided iACT and waitlist. The iACT intervention was a commercially available online Swedish program (*"Angesthjalpen"*) with a paper format exercise booklet and a compact disc with mindfulness and acceptance exercises. The program was transdiagnostic (i.e. relevant to both panic disorder and social anxiety disorder) and consisted of eight modules, which were completed over 10 weeks. Participants had access to all modules from the start, however they were recommended to work through them in order. Both guided and unguided intervention groups were given access to a smartphone application that included the material in the paper exercise book, and the ability to rate mood and leave comments. Guidance was provided by seven students in Masters of clinical psychology at the end of their clinical training, who provided participants with comments on treatment progress, reinforced specific desirable behaviours, provided encouragement, assisted with application of techniques to life situations and problem-solving, and ensured correct interpretations of techniques. The therapists were instructed to spend 15 minutes per participant per week and were supervised weekly by a licensed clinical psychologist.

Johansson et al.[14] examined internet-based psychodynamic therapy (iPDT) for social anxiety disorder compared with waitlist. The program consisted of nine modules, which were sent to participants by therapists, one-by-one, every week over a 10-week period. The concept of the program was emotional mindfulness and participants were guided on the relationship between feelings, anxiety, and defenses. Guidance was provided by four Master level students in their final year of a five-year clinical psychologist program. The therapists kept in contact with participants through text messages that were delivered through a secure online application. Participants could contact the therapist any time during the week, although most interaction took place at the end of the week after participants sent in homework assignments. The therapists were instructed to spend 10 to 15 minutes per participant per week, and were supervised by another therapist experienced in affect-focused psychotherapy.

Schulz et al.[15] compared therapist-guided group iCBT with individual iCBT and waitlist for people with social anxiety disorder. The program consisted of eight text-based modules that were completed on a weekly basis over a 12-week treatment period. The next module was made available once the participant indicated that they understood the content and agreed to complete the exercises. In the individual iCBT intervention, therapists monitored progress and contacted participants via email on a weekly basis. Participants who received individual iCBT could contact therapists through an integrated message function whenever they

needed and were informed that the therapist would answer within three working days. In the group iCBT intervention, participants had access to a therapist-guided discussion forum that consisted of six members per group. All messages posted on the forum by therapists or group members were available to everyone in the group. In addition, therapists contacted the group every week to introduce the module topic and provide feedback on the group's progress. The guidance in individual and group iCBT interventions was provided by four therapists; three were students in their last term of a graduate program in clinical psychology and psychotherapy and one had a Master degree in clinical psychology and was in the first year of a post-graduate CBT training program. The average therapist time for individual iCBT was 17 minutes per participant per week and for group iCBT 4.5 minutes per participant per week.

In the two RCTs that included participants with mixed anxiety disorders, iCBT was compared with weekly general email support from a clinician[10] or waitlist.[16] Silfvernagel et al.[10] developed online, therapist-guided and individually tailored iCBT programs, based on the symptom profiles and needs of participants. Each participant was prescribed six to eight modules, which were completed within eight weeks. The program was transdiagnostic and incorporated education, exposure exercises, behavioural experiments, and homework assignments. Guidance by therapists was provided over a secure treatment platform, and could be initiated either by the therapist or participant. Therapists provided feedback on homework assignments within 24 hours. The average total therapist time spent per participant in the intervention was 100 minutes. The control group received weekly general email support (as a form of attention), however the clinicians who provided this support were instructed not to engage in CBT.

Dear et al.[16] examined an iCBT intervention ("*Managing Stress and Anxiety Course*") against a waitlist control. The iCBT program consisted of five modules, presented as text-based instructions and case studies, and delivered over an 8-week treatment period. Participants could access the modules according to a timetable. Guidance was provided in the form of brief weekly contacts by two therapists over telephone or email. The weekly contact was generally limited to five to ten minutes, although more time was provided if needed. The average total therapist time spent per participant was 57.6 minutes. The therapists were registered and experienced clinical psychologists with doctoral degrees.

Outcomes

The included studies measured outcomes based on several different scales for anxiety and depression (Appendix 2). A description of all scales is beyond the scope of this rapid review, however a brief explanation is provided for some of the commonly used scales, disorder-specific scales, and scales that were primary outcomes.

(1) Beck Anxiety Inventory (BAI): An instrument that assesses 21 symptoms of anxiety on a scale of 0-3. The total score (sum of the 21 items) classifies anxiety severity: 0-21 (low anxiety), 22-35 (moderate anxiety), and ≥36 (potentially concerning levels of anxiety).[17]

(2) Generalized Anxiety Disorder 7 – Item Scale (GAD-7): To screen for generalized anxiety disorder, a self-report measure that assesses seven items on a scale of 0-3. A total score is calculated: ≥8 (possible presence of an anxiety disorder).[16]

(3) Liebowitz Social Anxiety Scale – Self Rated (LSAS-SR): An instrument that assesses 24 items on a scale of 0-3, separately for fear and avoidance. A total score is

calculated: no social anxiety (0-54), moderate (55-65), marked (65-80), severe (80-95), and very severe (>95).[18]

(4) Panic Disorder Severity Scale – Self Report (PDSS-SR): An instrument that assesses seven items on a five point Likert scale. A total score is calculated: a cut-off of six may indicate presence/absence of DSM-IV panic disorder and a cut-off of 14 may indicate mild/severe panic disorder.[12]

(5) Patient Health Questionnaire – 9 (PHQ-9): An instrument that assesses nine items on a scale of 0-3 for symptoms of major depressive disorder, based on DSM-IV criteria. A total score is calculated: minimal symptoms (5-9), minor/mild (10-14), moderately severe major depression (15-19), and severe major depression (>20).[19]

(6) Penn State Worry Questionnaire (PSWQ): An instrument that assesses 16 items on a scale of 1-5 to measure excessive, generalized, and uncontrollable worry. A total score is calculated, with higher scores representing more severe symptoms. A score ≥45 indicates generalized anxiety disorder.[20]

(7) Social Interaction Anxiety Scale (SIAS): A self-report instrument that assesses 20 items for fears in social interactions, with ratings on a five point Likert scale. A total score is calculated, with higher scores indicating more severe symptoms.[15]

(8) Social Phobia Scale (SPS): A self-report instrument that assesses 20 items for fears of being judged by others during daily activities. A total score is calculated, with higher scores indicating more severe symptoms.[15]

All but three[7-9] of the included studies calculated the post-treatment effect sizes as *Cohen's d*, which is the ratio of the mean difference (between intervention and control) and the pooled standard deviation. Andrews et al.[7] and Kampmann et al.[8] calculated *Hedges'g*, which is similar to *Cohen's d* except that the denominator is the pooled standard deviation weighted by sample size. As a rule of thumb, *Hedges'g* or *Cohen's d* value of 0.2 is considered a small effect, 0.5 a medium effect, and 0.8 a large effect.[8] Although the RCTs included longer term follow-up periods (from three to 24 months post-treatment), direct comparisons with the control groups could not be performed because participants in control groups were switched to the guided internet based programs after completion of the study. The follow-up periods provide within group comparative data.

Two RCTs additionally reported on diagnostic status post-treatment[12,15] or clinically significant improvement.[13,16] All RCTs reported a measure of attrition (e.g. number of drop-outs or number of modules completed).

Summary of Critical Appraisal

In all three systematic reviews, studies were quantitatively synthesized using random effects models.[7-9] The reviews by Andrews et al.[7] and Olthuis et al.[9] were based on *a priori* protocols. The evidence base for internet-delivered therapies is prone to significant heterogeneity due to variability in interventions, trial procedures, and outcome measurement scales. Andrews et al.[7] examined heterogeneity in meta-analysis according to study quality and Olthius et al.[9] examined heterogeneity by study quality, anxiety disorder, and time spent by therapists. In the review by Kampmann et al.,[8] however, an estimate of heterogeneity was not provided for the meta-analysis of guided iCBT. Olthuis et al.[9] conducted a comprehensive search of published and unpublished literature, whereas Andrews et al.[7] included only published or in press articles in English and Kampmann et al.[8]

did not search the grey literature. In addition, Kampmann et al.[8] did not describe the type of support provided in therapist-guided iCBT.

The RCT for generalized anxiety disorder[11] was properly randomized with an online random number service and the randomization was conducted by an employee of the university with no connection to the study. The waitlist control group had no contact with study administrators during the nine weeks of treatment. Guidance was provided by trained graduate students rather than licensed therapists and by the same students who conducted the initial diagnostic telephone interviews, which could have potentially affected the support provided based on knowledge of baseline scores, although there is no concrete evidence that this occurred.

The two RCTs for panic disorder were properly randomized: one with a software that balanced groups with respect to disease severity and chronicity[12] and one with a random number service that stratified participants by primary diagnosis of panic disorder or social anxiety disorder.[13] Both studies had an independent researcher carry out the randomization procedure and based analyses on intention-to-treat. In Ciuca et al.[12] there were a large number of drop-outs (27%) and the blinding of assessors was compromised. The Ivanova et al.[13] study had a small number of participants with panic disorder (n=39) and therapists in training conducted the intervention.

The RCTs on social anxiety disorder were randomized with a random number service or a computerized random number generator by independent researchers.[13-15] Intention-to-treat analysis was conducted in all three studies. In two studies, therapists in training conducted the intervention.[13,14] A large percentage (25%) of participants dropped out in the study by Shultz et al.[15]

Silfvernagel et al.[10] (mixed anxiety disorders) performed randomization with an online random number service, independent of investigators. The post-treatment semi-structured telephone interviews were conducted by blinded assessors who had no earlier contact with participants. Dear et al.[16] carried out permuted block randomization with a random number generator, at an independent institution. Both studies conducted intention-to-treat analysis. In Silfvernagel et al.[10] there were imbalances in treatment and control groups (e.g. more participants in control group were employed: 30.3% vs. 9.1%) and there was a large percentage of losses to follow-up (33%), with a higher percentage in the treatment group compared with control. Data were assumed to be missing at random, however, this assumption may not be accurate given the larger number of drop-outs in the treatment group. The study did not provide specific details about the email support given to the control group or the therapist guidance given to the intervention group. In Dear et al.,[16] an initial inclusion criterion of 8 or more on the GAD-7 was removed during the early stages of recruitment because many of the applicants did not meet this cut-off value.

Several studies mentioned potential conflicts of interest with respect to authors and their affiliations with the companies that develop or distribute the treatment programs.[11-13,16]

Summary of Findings

What is the clinical effectiveness of e-therapy interventions for the treatment of anxiety?

The main study findings and author's conclusions for the included studies are provided in Appendix 4.

Generalized Anxiety Disorder

In a meta-analysis of nine studies in participants with generalized anxiety disorder, *Hedges' g* for the post-treatment difference between treatment and control groups, across different measurement instruments, was 0.70 (95% CI: 0.39, 1.01), indicating a statistically significant medium effect size in favour of iCBT.[7]

A meta-analysis of two to four studies found that therapist-supported iCBT was significantly superior than waitlist in producing clinically important improvement in anxiety (determined by a diagnostic interview, a defined cut-off value on a validated scale, or Clinical Global Impression scores), reducing disorder-specific anxiety symptom severity (as measured by scores on a validated instrument), and reducing general anxiety (as measured by scores on a validated instrument).[9] However, statistical differences were not observed for iCBT compared with face-to-face individual or group CBT.[9]

An RCT (N = 103) found that acceptance based iCBT had statistically significant lower scores than waitlist on the BAI, GAD-7, PHQ-9, MADRS-S, PSWQ, and the Generalized Anxiety Disorder Questionnaire-IV(GAD-Q-IV).[11] A higher percentage of participants in the iCBT group achieved clinically significant improvement based on the PSWQ (35% iCBT vs. 6% control). However, there was no statistically significant difference between iCBT and waitlist on the Quality of Life Inventory (QOLI). The results were maintained or improved after six months follow-up. Of the 52 participants who received iCBT, 76% completed all seven modules. Losses to follow-up were similar between groups (19% iCBT and 16% control).

Panic Disorder

In a meta-analysis of 12 studies in participants with panic disorder, *Hedges'g* for the post-treatment difference between treatment and control groups, across different measurement instruments, was 1.31 (95% CI: 0.85, 1.76), indicating a statistically significant large effect size in favour of iCBT.[7]

A meta-analysis of two to five studies found that therapist-supported iCBT was significantly superior than waitlist in producing clinically important improvement in anxiety (determined by a diagnostic interview or a defined cut-off value on a validated scale), reducing disorder-specific anxiety symptom severity (as measured by scores on a validated instrument), and reducing general anxiety (as measured by scores on a validated instrument).[9] However, statistical differences were not observed for iCBT compared with face-to-face individual or group CBT.[9]

An RCT (N=111) found that the post-treatment PDSS-SR score for real-time, video guided iCBT was significantly lower than waitlist.[12] A statistically significant difference, in favour of iCBT, was also observed on the PHQ-9 and the Work and Social Adjustment Scale (WSAS), the Body Vigilance Scale (BVS), the Panic Attack Cognition Questionnaire (PACQ), the Agoraphobic Cognitions Questionnaire (ACQ), and the Body Sensations Questionnaire (BSQ). Improvements were also observed at three- and six-month follow-

ups. At post-treatment, fewer participants in the iCBT group fulfilled diagnostic status for panic disorder when assessed with clinical interview (31% vs. 87% control), PDSS-SR ≥6 (42% vs. 82%), or the Psychiatric Diagnostic Screening Questionnaire (PDSQ) (39% vs. 84%). In the iCBT and control groups, 81% and 71% respectively completed post-treatment questionnaires.

In an RCT that included participants with panic disorder (N=39), iACT ± smartphone application was not better than waitlist for reducing panic symptoms.[13] In fact, the post-treatment PDSS-SR scores were higher in the iACT group (6.98) than in the waitlist group (2.9) (formal statistical testing not conducted). Post-treatment questionnaires were completed by 69% of participants who received iACT and 100% in control group.

Social Anxiety Disorder

In a meta-analysis of 11 studies in participants with social anxiety disorder, *Hedges'g* for the post-treatment difference between iCBT and control (care as usual, waitlist, information, or placebo), across different measurement instruments, was 0.92 (95% CI: 0.76, 1.08), indicating a statistically significant large effect size in favour of iCBT.[7]

A meta-analysis comparing guided iCBT with passive control, at post-treatment across different measurement instruments, found a statistically significant large effect size in favour of iCBT (Hedges' g: 0.87, 95% CI: 0.72, 1.02).[8] Compared with active control, guided iCBT also had a statistically significant medium effect size (Hedges' g: 0.47, 95% CI: 0.15, 0.78). However, compared with pre-assessment, no statistically significant difference was found for guided iCBT at 5-month follow-up [*Hedges'g*: 0.12 (95% CI: -0.17, 0.42)] or at six-month to longer follow-up (Hedges' g: 0.28, 95% CI: -0.01, 0.57).[8]

A meta-analysis of one to seven studies found that therapist-supported iCBT was significantly superior than waitlist in producing clinically important improvement in anxiety (determined by a diagnostic interview or a defined cut-off value on a validated scale), reducing disorder-specific anxiety symptom severity (as measured by scores on a validated instrument), and reducing general anxiety (as measured by scores on a validated instrument).[9] However, statistical differences were not observed for iCBT compared with face-to-face individual or group CBT.[9]

In an RCT of iPDT versus waitlist (N=72), iPDT produced statistically significant lower LSAS-SR score at post-treatment with a large effect size (Cohen's d: 1.05, 95% CI: 0.62, 1.53).[14] Significantly more participants in the iPDT group achieved response, defined as at least 31% reduction in LSAS-SR (58.3% vs. 27.8%), and clinically improved as assessed by the Clinical Global Impression-Improvement (CGI-I) scale (85.3% vs. 45.7%). The two-year follow-up results indicated continued long-term improvement. However, while the percentage of participants achieving remission, defined as LSAS-SR ≤30, was higher with iPDT, statistical significance was not reached for this outcome. In addition, the post-treatment differences between iPDT and waitlist on PHQ-9 and GAD-7 were not statistically significant. The average number of modules completed was 7.2 out of nine (80%), and 69% completed all modules.

An RCT that included 113 participants with social anxiety disorder, found that iACT ± smartphone application produced lower scores on the LSAS-SR compared with waitlist.[13] The *Cohen's d* for post-treatment difference, which also included 39 participants with panic disorder, was 0.70 and statistically significant. After 12-months follow-up, results were

maintained. Completion of post-treatment questionnaires was similar among groups (89.2% iACT guided vs. 89.7% control).

An RCT (N=149) found that both group and individual iCBT were significantly superior to waitlist for producing lower scores on the SPS (Cohen's d for group iCBT vs. control: 0.84, 95% CI: 0.37, 1.29 and individual iCBT vs. control: 1.22, 95% CI: 0.75, 1.70), SIAS (Cohen's d for group iCBT vs. control: 0.74, 95% CI: 0.28, 1.20 and individual iCBT vs. control: 0.94, 95% CI: 0.48, 1.40), and the Brief Symptom Inventory (BSI) (Cohen's d for group iCBT vs. control: 0.54, 95% CI: 0.09, 0.99 and individual iCBT vs. control: 0.53, 95% CI: 0.08, 0.98).[15] No statistically significant post-treatment differences were observed for iCBT, either group or individual, and waitlist on the Beck Depression Inventory-II (BDI-II), the Inventory of Interpersonal Problems (IIP), or the Short Form Health Survey (SF-12). However, the scores on most instruments (excluding BDI-II, for which there was a slight increase) were maintained in the group and individual iCBT interventions after 6-months of follow-up. After treatment, 75% in the iCBT group and individual interventions were determined to have social anxiety disorder based on a diagnostic telephone interview, compared with 100% of participants on waitlist (differences were statistically significant). The average number of completed modules was 6.5 out of eight in individual iCBT (82%) and 6.4 out of eight in group iCBT (79%). Among participants in individual iCBT, 58% completed all modules and among those in iCBT, 57% completed all modules.

Mixed Anxiety Disorders

A meta-analysis of two to five studies found that therapist-supported iCBT was significantly superior than waitlist in producing clinically important improvement in anxiety (determined by a diagnostic interview or a defined cut-off value on a validated scale), reducing disorder-specific anxiety symptom severity (as measured by scores on a validated instrument), and reducing general anxiety (as measured by scores on a validated instrument).[9]

In older adults over 60 years of age (N=66), tailored and guided iCBT was found to perform significantly better (statistically significant) than weekly general email support on the BAI, GAD-7, PHQ-9, the Montgomery Asberg Depression Rating Scale – Self Rated (MADRD-S), the Clinical Outcomes in Routine Evaluation – Outcome Measure (CORE-OM), and the QOLI.[10] Of the original 33 iCBT participants, 19 completed a follow-up survey after one year. The effects of iCBT were sustained based on scores of the BAI, GAD-7, PHQ-9, MADRS-S, CORE-OM, and QOLI (Cohen's d = 0.63 to 1.13). Of the 33 participants who were randomized to iCBT, 33% completed all prescribed modules, 55% completed three-fourths of the program, 67% completed one-half of the program, and 12% did not complete the first module. Losses to follow-up were higher in the iCBT group (33%) compared with control (3%).

A second RCT in older adults 60 years of age or older (N=70) found a large effect size in favour of iCBT compared with waitlist on post-treatment GAD-7 (Cohen's d: 1.43, 95% CI: 0.89, 1.93) and PHQ-9 (Cohen's d: 1.79, 95% CI: 1.21, 2.32).[16] Improvement on the GAD-7 (defined as baseline GAD-7 ≥8 and decrease of >3.53) or recovery (improvement on the GAD-7 + GAD-7 <8) occurred in significantly more participants receiving iCBT compared with waitlist. Similarly, significantly more participants who received iCBT improved on the PHQ-9 (defined as baseline PHQ-9 ≥10 and decrease of >5.20) or recovered (improvement + PHQ-9 <10). The clinical improvements were maintained at three and 12-month follow-ups. All five modules were completed by 85% of participants.

Limitations

A considerable number of RCTs have explored the use of e-therapy interventions for anxiety and this is a rapidly progressing field. The review was restricted to recent publications, available from 2015 onwards.

In all RCTs, participants self-selected into the study by responding to advertisements or notices in newspapers, television, social media, websites, in university campuses, or hospitals. These participants may have represented a motivated subset of people with anxiety disorders and they may have been more likely to engage in e-therapy interventions. It is unclear if the results are applicable to the full spectrum of people with anxiety seen in clinical practice, including individuals with lower levels of motivation.

While all RCTs implemented some form of therapist-guided e-therapy, the interventions were heterogeneous with respect to program content, length, and focus (i.e. disorder-specific vs. transdiagnostic), type of therapist-guidance (i.e. email vs. video-sessions and time spent), and qualifications and expertise level of therapists (i.e. therapists in training vs. licensed therapists). The appropriateness of combining such heterogeneous studies is unclear. Andrews et al. reported I^2 statistics ranging from 35% to 84% for the various analyses.[7] Although Olthuis et al.[9] conducted subgroup analyses by anxiety disorder and therapist time, a comprehensive evaluation of how differences in interventions affect outcomes was not identified in the available literature. Additionally, some included studies provided few details of therapist-guidance, which made it difficult to compare with other publications.[7,8,10]

Blinding of participants was not possible due to the nature of the intervention. Although a few studies attempted to blind outcome assessors, the blinding could not be maintained because participants tended to disclose information about their treatments.[12,15] Participant or outcome assessor knowledge of the intervention may have affected outcomes given that the measurement instruments pose subjective questions.

Several studies had large percentage of participants who were lost to follow-up (25 to 33%).[10,12,15] In most studies the losses were similar among intervention and control groups, although, in one study of older adults a larger percentage was lost among participants who received iCBT. The follow-ups (from three to 24 months) were useful for assessing maintenance of treatment responses. However, the follow-up data usually could not be compared with a control group (due to provision of e-therapy to all participants upon study conclusion) and, since participants may have added other treatment modalities such as pharmacotherapy after completion of the study intervention, these results should be interpreted with caution.

No data were available for the subgroups of interest (i.e. military, para-military, and veteran populations). The RCTs were conducted primarily in European countries and Australia. The applicability of the study findings to Canadian patients with anxiety disorders and Canadian practice settings may be limited. The majority of participants in all studies were female. In few studies, the majority of participants were college or university-educated (53 to 77%).[10,11]

Conclusions and Implications for Decision or Policy Making

Three systematic reviews/meta-analyses and seven additional RCTs formed the evidence base for this review. The studies were categorized based on whether participants had generalized anxiety disorder, panic disorder, social anxiety disorder, or mixed anxiety disorders. All studies included therapist-guided e-therapy interventions, although there was considerable heterogeneity among studies in the intervention and guidance provided. The meta-analyses compared e-therapy with waitlist, care as usual, information or other psychological placebos. The additional RCTs compared e-therapy interventions with waitlist or general weekly email support. Blinding of participants was not possible and attempts at blinding outcome assessors were compromised. Participants in the studies may have represented a more motivated subset of those with anxiety disorders because they self-selected into trials by responding to advertisements or notices. The applicability of the evidence base to Canadian settings is unclear as studies were primarily conducted in European countries or Australia. The majority of participants were female.

No data were available for the subgroups of interest (i.e. military, para-military, and veteran populations). Across all three anxiety disorders, all but one study demonstrated benefits of therapist-guided e-therapy intervention across various measurement instruments. Most studies found that treatment responses were maintained at follow-ups of three to 24 months, although this data must be interpreted with caution as controls were not available and participants may have started other treatments during the follow-up period. Two studies demonstrated that e-therapy intervention may be beneficial in the older adult population. Three studies reported losses to follow-up ranging from 25% to 33%. Losses were similar among intervention and control groups in most studies.

The evidence base suggested that therapist-supported e-therapy interventions are effective for generalized anxiety disorder, panic disorder, and social anxiety disorder compared with waitlist and active controls, but may have similar effects as face-to-face CBT.

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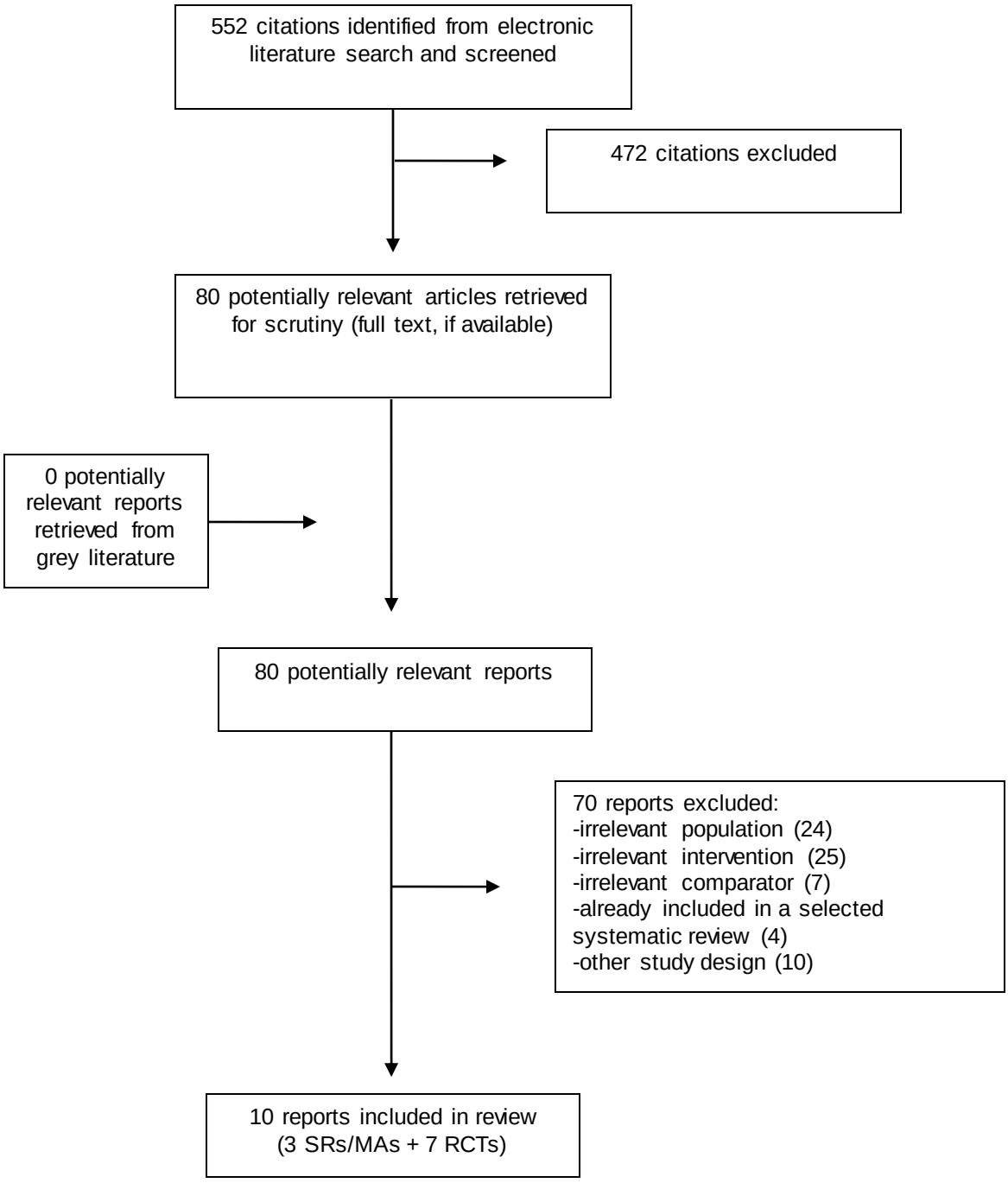
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

Author (Year)	Study Designs Included, No. Studies & Follow-up	Population*	Intervention	Control	Therapist Contact	Outcomes
Andrews (2018)[7]	RCTs (search: prior Sept. 2016) N = 32 studies (populations of interest) Follow-up: 1 – 36 months	≥ 18 years with GAD, PD (with or without agoraphobia) or SAD as primary diagnosis	iCBT	Care as usual, waitlist, information, or placebo	Several of the trials had intervention of iCBT + support, however further details not provided in the review	Change in symptom severity (Hedge's g statistic)
Kampmann (2016)[8]	RCTs (search: 1985-Jun. 2015) N = 18 studies (guided iCBT) Follow-up: 5 to >6 months	≥ 18 years with SAD	iCBT *Data on guided iCBT extracted only*	Passive control Active control	The review conducted a subgroup analysis on guided iCBT, however details of the guidance were not provided.	Change in symptom severity (Hedge's g statistic)
Olthuis (2015)[9]	RCTs (search: 1950-Sept. 2014) N = 23 studies (populations of interest) N = 5 (mixed anxiety disorders) Follow-up: 6-12 months	>18 years with different anxiety disorders, including GAD, PD, or SAD	Therapist-supported iCBT	Waitlist Unguided CBT Face-to-face CBT	Yes Subgroups analyses conducted by therapist contact (low: ≤90 min; medium: 91-299 min; and high: ≥300 min)	Clinically important improvement in anxiety Reduction in disorder-specific anxiety symptom severity Reduction in general anxiety

CBT = cognitive behavioural therapy; GAD = generalized anxiety disorder; iCBT = internet-supported cognitive behaviour therapy; PD = panic disorder; RCT = randomized controlled trial; SAD = social anxiety disorder

* Only those populations of interest to this review , as specified in Table 1, are described.

Table 3: Characteristics of Included Randomized Controlled Trials

Author (Year)	Recruitment Procedures & Location	Length of Treatment & Follow-up	Population	Intervention (I) & Control (C)	Therapist Contact	Outcomes
Generalized Anxiety Disorder						
Dahlin (2016)[11]	Advertisements (internet) and flyers (university campuses and city) followed by online screening and diagnostic telephone inter-view by trained grad. students (SCID-I). Sweden	Treatment: 9 weeks Last follow-up: 6 months	Adults (≥18 years) with ≥45 points on PSWQ, ≤30 MADRS-S, and diagnosis of GAD (DSM-IV). N = 103 Mean age: 39.5 Female: 83.5%	I = acceptance-based iCBT (guided) + audio CD + workbook C = waitlist	Clinical psychologist graduate students provided support for intervention group through a secure messaging system. Mean student time: 78.8 min per participant (over 9 weeks) and 9.3 min per participant per week	BAI GAD-7 GAD-Q-IV MADRS-S PHQ-9 PSWQ (primary) QOLI Attrition
Panic Disorder						
Ciuca (2018)[12]	Notices on media (television news, internet, social media), advertisements in emergency rooms, recommendation of general practitioners and psychotherapists followed by online screening and diagnostic telephone/Skype interview. Romania	Treatment: 12 weeks Last follow-up: 3 months (iCBT guided vs. waitlist data available) and 6 months (iCBT guided only)	Adults (18-65 years) with PDSS-SR ≥6 and meeting diagnostic criteria for panic disorder (PDSQ). N = 111 Mean age: 35.2 Female: 68%	I = guided iCBT (via real-time video sessions) C = unguided iCBT C = waitlist	Licensed therapist guidance included in intervention group. 10 regular 15-45 min video sessions (weekly or upon completion of module). Mean therapist time: 247.2 min per participant Avg. number of sessions: 7.78	PDSS-SR PHQ-9 WSAS BVS PACQ ACQ BSQ Diagnostic status Attrition
Ivanova (2016)[13]	Advertisements	Treatment:	Adults (≥18 years)	I = guided iACT ±	The guided group	PDSS-SR

Author (Year)	Recruitment Procedures & Location	Length of Treatment & Follow-up	Population	Intervention (I) & Control (C)	Therapist Contact	Outcomes
	in regional and national newspapers, Internet forums, and healthcare institutions followed by online screening and diagnostic telephone interview. Sweden	10 weeks Last follow-up: 12 months	with PDSS-SR ≥8 and meeting diagnostic criteria for panic disorder (DSM-IV). N = 39 Mean age: 35.3 (PD + SAD sample, N=152) Female: 64.5% (PD + SAD sample, N=152)	smartphone C = unguided iACT ± smartphone C = waitlist	received comments on their treatment progress from a therapist about twice per week. The therapists were Masters students in clinical psychology at end of their clinical training. Therapists were instructed to spend 15 min per patient per week.	Clinically significant improvement Attrition
Social Anxiety Disorder						
Johansson (2017)[14]	Advertisements in newspapers and social media followed by online screening and diagnostic telephone interview. Sweden	Treatment: 10 weeks Last follow-up: 24 months	Adults (≥18 years) with LSAS-SR ≥30 and meeting diagnostic criteria for SAD (DSM-IV, MINI). N = 72 Mean age: 42.9 Female: 61.1%	I = iPDT C = waitlist	Therapists (Master level students in final year of a 5-year clinical psychologist program) kept in contact with participants through text messages. Therapist time was not logged. They were instructed to spend 10-15 min per participant per week.	LSAS-SR (primary) PHQ-9 GAD-7 CGI-I Attrition *CGI-I was assessed via telephone interview.*
Ivanova (2016)[13]	Advertisements in regional and national newspapers, Internet forums, and healthcare institutions followed by online screening and diagnostic telephone	Treatment: 10 weeks Last follow-up: 12 months	Adults (≥18 years) with LSAS-SR ≥30 and meeting diagnostic criteria for SAD (DSM-IV). N = 113 Mean age: 35.3 (PD + SAD sample, N=152)	I = guided iACT ± smartphone C = unguided iACT ± smartphone C = waitlist	The guided group received comments on their treatment progress from a therapist about twice per week. The therapists were Masters students in clinical psychology at end of their clinical training. Therapists were	LSAS-SR Clinically significant improvement Attrition

Author (Year)	Recruitment Procedures & Location	Length of Treatment & Follow-up	Population	Intervention (I) & Control (C)	Therapist Contact	Outcomes
	interview. Sweden		Female: 64.5% (PD + SAD sample, N=152)		instructed to spend 15 min per patient per week.	
Schulz (2016)[15]	Notices on study website and internet forums followed by online screening and diagnostic telephone interview (SCID-I). Switzerland, Austria, and Germany	Treatment: 12 weeks Last follow-up: 6 months	Adults (≥18 years) with SAD (DSM-IV). N = 149 Mean age: 35.4 Female: 53%	I = group iCBT (guided) I = individual iCBT (guided) C = waitlist	Individual iCBT : therapist monitored progress and contacted participants via email on weekly basis. Group iCBT: participants had access to a therapist-guided discussion forum (6 members/group). Mean therapist time: iCBT individual: 17 min per participant per week iCBT group: 4.5 min per participant per week	SPS (primary) SIAS (primary) BDI-II BSI IIP SF-12 Diagnostic status Attrition
Mixed						
Silfvernagel (2017)[10]	Advertisements in newspaper followed by online screening and diagnostic telephone interview. Sweden	Treatment: 8 weeks Last follow-up: 12 months	Older adults (>60 years) with recurring anxiety symptoms ± major depression N = 66 Mean age: 66.1 Female: 75.8%	I = iCBT (guided & tailored) C = weekly general e-mail support from a clinician	Therapist guidance included in intervention group. Mean therapist time: 100 min per participant in intervention group	BAI (primary) GAD-7 MADRS-S PHQ-9 CORE-OM QOLI Attrition
Dear (2015)[16]	Via a website that provides information about mental health, followed	Treatment: 8 weeks Last follow-up: 12 months	Older adults (≥60 years) with anxiety. N = 70	I = iCBT C = waitlist	Intervention group received brief weekly contact with a clinical psychologist via telephone or email.	GAD-7 PHQ-9 Improvement Recovery Attrition

Author (Year)	Recruitment Procedures & Location	Length of Treatment & Follow-up	Population	Intervention (I) & Control (C)	Therapist Contact	Outcomes
	by diagnostic telephone interview (MINI). Australia		Mean age: 65.4 (intervention) and 65.5 (control) Female: 60%		Mean therapist time: 57.6 min per participant (total time)	Cost-effectiveness

ACQ = Agoraphobic Cognitions Questionnaire; BAI = Beck Anxiety Inventory; BDI-II = Beck Depression Inventory-II; BSI = Brief Symptom Inventory; BSPS = Brief Social Phobia Scale; BSQ = Body Sensations Questionnaire; BVS = Body Vigilance Scale; CBT = internet-supported cognitive behavior therapy; CD = compact disc; CGI-I = Clinical Global Impression-Improvement scale; CORE-OM = Clinical Outcomes in Routine Evaluation – Outcome Measure; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th edition; GAD = generalized anxiety disorder; GAD-7 = Generalized Anxiety Disorder 7-item scale; GAD-Q-IV = Generalized Anxiety Disorder Questionnaire-IV; HAMA = Hamilton Anxiety Rating Scale; iACT = internet-delivered acceptance and commitment therapy; iCBT = internet-supported cognitive behavioural therapy; iPDT = internet-based psychodynamic therapy; IIP = Inventory of Interpersonal Problems; LSAS-SR = Liebowitz Social Anxiety Scale – Self Rated; MADRS-S = Montgomery Asberg Depression Rating Scale - Self Rated; MINI = Mini International Neuropsychiatric Interview; PACQ = Panic Attack Cognition Questionnaire; PAS = Panic and Agoraphobia Scale; PD = panic disorder; PDSQ = Psychiatric Diagnostic Screening Questionnaire; PDSS-SR = Panic Disorder Severity Scale – Self Report; PHQ-9 = Patient Health Questionnaire-9; PSWQ = Penn State Worry Questionnaire; QOLI = Quality of Life Inventory; SAD = social anxiety disorder; SCID-I = Structural Clinical Interview for DSM-IV Axis I disorders; SF-12 = Short Form Health Survey (condensed version of SF-36); SIAS = Social Interaction Anxiety Scale; SPS = Social Phobia Scale; WSAS = Work and Social Adjustment Scale

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR II[5]

Strengths	Limitations
Andrews (2018)[7]	
• An *a priori* protocol is available. • Data extraction and quality assessment were conducted in duplicate, with disagreements resolved by a third party. • Meta-analysis was conducted with random effects model (heterogeneity among studies was significant). • Heterogeneity in meta-analysis was examined according to study quality.	• Authors considered publications in English only, that were either published or in press. • Minimal details provided about support interventions that were administered alongside iCBT. • In the methods the authors state that they tested for publication bias, however the results of this analysis were not presented.
Kampmann (2016)[8]	
• Study selection, data extraction, and quality assessment were conducted in duplicate. • Meta-analysis was conducted using random effects model. • Meta-analysis included data based on intention-to-treat.	• No *a priori* protocol available. • The grey literature was not searched. • No details provided about the type of guidance provided with iCBT. • Estimates for statistical heterogeneity were not provided for meta-analyses of guided iCBT.
Olthuis (2015)[9]	
• An *a priori* protocol is available. • A comprehensive search was conducted. • Study selection, data extraction, and quality assessment conducted in duplicate. • Meta-analysis was conducted using random effects models. • Subgroup analyses were conducted by study quality, anxiety disorder, and therapist time. • Meta-analysis was based on intention-to-treat.	• Studies were heterogeneous, although findings were robust in sensitivity analyses.

iCBT = internet-supported cognitive behavioural therapy

Table 5: Strengths and Limitations of Randomized Controlled Trials using The Cochrane Risk of Bias Tool[6]

Strengths	Limitations
Generalized Anxiety Disorder	
Dahlin (2016)[11]	
• Randomization was performed with an online random-number service by an employee of the university with no connection to the study. • During the nine weeks of treatment administration, the control group had no contact with study administrators. • Intention-to-treat analysis was conducted. • Drop-outs were relatively balanced between treatment and control groups.	• The study was conducted in Sweden and the generalizability to patients in Canada is unclear. The majority of participants (76.7%) had university education. • Treatment support was provided by trained graduate students rather than licensed therapists. In addition, the same students who provided guidance conducted the initial diagnostic telephone interview, which may have affected the type of support provided (based on knowledge of scores on the diagnosis questionnaires). • The primary author is employed by the company that developed the treatment program, which is a potential conflict of interest.
Panic Disorder	
Ciuca (2018)[12]	
• Randomization was performed with software that implemented a minimization algorithm, which balanced groups with respect to disease severity and chronicity. • Allocation was conducted by an independent researcher. Also, researchers involved in recruitment and screening had no knowledge or control over allocation. • Treatment groups were overall balanced in baseline characteristics. • Missing data were imputed as treatment failures, which resulted in conservative estimates. • Intention-to-treat analysis was conducted.	• The study was conducted in Romania and the generalizability to patients in Canada is unclear. • Large number of drop-outs (27%). • Blinding of assessors was compromised because some participants disclosed information about treatment during interviews. • Authors of study had affiliations with the web-based software used to deliver the iCBT program.
Ivanova (2016)[13]	
• Randomization was performed with a random number service and stratified by primary diagnosis (i.e. panic disorder and social anxiety disorder). • The randomization was conducted by a researcher with no relation to the study. • Intention-to-treat analysis was conducted.	• The study was conducted in Sweden and the generalizability to patients in Canada is unclear. • Therapists in training conducted the intervention, although they were supervised by a licensed clinical psychologist. • Small sample size (N=39). • Baseline characteristics combined for panic disorder and social anxiety disorders (unclear if characteristics were balanced for participants with panic disorder). • Two of the authors were employed by the company that develops and distributes the research products used in the study.
Social Anxiety Disorder	
Johansson (2017)[14]	
• Randomization was performed with a random number service. • An independent researcher conducted the randomization and allocation of participants.	• The study was conducted in Sweden and the generalizability to patients in Canada is unclear. • Therapists in training conducted the intervention, although they were supervised by more experienced therapists.

Strengths	Limitations
• Intention-to-treat analysis was conducted. • Small number of drop-outs at post-treatment (1/36 in treatment group and 1/36 in control). • Long-term follow-up of treatment group (24 months). • The CGI-I telephone interviewers were conducted by final-year clinical psychology students who were blind to treatment allocation.	• The control group had more females than males (72.2% vs. 27.8%).
Ivanova (2016)[13]	
• Randomization was performed with a random number service and stratified by primary diagnosis (i.e. panic disorder and social anxiety disorder). • The randomization was conducted by a researcher with no relation to the study. • Intention-to-treat analysis was conducted.	• The study was conducted in Sweden and the generalizability to patients in Canada is unclear. • Therapists in training conducted the intervention, although they were supervised by a licensed clinical psychologist. • Baseline characteristics combined for panic disorder and social anxiety disorders (unclear if characteristics were balanced for participants with social anxiety disorder). • Two of the authors were employed by the company that develops and distributes the research products used in the study.
Schulz (2016)[15]	
• Randomization was performed with a computerized random number generator and concealed from investigators. • Participants were informed about their group allocation via email. • Intention-to-treat analysis was conducted. • Drop-outs were regarded as treatment failures for post-treatment diagnostic status (for other outcomes, missing data were imputed with mixed-effect models, which use all available data on a subject). • Treatment groups were balanced overall.	• The study was conducted in Switzerland, Austria, and Germany; generalizability to patients in Canada is unclear. • The assessors of post-diagnostic status were not blinded to treatment allocation. • Large percentage of drop-outs (25%).
Mixed	
Silfvernagel (2017)[10]	
• Randomization was performed with an online random number-generation service independent of investigators and therapists. • At post-treatment, semi-structured telephone interviews were conducted by blinded assessors who had no earlier contact with participants. • Intention-to-treat analysis was conducted.	• The study was conducted in Sweden and the generalizability to older adults in Canada is unclear. The majority of participants (53%) had college or university education. • Some imbalances were present in the treatment and control groups: more participants were employed in the control group (30.3% vs. 9.1%) and more participants in the control group had no experience with psychotherapy (46% vs. 24.2%). Although unclear, this suggests that potentially allocation to randomized groups may have been affected. • A large percentage of participants were lost to follow-up in the treatment group (33.3%). Data were assumed to be missing at random, however, given the larger number of drop-outs in treatment group vs. control, this assumption may not be accurate. • The control group was administered general weekly e-mail support, however details of this intervention were not provided (e.g. did all participants in the control group

Strengths	Limitations
	receive the same support or were there any overlaps with the treatment group). • Details about the nature of therapist guidance were not provided.
Dear (2015)[16]	
• Permuted block randomization sequence was generated with a random number generator by an independent researcher at another institution. • Allocation assignments were kept in sealed envelopes. • Overall, groups were balanced in baseline characteristics. • Intention-to-treat analysis was conducted (assumed that data missing at random) • Small number of withdrawals or post-treatment non-responders (10% in treatment group and 13.5% in control).	• The study was conducted in Australia; generalizability to patients in Canada is unclear. • An initial inclusion criterion of ≥8 on the Generalized Anxiety Disorder-7 Item Scale was removed during early stages of recruitment because many applicants did not meet this cut-off value. However, analyses were conducted separately for the subgroup of participants that did meet the criterion. • Two participants randomized to treatment group were subsequently excluded from analyses (reason unclear). • Two of the authors are developers of the internet-delivered cognitive behavior therapy course used in the study.

Appendix 4: Main Study Findings and Author's Conclusions

Table 6: Summary of Findings of Included Systematic Reviews and Meta-Analyses

Main Study Findings	Author's Conclusion
Andrews (2018)[7]	
GAD: 9 studies Hedges' g (95% CI) = 0.70 (0.39, 1.01) **PD: 12 studies** Hedges' g (95% CI) = 1.31 (0.85, 1.76) **SAD: 11 studies** Hedges' g (95% CI) = 0.92 (0.76, 1.08)	"In conclusion, the 64 identified iCBT trials generated large effect size superiority over control groups, with maintenance of benefit at follow-up, acceptable patient adherence and high rates of satisfaction and now with evidence of effectiveness in routine practice." (p.77)
Kampmann (2016)[8]	
Guided iCBT vs. passive control: Hedges' g (95% CI) - Post-assessment: 0.87 (0.72, 1.02), p<0.001 **Guided iCBT vs. active control: Hedges' g (95% CI)** - Post-assessment: 0.47 (0.15, 0.78), p<0.01 **Guided iCBT vs. pre-assessment: Hedges' g (95% CI)** - Five-month follow-up: 0.12 (-0.17, 0.42), p=0.412 - ≥ Six-month follow-up: 0.28 (-0.01, 0.57), p=0.056	"When discriminating between different levels of guidance for ICBT, results revealed that guided ICBT was effective in reducing SAD [social anxiety disorder] complaints compared to passive control conditions at post assessment. This effect did not sustain at follow-up 1 [five months], however implications of this finding are limited by the fact that only two studies were included. The medium effect of guided ICBT relative to active control conditions indicated that guided ICBT might have an advantage over the active control conditions it was compared to. No effect was found in an exploratory analysis at follow-up 2 [≥6 months]." (p.82)
Olthuis (2015)[9]	
Therapist-Supported iCBT vs. Waitlist *Clinically important improvement in anxiety: RR (95% CI)* GAD (3 studies): 2.58 (1.48, 4.51) PD (2 studies): 18.32 (2.50, 134.18) SAD (1 study): 6.00 (2.64, 13.62) Mixed* (2 studies): 6.12 (2.54, 14.77) *Reduction in disorder-specific anxiety symptom severity: SMD (95% CI)* GAD (4 studies): -0.91 (-1.40, -0.43) PD (5 studies): -1.58 (-2.79, -0.37) SAD (7 studies): -1.44 (-1.65, -1.23) Mixed* (5 studies): -0.75 (-1.10, -0.40) *Reduction in general anxiety: SMD (95% CI)* GAD (2 studies): -1.91 (-3.57, -0.26) PD (4 studies): -0.74 (-1.35, -0.13) SAD (3 studies): -0.64 (-0.85, -0.42) Mixed* (4 studies): -0.49 (-0.75, -0.23) **Therapist-Supported iCBT vs. Unguided CBT** *Clinically important improvement in anxiety: RR (95% CI)* SAD (1 study): 1.07 (0.67, 1.69) *Reduction in disorder-specific anxiety symptom severity:*	"The present findings suggest that therapist-supported ICBT is more efficacious than a waiting list, attention, information, or online discussion group only control in leading to clinically important improvement in anxiety, reducing anxiety symptoms (both disorder-specific and general), and improving quality of life. Results also generally showed no difference in outcomes following therapist-supported ICBT versus unguided CBT at post-treatment, though results are limited by low quality evidence due to a limited number of studies (that is, imprecision). Moreover, results suggest that therapist-supported ICBT may not be significantly different from face-to-face group and individual CBT in treating anxiety disorders. Meta-analyses revealed no significant differences in clinically important improvement in anxiety or reduction in anxiety symptoms (both disorder-specific and general) at post treatment or follow-up for these two interventions." (p.33) "Therapist-supported ICBT appears to be an efficacious treatment for anxiety in adults. The evidence comparing therapist-supported ICBT to waiting list, attention, information, or online discussion group only control was low to moderate quality, the evidence comparing therapist-supported ICBT to unguided ICBT was low to very low quality, and comparisons of therapist-supported ICBT to face-to-face CBT was low to moderate quality." (p.2)

Main Study Findings	Author's Conclusion
SMD (95% CI) SAD (4 studies): -0.24 (-0.69, 0.21) SAD, 6-12 month follow-up (3 studies): -0.30 (-0.58, -0.01) *Reduction in general anxiety: SMD (95% CI)* SAD (2 studies): 0.28 (-2.21, 2.78) SAD, 12 month follow-up (2 studies): 0.72 (-2.12, 3.57) **Therapist-Supported iCBT vs. Face-to-Face CBT** *Clinically important improvement in anxiety: RR (95% CI)* PD (3 studies): 1.06 (0.85, 1.32) PD, 6-12 month follow-up (2 studies): 1.09 (0.93, 1.28) SAD (1 study): 1.45 (0.77, 2.76) SAD, 6-12 month follow-up (1 study): 1.15 (0.73, 1.83) *Reduction in disorder-specific anxiety symptom severity: SMD (95% CI)* PD (3 studies): 0.29 (0.03, 0.54) PD, 6-12 month follow-up (2 studies): -0.04 (-0.36, 0.28) SAD (2 studies): -0.18 (-0.92, 0.57) SAD, 6-12 month follow-up (2 studies): -0.39 (-0.71, -0.08) *Reduction in general anxiety: SMD (95% CI)* PD (2 studies): 0.42 (-0.75, 1.60) PD, 6-12 month follow-up (1 study): -0.17 (-0.74, 0.39) SAD (2 studies): -0.18 (-0.49, 0.13) SAD, 6-12 month follow-up (2 studies): -0.14 (-0.45, 0.17)	

CBT = cognitive behavioural therapy; CI = confidence interval; GAD = generalized anxiety disorder; iCBT = internet-supported cognitive behavioural therapy; PD = panic disorder; RR = relative risk; SAD = social anxiety disorder; SMD = standardized mean difference

[*] PD, agoraphobia, social phobia, post-traumatic stress disorder, acute stress disorder, GAD, obsessive compulsive disorder, and specific phobia

Table 7: Summary of Findings of Included Randomized Controlled Trials

Main Study Findings	Author's Conclusions
Generalized Anxiety Disorder	
Dahlin (2016)[11]	
BAI: iCBT: Pre-treatment = Mean 21.12 (SD 8.81) & Post = 12.67 (8.24) iCBT (6-month): Mean 10.88 (SD 8.25) Control: Pre-treatment = Mean 22.04 (SD 8.2) & Post = 17.09 (7.78) Cohen's d (95% CI) (between group effect): 0.55 (0.07, 0.99) **GAD-7:** iCBT: Pre-treatment = 13.83 (3.66) & Post = 6.9 (3.52) iCBT (6-month): 6.56 (4.18) Control: Pre-treatment = 13.51 (4.14) & Post = 10.72 (4.2) Cohen's d (95% CI) (between group effect): 0.98 (0.52, 1.43) **GAD-Q-IV:** iCBT: Pre-treatment = 10.54 (1.35) & Post = 7.35 (2.65) iCBT (6-month): 5.4 (1.18) Control: Pre-treatment = 10.49 (1) & Post = 9 (2.01) Cohen's d (95% CI) (between group effect): 0.70 (0.20, 1.14) **MADRS-S:** iCBT: Pre-treatment = 18.62 (6.06) & Post = 12.17 (6.89) iCBT (6-month): 10.06 (8.75) Control: Pre-treatment = 19.86 (5.87) & Post = 15.79 (5.97) Cohen's d (95% CI) (between group effect): 0.56 (0.12, 1.08) **PHQ-9:** iCBT: Pre-treatment = 11.1 (4.69) & Post = 5.83 (5.14) iCBT (6-month): 5.19 (5.25) Control: Pre-treatment = 11.47 (4.87) & Post = 8.33 (4.63) Cohen's d (95% CI) (between group effect): 0.51 (0.05, 0.95) **PSWQ:** iCBT: Pre-treatment = 66.88 (7.16) & Post = 55.29 (10.02) iCBT (6-month): 51.22 (10.39) Control: Pre-treatment = 67.45 (6.77) & Post = 63.35 (8.4) Cohen's d (95% CI) (between group effect): 0.87 (0.35, 1.33) Achieving Clinically Significant Improvement (cut-off score 56.9): iCBT: 18/52 (35%) Control: 3/51 (6%) *p (Fischer's exact test) = 0.0004* **QOLI:** iCBT: Pre-treatment = 0.58 (1.76) & Post = 1.68 (1.33) iCBT (6-month): 2.13 (1.56) Control: Pre-treatment = 0.95 (1.57) & Post = 1.51 (1.4) Cohen's d (95% CI) (between group effect): 0.12 (-0.55, 0.33) **Attrition:**	"The results indicate that the treatment was effective compared to a waiting list control condition. Significant differences with moderate to large between group effect sizes were found on all measures with the exception of the QOLI." (p.93) "At six-month followup the results were largely maintained or further improved." (p.93) ". . .we used a self-recruited sample and the level of education was very high (e.g., many had a university education)." (p.94)

Main Study Findings	Author's Conclusions
iCBT: 10/52 (19.2%) iCBT (6-month): 19/52 (36.5%) Control: 8/51 (15.7%) *Of participants who received iCBT* Completed all 7 modules: 76% Completed 6 modules: 88% Completed module 5: 93% Completed modules 3 and 4: 95% Completed modules 1 and 2: 100%	
Panic Disorder	
Ciuca (2018)[12]	
PDSS-SR: iCBT guided: Pre-treatment = Mean 16.42 (SD 4.76) & Post = 4.93 (3.64) iCBT unguided: Pre-treatment = Mean 15.54 (SD 4.51) & Post = 7.36 (5.28) Control: Pre-treatment = Mean 15.74 (SD 4.91) & Post = 11.26 (6.38) *Statistically significant post-treatment differences between iCBT guided vs. control (p<0.001) and iCBT unguided vs. control (p=0.002).* Cohen's d (95% CI) (between group effect iCBT guided vs. control): 1.36 (0.84, 1.85) 3-month follow-up: iCBT guided: 3.82 (SD 3.43); Control: 5.53 (3.6) 6-month follow-up: iCBT guided: 3.91 (SD 3.44) **PHQ-9:** iCBT guided: Pre-treatment = 13.45 (6.33) & Post = 5.38 (4.39) iCBT unguided: Pre-treatment = 11.47 (6.63) & Post = 6.48 (5.51) Control: Pre-treatment = 12.46 (6.9) & Post = 10.19 (6.56) *Statistically significant post-treatment differences between iCBT guided vs. control (p<0.001) and iCBT unguided vs. control (p=0.003).* Cohen's d (95% CI) (between group effect iCBT guided vs. control): 1.05 (0.52, 1.56) 3-month follow-up: iCBT guided: 3.67 (3.96); Control: 3.67 (4.05) 6-month follow-up: iCBT guided: 3.09 (2.31) **WSAS:** iCBT guided: Pre-treatment = 19.70 (9.55) & Post = 7.66 (7.9) iCBT unguided: Pre-treatment = 18.93 (9.35) & Post = 9.72 (9.11) Control: Pre-treatment = 18.57 (10.15) & Post = 16.04 (9.94) *Statistically significant post-treatment differences between iCBT guided vs. control (p<0.001) and iCBT unguided vs. control (p=0.001).* Cohen's d (95% CI) (between group effect iCBT guided vs. control): 1.18 (0.66, 1.67) 3-month follow-up: iCBT guided: 5 (5.7); Control: 7 (7.36)	"We found significant treatment effects on panic symptoms severity, depressive symptoms, functional impairment, catastrophic cognitions, body vigilance, and fear of sensations immediately after the treatment and through followups, indicating that treatment gains were maintained by most of the participants." (p.9) "The study shows that real-time video guidance sessions are beneficial for improving adherence, satisfaction, diagnostic status at post-treatment and long-term outcomes." (p.11)

Main Study Findings	Author's Conclusions
6-month follow-up: iCBT guided: 4.22 (3.61) **BVS:** iCBT guided: Pre-treatment = 10.38 (4.01) & Post = 3.97 (3) iCBT unguided: Pre-treatment = 10.51 (4.04) & Post = 5.73 (4.7) Control: Pre-treatment = 10.95 (4.34) & Post = 9.21 (5.26) *Statistically significant post-treatment differences between iCBT guided vs. control (p<0.001) and iCBT unguided vs. control (p=0.006).* Cohen's d (95% CI) (between group effect iCBT guided vs. control): 1.30 (0.78, 1.79) 3-month follow-up: iCBT guided: 3.11 (3.23); Control: 4.65 (3.52) 6-month follow-up: iCBT guided: 3.29 (2.34) **PACQ:** iCBT guided: Pre-treatment = 35.57 (13.26) & Post = 14.03 (12.16) iCBT unguided: Pre-treatment = 32.68 (12.94) & Post = 18.04 (13.72) Control: Pre-treatment = 33.95 (12.55) & Post = 34.93 (17.62) *Statistically significant post-treatment differences between iCBT guided vs. control (p<0.001) and iCBT unguided vs. control (p<0.001).* Cohen's d (95% CI) (between group effect iCBT guided vs. control): 1.45 (0.91, 1.95) 3-month follow-up: iCBT guided: 10.48 (12.19); Control: 15.47 (15.65) 6-month follow-up: iCBT guided: 10.78 (11.25) **ACQ:** iCBT guided: Pre-treatment = 2.54 (0.67) & Post = 1.61 (0.49) iCBT unguided: Pre-treatment = 2.16 (0.62) & Post = 1.78 (0.64) Control: Pre-treatment = 2.43 (0.71) & Post = 2.27 (0.88) *Statistically significant post-treatment differences between iCBT guided vs. control (p<0.001) and iCBT unguided vs. control (p<0.005).* Cohen's d (95% CI) (between group effect iCBT guided vs. control): 1.04 (0.53, 1.52) 3-month follow-up: iCBT guided: 1.28 (0.33); Control: 1.43 (0.46) 6-month follow-up: iCBT guided: 1.3 (0.32) **BSQ:** iCBT guided: Pre-treatment = 3 (0.59) & Post = 2.02 (0.54) iCBT unguided: Pre-treatment = 2.93 (0.71) & Post = 2.16 (0.7) Control: Pre-treatment = 3.14 (0.8) & Post = 2.9 (0.85) *Statistically significant post-treatment differences between iCBT guided vs. control (p<0.001) and iCBT unguided vs. control (p<0.001).* Cohen's d (95% CI) (between group effect iCBT guided vs. control): 1.33 (0.80, 1.83) 3-month follow-up: iCBT guided: 1.63 (0.48); Control: 2.03 (0.73) 6-month follow-up: iCBT guided: 1.71 (0.58)	

Main Study Findings	Author's Conclusions
Diagnostic status (post-treatment, with panic disorder): *Based on Clinical Interview:* iCBT guided: 31%; iCBT unguided: 73%; Control: 87% *Based on PDSS-SR ≥6:* iCBT guided: 42%; iCBT unguided: 70%; Control: 82% *Based on PDSQ:* iCBT guided: 39%; iCBT unguided: 65%; Control: 84% **Attrition:** *Completion of post-treatment questionnaires:* iCBT guided: 29/36 (80.6%) iCBT unguided: 25/37 (67.6%) Control: 27/38 (71.0%)	
Ivanova (2016)[13]	
PDSS-SR: iACT guided: Pre-treatment = Mean 14.00 (SD 5.05) & Post = 6.98 (6.71) iACT guided (12-month): Mean 4.94 (SD 3.68) iACT unguided: Pre-treatment = Mean 2.93 (SD 0.71) & Post = 2.16 (0.7) iACT guided (12-month): Mean 5.42 (SD 3.44) Control: Pre-treatment = Mean 3.14 (SD 0.8) & Post = 2.9 (0.85) Cohen's d (between group effect, including SAD + PD): 0.05 (p<0.0167) **Clinically significant improvement (GAD-7 <5.2 + PDSS-SR <10.44):** "Analyses of clinically significant improvement showed no significant differences in any of the diagnosis groups." (p.32) **Attrition:** *Completion of post-treatment questionnaires:* iACT guided: 9/13 (69.2%) iACT unguided: 11/14 (78.6%) Control: 12/12 (100%)	"For the participants suffering primarily from PD, the treatment group was not significantly superior to the control group in terms of reduction of their panic symptoms." (p.32) "All the results, both those diagnosis-specific and not, were maintained at the 12-months follow-up for the guided and the unguided groups. However, at least 31% of the participants received either psychological or pharmacological help after the treatment period was over, therefore these results should be interpreted with caution." (p.33)
Social Anxiety Disorder	
Johansson (2017)[14]	
LSAS-SR: iPDT: Pre-treatment = Mean 69.50 (SD 21.00) & Post = 43.29 (23.69) iPDT (24-month): Mean 38.68 (SD 19.69) Control: Pre-treatment = Mean 63.25 (SD 16.88) & Post = 55.20 (24.00) Cohen's d (95% CI) (between group effect): 1.05 (0.62, 1.53) *Response (LSAS-SR reduction at least 31%):* iPDT: 58.3%; Control: 27.8% (p<0.01) *Remission (LSAS-SR ≤30)::*	"The main finding is that the treatment had a large effect (d=1.05) on symptoms of social anxiety as compared with the wait-list control condition." (p.357) "The pre-post effect was substantial in the treatment group (d=1.45), and we also found small but significant long-term effects, suggesting continued improvement between termination and the 2-year follow-up." (p.357) "Lastly, our IPDT protocol seems to have been well tolerated, given that patients completed 80% of the

Main Study Findings	Author's Conclusions
iPDT: 27.8%; Control: 11.1% (p=0.07) **PHQ-9:** iPDT: Pre-treatment = 8.72 (6.04) & Post = 5.37 (4.34) iPDT (24-month): 4.57 (4.16) Control: Pre-treatment = 10.53 (6.63) & Post = 8.86 (6.55) Cohen's d (95% CI) (between group effect): 0.25 (-0.07, 0.63) **GAD-7:** iPDT: Pre-treatment = 8.00 (4.30) & Post = 5.29 (4.38) iPDT (24-month): 3.82 (2.76) Control: Pre-treatment = 9.19 (6.20) & Post = 7.03 (5.61) Cohen's d (95% CI) (between group effect): 0.10 (-0.30, 0.47) **CGI-I: Improved** iPDT: 85.3%; Control: 45.7% (p<0.01) **Attrition:** Mean number of completed modules: 7.2 (80%) Completion of all modules: 25/36 (69.4%)	modules on average and only three participants did not complete any treatment module." (p.358)
Ivanova (2016)[13]	
LSAS-SR: iACT guided: Pre-treatment = Mean 68.27 (SD 21.90) & Post = 51.04 (22.45) iACT guided (12-month): Mean 47.25 (SD 24.70) iACT unguided: Pre-treatment = Mean 70.19 (SD 21.90) & Post = 54.87 (23.24) iACT guided (12-month): Mean 48.98 (SD 25.24) Control: Pre-treatment = Mean 69.62 (SD 21.92) & Post = 68.98 (22.73) Cohen's d (between group effect, including SAD + PD): 0.70 (p<0.001) **Clinically significant improvement (GAD-7 <5.2 + LSAS-SR <34.06):** "Analyses of clinically significant improvement showed no significant differences in any of the diagnosis groups." (p.32) **Attrition:** *Completion of post-treatment questionnaires:* iACT guided: 33/37 (89.2%) iACT unguided: 28/37 (75.7%) Control: 35/39 (89.7%)	"The treatment was effective for participants suffering primarily from SAD." (p.32) "All the results, both those diagnosis-specific and not, were maintained at the 12-months follow-up for the guided and the unguided groups. However, at least 31% of the participants received either psychological or pharmacological help after the treatment period was over, therefore these results should be interpreted with caution." (p.33)
Schulz (2016)[15]	
SPS: iCBT individual: • Pre-treatment = Mean 39.32 (SD 11.64) & Post = 21.07 (10.94) • 6-month: Mean 20.61 (SD 11.85) iCBT group: • Pre-treatment = 38.90 (SD 14.04) & Post = 23.78 (13.16)	Overall, results suggest that SAD [social anxiety disorder] can be successfully treated with a clinician-guided group ICBT. We found significant treatment effects on social anxiety symptom severity, depressive symptoms, interpersonal problems, general symptom severity and psychological wellbeing immediately after the treatment and significant time effects at a six-month follow-up

Main Study Findings	Author's Conclusions
• 6-month: 20.66 (SD 10.49) Control: • Pre-treatment = 37.35 (12.45) & Post = 34.58 (12.30) *Statistically significant post-treatment differences between iCBT individual vs. control (p<0.001) and iCBT group vs. control (p=0.002).* Cohen's d (95% CI): • iCBT individual vs. control: 1.22 (0.75, 1.70) • iCBT group vs. control: 0.84 (0.37, 1.29) **SIAS:** iCBT individual: • Pre-treatment = 50.48 (14.48) & Post = 33.87 (14.47) • 6-month: 32.36 (15.38) iCBT group: • Pre-treatment = 50.93 (14.00) & Post = 36.56 (16.01) • 6-month: 34.28 (16.09) Control: • Pre-treatment = 50.97 (13.58) & Post = 47.67 (10.97) *Statistically significant post-treatment differences between iCBT individual vs. control (p=0.001) and iCBT group vs. control (p=0.007).* Cohen's d (95% CI): • iCBT individual vs. control: 0.94 (0.48, 1.40) • iCBT group vs. control: 0.74 (0.28, 1.20) **BDI-II:** iCBT individual: • Pre-treatment = 19.43 (10.22) & Post = 10.35 (10.22) • 6-month: 11.13 (10.80) iCBT group: • Pre-treatment = 17.88 (10.46) & Post = 10.27 (9.87) • 6-month: 11.16 (10.66) Control: • Pre-treatment = 17.97 (11.59) & Post = 14.41 (11.42) *No statistically significant post-treatment differences between iCBT individual vs. control (p=0.29) and iCBT group vs. control (p=0.18).* Cohen's d (95% CI): • iCBT individual vs. control: 0.40 (-0.05, 0.84) • iCBT group vs. control: 0.46 (0.01, 0.91) **BSI:** iCBT individual: • Pre-treatment = 1.28 (0.54) & Post = 0.89 (0.59) • 6-month: 0.75 (0.48) iCBT group: • Pre-treatment = 1.30 (0.65) & Post = 0.88 (0.60) • 6-month: 0.74 (0.62) Control: • Pre-treatment = 1.25 (0.64) & Post = 1.13 (0.73) *Statistically significant post-treatment differences between iCBT individual vs. control (p=0.05) and iCBT group vs. control (p=0.04).*	indicating that treatment gains could be maintained by most of the participants." (p.23) "There was no significant difference between the two active treatment arms regarding social phobic symptom reduction." (p.23) "It should be noted that the baseline impairment caused by social anxiety symptoms in the present sample was comparatively high." (p.24) "Further, we only found marginally significant post-hoc differences between the wait-list control group and the active conditions on the secondary outcome measures, indicating that the intervention mainly targeted the social phobic symptoms." (p.24)

Main Study Findings	Author's Conclusions
Cohen's d (95% CI): • iCBT individual vs. control: 0.53 (0.08, 0.98) • iCBT group vs. control: 0.54 (0.09, 0.99) **IIP:** iCBT individual: • Pre-treatment = 1.91 (0.45) & Post = 1.46 (0.55) • 6-month: 1.38 (0.62) iCBT group: • Pre-treatment = 1.81 (0.52) & Post = 1.44 (0.55) • 6-month: 1.44 (0.62) Control: • Pre-treatment = 1.75 (0.55) & Post = 1.70 (0.55) *No statistically significant post-treatment differences between iCBT individual vs. control (p=0.13) and iCBT group vs. control (p=0.07).* Cohen's d (95% CI): • iCBT individual vs. control: 0.49 (0.40, 0.94) • iCBT group vs. control: 0.56 (0.11, 1.02) **SF-12 (mental health subscale):** iCBT individual: • Pre-treatment = 31.92 (9.62) & Post = 41.09 (10.72) • 6-month: 39.49 (10.56) iCBT group: • Pre-treatment = 32.66 (10.34) & Post = 42.19 (12.17) • 6-month: 40.95 (13.32) Control: • Pre-treatment = 35.11 (10.67) & Post = 38.88 (11.27) *No statistically significant post-treatment differences between iCBT individual vs. control (p=0.97) and iCBT group vs. control (p=0.35).* Cohen's d (95% CI): • iCBT individual vs. control: 0.24 (-0.68, 0.21) • iCBT group vs. control: 0.35 (-0.78, 0.11) **Diagnostic status (post-treatment, with social anxiety disorder, telephone interview):** iCBT individual: 75%; iCBT group: 75%; control: 100% *Statistically significant differences between iCBT individual vs. control and iCBT group vs. control.* **Attrition:** *Completion of post-treatment questionnaires:* iCBT individual: 46/60 (76.7%) iCBT group: 45/60 (75%) Control: 24/29 (82.8%) *Mean number of completed modules:* iCBT individual: 6.52 (81.5%) iCBT group: 6.35 (79.4%) *Completion of all modules:*	

Main Study Findings	Author's Conclusions
iCBT individual: 35/60 (58.3%) iCBT group: 34/60 (56.7%)	
Mixed	
Silfvernagel (2017)[10]	
BAI: iCBT: Pre-treatment = Mean 18.4 (SD 12.53) & Post = 10.11 (10.07) Control: Pre-treatment = Mean 18.4 (SD 12.53) & Post = 10.11 (10.07) Cohen's d = 0.50 Statistically significant interaction effect between group and time, in favour of iCBT (p=0.034) **GAD-7:** iCBT: Pre-treatment = 8.88 (5.04) & Post = 4.68 (3.71) Control: Pre-treatment = 8.82 (3.80) & Post = 7.64 (5.12) Cohen's d = 0.67 Statistically significant interaction effect between group and time, in favour of iCBT (p=0.022) **MADRS-S:** iCBT: Pre-treatment = 20.27 (6.75) & Post = 11.75 (8.36) Control: Pre-treatment = 20.03 (7.73) & Post = 16.99 (8.84) Cohen's d = 0.61 Statistically significant interaction effect between group and time, in favour of iCBT (p=0.006) **PHQ-9:** iCBT: Pre-treatment = 10.88 (5.57) & Post = 5.47 (3.99) Control: Pre-treatment = 10.06 (5.33) & Post = 8.66 (6.25) Cohen's d = 0.62 Statistically significant interaction effect between group and time, in favour of iCBT (p=0.005) **CORE-OM:** iCBT: Pre-treatment = 55.61 (SD 11.61) & Post = 43.71 (SD 10.86) Control: Pre-treatment = 57.06 (SD 10.13) & Post = 52.85 (SD 11.29) Cohen's d = 0.83 Statistically significant interaction effect between group and time, in favour of iCBT (p=0.009) **QOLI:** iCBT: Pre-treatment = 0.12 (1.50) & Post = 1.52 (1.91) Control: Pre-treatment = 0.48 (2.06) & Post = 1.1 (1.93) Cohen's d = 0.22 Statistically significant interaction effect between group and time, in favour of iCBT (p=0.048)	"Nineteen out of the original 33 treatment group participants completed a one-year follow-up survey. On the primary outcome measure BAI, a score of 10.37 (SD = 6.83) was obtained, suggesting that improvements were sustained (within-group pre- to follow-up Cohen's d = .80). Similar effects were found for the secondary outcomes: GAD-7 (M= 4.68, SD 4.16), PHQ-9 (M = 4.58, SD = 3.86), MADRS-S (M = 11.47, SD = 7.47), CORE-OM (M= 42.42, SD = 12.94), and QOLI (M= 1.44, SD =1.33), with within-group effect sizes ranging between d = .63 and 1.13. All pre- to follow-up changes were confirmed by paired t-tests (all p's < .05)." (p.9) "In the treatment group, the average improvement on the BAI was 45.1% (CI 95% 27.4 - 62.8), and for the control group it was 14.7% (C1 95% 5.8 - 35.3). The proportion that had improved at least 30% in the treatment group was 45.5% (15/33; CI 95% 29.8 - 62.0), and in the control group it was 33.3% (1 1/33; CI 95% 19.7 - 50.4). Deterioration by at least 30% was found in 3.0% (1/33; CI 95% .5—15.3) of the treatment group participants and in 15.2% (5/33; CI 95% 6.7—30.9) the control group. The differences in proportions did not reach statistical significance: χ^2 (1) = .58, p = .31 for improvement and χ^2 (1) = 3.22, p = .07 for deterioration." (p.9) "Effect sizes for the outcome measures were moderate overall, with the exception of quality of life, for which a low between-group effect was found." (p.10)

Main Study Findings	Author's Conclusions
Attrition: iCBT: 11/33 (33.3%) iCBT (1-year): 14/33 (42.4%) Control: 1/33 (3.0%) *Of 33 participants randomized to iCBT* Completed all prescribed modules: 11 (33%) Completed 75% prescribed modules: 18 (55%) Completed 50% prescribed modules: 22 (67%) Did not complete first module: 4 (12%)	
Dear (2015)[16]	
GAD-7: iCBT: Pre-treatment = Mean 11.41 (SD 3.10) & Post = 3.56 (3.26) iCBT (12-month): Mean 3.74 (SD 3.29) Control: Pre-treatment = Mean 10.94 (SD 3.11) & Post = 10.22 (3.35) Cohen's d (95% CI) (between group effect): 1.43 (0.89, 1.93) *Clinical Sample (baseline GAD-7 ≥8):* iCBT: Pre-treatment = 14.03 (3.10) & Post = 4.46 (3.24) iCBT (12-month): 4.40 (3.29) Control: Pre-treatment = 13.16 (3.14) & Post = 11.93 (3.32) Cohen's d (95% CI) (between group effect): 1.62 (0.95, 2.23) *Improvement (baseline GAD-7 ≥8 and decrease in GAD-7 >3.53):* iCBT: Post-treatment = 82.6%; 12-month = 82.6% Control: Post-treatment = 18.5% (p<0.001) *Recovery (improvement + GAD-7 <8):* iCBT: Post-treatment = 78%; 12-month = 69% Control: Post-treatment = 18% (p<0.001) **PHQ-9:** iCBT: Pre-treatment = 10.74 (2.96) & Post = 3.63 (3.11) iCBT (12-month): 3.90 (3.15) Control: Pre-treatment = 10.75 (2.96) & Post = 10.56 (3.18) Cohen's d (95% CI) (between group effect): 1.79 (1.21, 2.32) *Clinical Sample (baseline GAD-7 ≥8):* iCBT: Pre-treatment = 12.64 (4.09) & Post = 4.02 (2.93) iCBT (12-month): 3.84 (2.99) Control: Pre-treatment = 12.46 (2.80) & Post = 12.43 (2.97) Cohen's d (95% CI) (between group effect): 2.18 (1.45, 2.84) *Improvement (PHQ-9 ≥10 and decrease in PHQ-9 >5.20):* iCBT: Post-treatment = 78.9%; 12-month = 73.6% Control: Post-treatment = 13% (p<0.001) *Recovery (improvement + PHQ-9 <10) :* iCBT: Post-treatment = 73%; 12-month = 68.4% Control: Post-treatment = 13% (p<0.001) **Attrition:** Completion of all modules: 28/33 (84.8%)	"The clinical outcomes were greater for the treatment group on all of the outcome measures at posttreatment and the observed clinical improvements were maintained at 3-month and 12-month follow-up." (p.215) "The intervention was also found to be cost-effective over a range of commonly used willingness-to-pay thresholds in Australia." (p.215) "First, to date, there have been no RCTs [randomized controlled trials] conducted examining iCBT for older adults with anxiety. Second, with a 12-month follow-up, the present study provides much needed data on the longer-term outcomes following iCBT for older adults." (p.215)

Main Study Findings	Author's Conclusions
Completion of post-treatment questionnaires: iCBT:90%; Control:86% **Cost-effectiveness:** *Mean costs (95% CI):* iCBT: $229.5 (184.9, 276.4) Control: $137.4 (98.4, 173.5) Difference: $92.2 (38.7, 149.2) *Mean QALYs (95% CI):* iCBT: 0.102 (0.044, 0.139) Control: 0.092 (0.033, 0.128) Difference: 0.010 (0.003, 0.0180) *ICER (95% CI):* $8 806 (2 849, 39 522)	

ACQ = Agoraphobic Cognitions Questionnaire; BAI = Beck Anxiety Inventory; BDI-II = Beck Depression Inventory-II; BSI = Brief Symptom Inventory; BSQ = Body Sensations Questionnaire; BVS = Body Vigilance Scale; CGI-I = Clinical Global Impression-Improvement scale; CI = confidence interval; CORE-OM = Clinical Outcomes in Routine Evaluation – Outcome Measure; GAD-7 = Generalized Anxiety Disorder 7-item scale; GAD-Q-IV = Generalized Anxiety Disorder Questionnaire-IV; iACT = internet-delivered acceptance and commitment therapy; iCBT = internet-supported cognitive behavior therapy; iPDT = internet-based psychodynamic therapy; ICER = incremental cost-effectiveness ratio; IIP = Inventory of Interpersonal Problems; LSAS-SR = Liebowitz Social Anxiety Scale – Self Rated; MADRS-S = Montgomery Asberg Depression Rating Scale - Self Rated; PACQ = Panic Attack Cognition Questionnaire; PD = panic disorder; PDSQ = Psychiatric Diagnostic Screening Questionnaire; PDSS-SR = Panic Disorder Severity Scale – Self Report; PHQ-9 = Patient Health Questionnaire-9; PSWQ = Penn State Worry Questionnaire; QALY = quality-adjusted life-years; QOLI = Quality of Life Inventory; SAD = social anxiety disorder; SD = standard deviation; SF-12 = Short Form Health Survey (condensed version of SF-36); SIAS = Social Interaction Anxiety Scale; SPS = Social Phobia Scale; WSAS = Work and Social Adjustment Scale

Appendix 5: Additional References of Potential Interest

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